Epicardial fat thickness as associated with left ventricular myocardial performance in patients with newly diagnosed hypertension

Yeni tanı konmuş hipertansiyonlu hastalarda epikardiyal yağ kalınlığının sol ventrikül miyokart performansı ile ilişkisi

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ABSTRACT

Objective: Epicardial fat thickness (EFth) is associated with both left ventricular hypertrophy (LVH) and diastolic dysfunction. However, the effect of EFth on myocardial performance is not known. The aim of this study was to investigate the relationship between EFth and tissue Doppler myocardial performance index (TD-MPI), which incorporates both systolic and diastolic left ventricular (LV) function, in newly diagnosed hypertension (HT) patients.

Methods: A total of 314 consecutive, newly diagnosed HT patients were prospectively included (mean age: 51.9±1.7 years). EFth was measured perpendicularly on the free wall of the right ventricle at the end of the systole in 2 echocardiographic views (parasternal short and long axis). Myocardial performance index (MPI) was calculated using tissue Doppler (TD) echocardiography. Patients were divided into 2 groups according to median TD-MPI levels (TD-MPI_{low} and TD-MPI_{high}).

Results: EFth values of the TD-MPI_{high} group were higher than those of the TD-MPI_{low} group ($p<0.05$). Patients in the TD-MPI_{high} group also had higher age, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular mass index (LVMI), E/A ratio, and aortic distensibility, compared with the TD-MPI_{low} group ($p<0.05$ for all). Multivariate linear regression analysis showed that TD-MPI was independently associated with age ($\beta=0.089$, $p=0.012$), LVMI ($\beta=0.090$, $p=0.05$), E/A ($\beta=-0.118$, $p=0.005$), and EFth ($\beta=0.432$, $p<0.001$).

Conclusion: TD-MPI was independently associated with EFth in patients with newly diagnosed HT. EFth may be used as a predictor of impaired LV global functions in patients with normal left ventricular ejection fraction (LVEF) and newly diagnosed HT.

ÖZET

Amaç: Epikardiyal yağ kalınlığının (EYK) sol ventrikül hipertrofisi ve diyastolik fonksiyon bozukluğu ile ilişkisi bilinmektedir. Ancak, epikardiyal yağ dokusunun miyokart performansı üzerine etkisi bilinmemektedir. Bu çalışmada yeni tanı konmuş hipertansiyonlu hastalarda EYK ile sol ventrikülün hem sistolik hem de diyastolik fonksiyonunu içeren doku Doppler miyokart performans indeksi (MPI) arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Bu çalışmaya, ileriye dönük olarak (ortalama yaş: 51.9±1.7 yıl) olan 314 ardışık yeni tanı konmuş hipertansiyonlu hasta dahil edildi. EYK iki ekokardiyografik görüntüde (parasternal uzun ve kısa aks) sistol sonunda sağ ventrikül serbest duvarına dik olarak ölçüldü. MPI doku Doppler (tD) ekokardiyografi kullanılarak hesaplandı. Hastalar ortalama tD-MPI değerlerine göre iki gruba ayrıldı (tD-$MPI_{düşük}$ ve tD-$MPI_{yüksek}$ grup).

Bulgular: Doku Doppler MPI yüksek grubun EYK değerleri tD-$MPI_{düşük}$ gruptan yüksek bulundu ($p<0.05$). Ayrıca tD-$MPI_{yüksek}$ grupta tD-$MPI_{düşük}$ grup ile karşılaştırıldığında daha yüksek yaş, beden kütle indeksi, sistolik kan basıncı, diyastolik kan basıncı, sol ventrikül kitle indeksi (LVMI), E/A oranı ve aort distansibilitesi tespit edildi (hepsinde, $p<0.05$). Çok değişkenli lineer regresyon analizinde MPI yaş ($\beta=0.089$, $p=0.012$), LVMI ($\beta=0.090$, $p=0.05$), E/A ($\beta=-0.118$, $p=0.005$) ve EYK ($\beta=0.432$, $p<0.001$) ile bağımsız ilişkili bulundu.

Sonuç: Doku Doppler MPI yeni tanı konmuş hipertansiyonlu hastalarda EYK ile bağımsız ilişkilidir. EYK, sol ventrikül ejeksiyon fraksiyonu normal olan ve yeni hipertansiyon tanısı konmuş hastalarda sol ventrikül global fonksiyon bozukluğunun belirlenmesinde öngördürücü olarak kullanılabilir.

Received: February 13, 2015 *Accepted:* June 03, 2015

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Adipose tissue carries risk for cardiovascular diseases due to unfavorable metabolic results.[1] Increased adipose tissue is an important clinical condition.[1] In addition to increased adiposity, storage location of fat tissue is an important issue. It is well known that visceral fat is metabolically more active and dangerous than subcutaneous fat.[2] Epicardial fat tissue (EFT) is visceral fat deposition around the heart, encircled by the visceral pericardial layer. Evidence has shown that EFT is a metabolically active organ that produces several proinflammatory, proatherogenic cytokines and has emerged as a new cardiovascular risk factor.[3,4] Studies report that an increase in epicardial fat thickness (EFth) is associated with insulin resistance, metabolic syndrome, subclinical atherosclerosis, coronary artery disease, and hypertension (HT).[5–9] A recent study showed that EFT was associated with left ventricular (LV) hypertrophy.[10]

Studies have also shown that increased EFth was associated with impaired LV diastolic function in hypertensive patients.[11] Although these relationships are well-known, there has been no investigation of possible association between LV global function and EFth in hypertensive patients.

Ejection fraction is the most reliable estimator of systolic function. However, when the elliptical cardiac chamber is transformed to a spherical one, accuracy of ejection fraction tends to be low.[12] Myocardial performance index (MPI) has been widely used to quantitatively assess myocardial performance.[13] It is more reflective of overall cardiac function than systolic or diastolic function alone and is used to independently assess myocardial performance of the left and right ventricles.[14,15] MPI obtained using tissue Doppler (TD) echocardiography has been studied in several other cardiac disorders, including heart failure, myocardial infarction, HT, and diabetes mellitus, and was found to predict worsened morbidity and mortality.[15–18]

The aim of this study was to evaluate whether echocardiographic EFth is related to global myocardial performance in newly diagnosed hypertensive patients.

METHODS

Study population

Between January and June 2013, 354 consecutive patients with newly diagnosed HT were included. All patients with newly diagnosed HT according to office blood pressure measurements underwent ambulatory blood pressure monitoring. Of the 354 patients with office blood pressure ≥140/90 mmHg, 40 were excluded because blood pressure was normal according to ambulatory blood pressure monitoring (white-coat HT). The final group consisted of 314 patients with newly diagnosed essential HT (159 males and 155 females; mean age 51.9±11.7 years). Three clinic blood pressure measurements (≥140/90 mmHg) were taken of hypertensive patients at weekly intervals in the absence of any previous antihypertensive treatment to exclude pharmacological effects on hemodynamics or ventricular hypertrophy and function. Criteria for exclusion were secondary or malignant HT, heart failure, positive history or clinical signs of ischemic heart disease, cerebrovascular disease, concomitant valvular disease, atrial fibrillation, drug use, renal insufficiency, hepatic dysfunction, major non-cardiovascular diseases such as auto-immune disease, hematological disease, cancer, thrombocytopenia, morbid obesity, severe chronic obstructive pulmonary disease and systemic inflammatory conditions, and known diabetes or fasting glycemia ≤126 mg/dl. The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Abbreviations:

2D	*2-dimensional*
AD	*Aortic distensibility*
DBP	*Diastolic blood pressure*
EFT	*Epicardial fat tissue*
EFth	*Epicardial fat thickness*
FFA	*Free fatty acids*
HT	*Hypertension*
LV	*Left ventricular*
LVEF	*Left ventricular ejection fraction*
LVH	*Left ventricular hypertrophy*
LVID	*Left ventricular end-diastolic diameter*
LVM	*Left ventricular mass*
LVMI	*Left ventricular mass index*
MPI	*Myocardial performance index*
PWT	*Posterior wall thickness*
RWT	*Relative wall thickness*
SBP	*Systolic blood pressure*
TD	*Tissue Doppler*
TD-MPI	*Tissue Doppler myocardial performance index*

After taking detailed history and complete physical examination, all patients were questioned for major cardiovascular risk factors such as age, sex, diabetes mellitus, smoking status, HT, and family history of coronary artery disease. In addition, body mass index and heart rate were recorded. Fasting venous blood samples were obtained from all patients to determine plasma levels of fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and creatinine.

Echocardiography

All echocardiographic examinations were performed using commercially available equipment (Vivid-7; GE Vingmed Ultrasound, Horten, Norway) with a 2.5–3.5 MHz transducer. Simultaneous electrocardiographic recordings were also obtained. All echocardiograms were performed and analyzed by 2 observers. TD and 2-dimensional (2D) tracings were recorded on strip charts at a paper speed of 50 mm/s or 100 mm/s and video was recorded for later analysis. Patients were examined at rest in the left lateral decubitus position. Echocardiographic techniques and calculations of cardiac dimensions were performed in accordance with the recommendations of the American Society of Echocardiography.[19] Left ventricular ejection fraction (LVEF) was calculated using modified Simpson's rule.[19]

Mitral pulsed-wave Doppler measurements were obtained with transducer in apical 4-chamber view. Peak velocities of early (E) and late (A) filling were derived from mitral inflow velocity curve. Ratio of early to late peak velocities (E/A) was subsequently calculated. After proper acquisition adjustments were made, LV-TD echocardiographic evaluation was performed in apical 4-chamber position by placing pulsed-wave Doppler beam on the part of the mitral annulus close to the LV lateral wall and interventricular septum. Final values were accepted as average of lateral and interventricular septum measurements. Special attention was paid to place Doppler beam in the myocardium, not the endocardium or epicardium. Measurements were made for 3 consecutive heartbeats in all positions, and their average was taken. Doppler measurements were made at a recording rate of 100 mm/sec. MPI obtained by TD echocardiographic evaluation was defined as sum of isovolumetric relaxation time and isovolumetric contraction time divided by ejection time (Figure 1).[13] Three consecutive beats were measured and averaged for each parameter.

EFth was measured on the free wall of the right ventricle from parasternal long-axis views.[13] Epicardial fat was identified as echo-free space in the pericardial layers on 2D echocardiography, and its thickness was measured perpendicularly on the free wall of the right ventricle at end-systole for 3 cardiac cycles. To standardize the measuring point among different observers, the aortic annulus was used as anatomical reference. Measurement was performed at a point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus (Figure 2). Average reading from 3 cardiac cycles for each echocardiographic view was used for statistical analysis. Echocardiographic images were recorded onto a computerized database. Offline measurement of EFth was performed by 2 cardiologists who were blinded to the clinical data (Figure 3).

Left ventricular mass index (LVMI) measurements were made during normal breathing at end-expiration. LV end-systolic and LV end-diastolic diameter (LVID), end-diastolic interventricular septal thickness, and end-diastolic LV posterior wall thickness (PWT) were measured at end-diastole according to established standards of the American Society of Echocardiography.[20] LVEF was determined by biplane Simpson's method. Left ventricular mass (LVM) was calculated

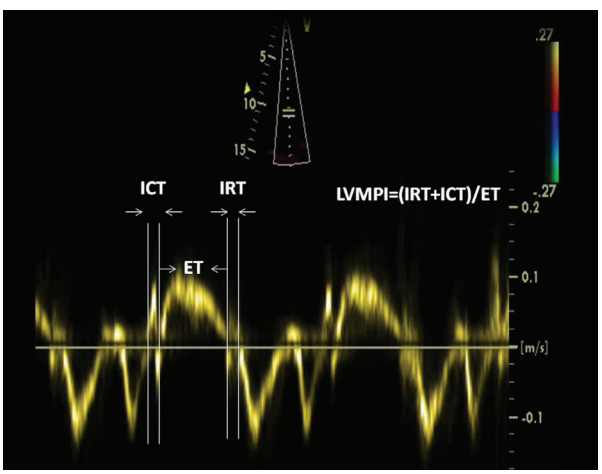

Figure 1. Calculation of tissue Doppler-derived left ventricular myocardial performance index (Tei index).

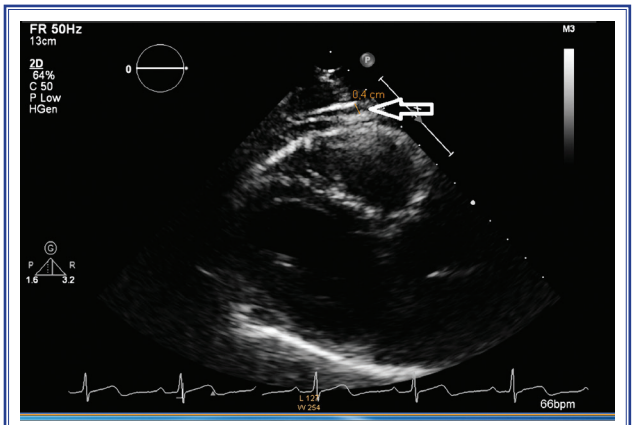

Figure 2. Measurement of epicardial fat thickness (EFth).

using Devereux formula: LVM=(1.04[(LVID+interventricular septal thickness+PWT)3-(LVID)3]-13.6).[21]

LVMI (g/m^2) was obtained using the following formula: LVM/body surface area. LV hypertrophy (LVH) was defined, according to more stringent criteria, as LVMI values exceeding 125 g/m^2 in men and 110 g/m^2 in women.[22] Relative wall thickness (RWT) was measured at end-diastole as (2 x PWT)/LVID. Increased RWT was defined as ≥0.45.

Echocardiographic measurements were repeated by a second observer blinded to the values obtained by the first. Interobserver variability was assessed by calculating coefficient of variation, which was <8% for all measurements. Any discrepancy was resolved by consensus.

Aortic distensibility

Ascending aortic diameters were measured from the same view on the M-mode tracing at 3 cm above the aortic valve. Systolic diameter was measured at the maximum anterior motion of the aorta, and diastolic diameter was measured at the peak of the QRS complex on the simultaneously recorded electrocardiogram. Pulse pressure was obtained simultaneously by cuff sphygmomanometry of the left brachial artery as systolic blood pressure (SBP) minus diastolic blood pressure (DBP). Aortic distensibility (AD) was calculated as AD=2 x (aortic systolic diameter - aortic diastolic diameter) /(aortic diastolic diameter x PP) (cm^2 dyn-1 x 10-6).[23]

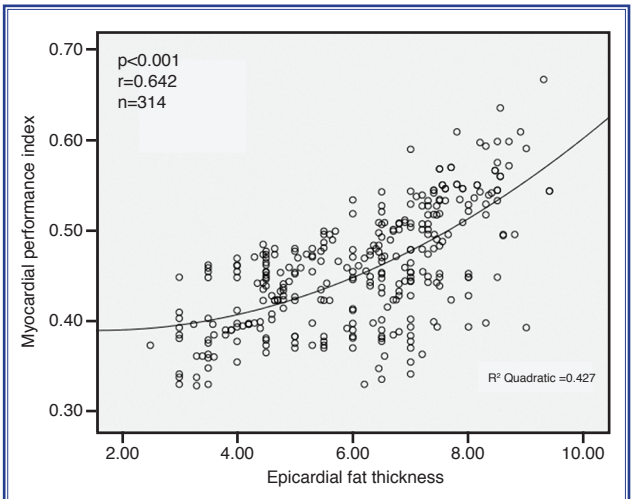

Figure 3. Relationship between tissue Doppler myocardial performance index (TD-MPI) and epicardial fat thickness (EFth).

Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Data are expressed as mean±SD. Categorical variables were compared by chi-square test. Distribution of parametric variables was evaluated with one-sample Kolmogorov-Smirnov test. For continuous variables, difference between the 2 groups was assessed using unpaired t-test. Associations between tissue Doppler myocardial performance index (TD-MPI) and other variables were evaluated by Pearson correlation analysis. Independent relationships of MPI were examined by multiple linear regression analysis. All significant parameters in Pearson correlation analysis were selected in multivariate model, and p<0.05 was considered statistically significant.

RESULTS

Patients were divided into 2 groups according to median TD-MPI values: TD-MPI$_{low}$ group (TD-MPI ≤0.45) and TD-MPI$_{high}$ group (TD-MPI>0.45). Based on median TD-MPI value, 157 patients were included in the TD-MPI$_{low}$ group, and 157 patients were included in the TD-MPI$_{high}$ group.

Baseline characteristics

Comparison of baseline, laboratory, echocardiographic, and clinical characteristics of groups is shown in Table 1. Patients in the TD-MPI$_{high}$ group were older, and had higher body mass index, SBP, and DBP (p<0.05 for all).

Echocardiographic findings

Patients in the TD-MPI$_{high}$ group had higher EFth and aortic distensibility (p<0.05 for all), compared with the TD-MPI$_{low}$ group. In addition, patients in the TD-MPI$_{high}$ group had higher interventricular septum thickness, PWT, right ventricle wall thickness (RWT), LVMI, TD-isovolumetric relaxation time, TD-isovolumetric contraction time, TD-ejection time, and E/A values (p<0.05 for all; Table 1).

Bivariate and multivariate relationships of MPI

Bivariate and multivariate relationships of TD-MPI are shown in Table 2. TD-MPI was significantly associated in bivariate analysis with age (r=0.120, p=0.033), SBP (r=0.282, p<0.001), DBP (r=0.282, p<0.001), LVMI (r=0.527, p<0.001), E/A ratio (r=-

Table 1. Comparison of baseline, laboratory, and echocardiographic characteristics between groups

Variables	tD-MPI$_{low}$ Group (n=157)			tD-MPI$_{high}$ Group (n=157)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Baseline characteristics							
Age (years)			51.1±4.6			52.5±6.7	**0.041**
Gender (male)	82	51.6		77	48.4		0.327
Body mass index (kg/m^2)			28.5±3.8			29.5±3.7	**0.017**
Smoking	40	25.2		49	30.8		0.159
Systolic blood pressure (mmHg)			154.8±19.4			161.7±15.7	**0.001**
Diastolic blood pressure (mmHg)			99.8±13.3			105.5±12.8	**<0.001**
Heart rate (beat/minute)			77.9±11.9			76.6±11.3	0.358
Laboratory findings							
Glucose (mg/dl)			88.9±8.1			90.3±9.1	0.168
Total cholesterol (mg/dl)			193.0±27.8			189.3±34.7	0.300
Triglyceride (mg/dl)			176.7±45.2			166.5±48.4	0.053
High density lipoprotein cholesterol (mg/dl)			41.0±6.0			40.5±6.6	0.437
Low density lipoprotein cholesterol (mg/dl)			116.3±23.4			112.9±28.6	0.238
Creatinin (mg/dl)			0.82±0.30			0.82±0.43	0.850
Echocardiography							
Left atrial diameter (mm)			33.9±3.5			34.1±4.0	0.612
Left ventricle end diastolic diameter (mm)			45.5±4.1			46.1±4.0	0.218
Interventricular septal thickness (mm)			10.3±1.6			12.2±2.0	**<0.001**
Posterior wall thickness (mm)			9.8±1.6			10.9±1.7	**<0.001**
Relative wall thickness (mm)							
Left ventricle mass index (g/m^2)			103.2±21.7			129.6±32.0	**<0.001**
Left ventricle mass index (%)			66.4±4.4			65.5±4.4	0.070
TD-Isovolumic relaxation time (ms)			77.3±7.4			95.2±11.6	**<0.001**
TD-Isovolumetric contraction time (ms)			38.9±5.6			46.8±7.4	**<0.001**
TD-Ejection time (ms)			286.0±14.2			278.1±19.5	**<0.001**
TD-Myocardial performance index			0.41±0.03			0.51±0.04	**<0.001**
E/A ratio			1.05±0.3			0.82±0.2	**<0.001**
Epicardial fat thickness (mm)			5.3±1.5			6.7±1.4	**<0.001**
Aortic distensibility			2.0±0.9			1.3±0.6	**<0.001**

TD: Tissue Doppler. Bold indicate significant values.

0.377, p<0.001), EFth (r=0.642, p<0.001), and AD (r=-410, p<0.001).

Multivariate logistic regression analysis showed that TD-MPI was independently associated with age (β=0.089, p=0.012), LVMI (β=0.090, p=0.05), E/A ratio (β= -0.118, p=0.005), and EFth (β=0.432, p<0.001). In multivariate logistic regression analysis, a relationship was demonstrated, though not strongly, between TD-MPI and AD (β=-0.086, p=0.070).

DISCUSSION

The present study was the first to evaluate the relationship between TD-MPI and EFth in newly diagnosed hypertensive patients. It demonstrated that TD-MPI was significantly correlated with EFth, as well as age, LVMI, and E/A ratio.

Table 2. Bivariate and multivariate relationships of tissue Doppler myocardial performance index

Variables	Pearson correlation coefficient	*p*	Standardized β-regression coefficient	*p*
Age (years)	0.120	0.033	0.089	0.012
Systolic blood pressure (mmHg)	0.282	<0.001	-0.016	0.816
Diastolic blood pressure (mmHg)	0.282	<0.001	0.025	0.712
Left ventricle mass index (kg/m^2)	0.527	<0.001	0.090	0.05
E/A ratio	-0.377	<0.001	-0.118	0.005
Epicardial fat thickness (mm)	0.642	<0.001	0.432	<0.001
Aortic distensibility	-0.410	<0.001	-0.086	0.070

Association of EFT with HT has been demonstrated in previous studies.[9] EFth increases in non-hypertensive, healthy patients with exaggerated blood pressure response to exercise stress testing.[24] Echocardiographic EFT was found to be increased in untreated hypertensive patients with non-dipper blood pressure pattern.[25] Increased EFT is also associated with changes in right ventricular mass, LVM, and diastolic function.[10,26]

Underlying pathophysiology that demonstrates association of EFT with HT and LVH is not yet fully clear. EFT is very metabolically active and can secrete a large number of cytokines and vasoactive peptides, including free fatty acids (FFA), interleukin-6, TNF-α, angiotensin II, and plasminogen activator inhibitor-1, which may activate the renin-angiotensin system.[27] Activation of this system can independently increase blood pressure and LVH.

On the other hand, HT is a common cause of diastolic and systolic heart failure, and some studies have reported that these disorders can be present in same patient.[28,29] LVEF and mitral inflow velocities are commonly used to evaluate global LV systolic and diastolic functions, respectively. However, measurement of LVEF has a number of well-known limitations. Evaluation of LV systolic function is difficult in abnormally shaped ventricles or poorly defined LV endocardium. MPI is more accurate, reproducible, and simple, and it is easier to estimate clinical index of LV global function for evaluating systolic and diastolic function using MPI than conventional methods.[12,30]

MPI has prognostic value in various clinical settings. Correlation between MPI and age, HT, and diabetes has been reported.[17,18] However, in contrast to these reports, a negative association between TD-MPI and SBP, as well as DBP, was found in patients with newly diagnosed HT in the present study, though on multivariate analysis this relationship was lost. The reason for this discrepancy may have been the strong correlation between TD-MPI and other variables.

In the present study, the relationship between EFth and TD-MPI, which assesses global LV functions, was investigated in newly diagnosed HT patients, and a significant correlation between these parameters was demonstrated. While little information is available regarding the relationship between EFth and TD-MPI, several mechanisms may explain this finding. EFth is a true visceral fat that plays an important role in both lipid and energy metabolism, and is responsible for protecting the heart through mechanical and biochemical means.[31] EFth is also characterized by a high rate of FFA release.[31] FFA encounter no physical barrier or fascia before reaching cardiomyocytes,[32] so the myocardium receives a double dose of FFA from both EFth and systemic circulation. LV function can be harmed by pathological epicardial fat deposition.[33] Because EFth is a source of several bioactive molecules and secretes a large number of proatherogenic and proinflammatory cytokines and vasoactive peptides that affect the heart through systemic or local paracrine pathways, EFT triggers inflammatory milieu on the myocardium by virtue of these mediators.[34] These mediators may negatively affect the myocardium, not only directly, but also indirectly by causing HT, which leads to myocardial injury.[35] Angiotensin II released from EFT in particular[27] can result in HT and may be responsible for increased LV myo-

cardial mass and diastolic dysfunction. In metabolic and cardiovascular disease states, these fat tissues expand, becoming hypoxic and dysfunctional,[36] and recruiting phagocytic cells[37] that lead to a reduction in the production of protective cytokines, eventually increasing detrimental adipocytokines and impaired cardiac function.

Increased EFT is also related to systemic inflammatory response to a greater extent than general risk factors and body fat composition.[38] In addition, echocardiographic and autopsy findings show that increased epicardial fat is closely correlated with increased ventricular myocardial mass.[39] All these mechanisms may be used to explain how increase in EFT causes global LV dysfunction.

Relationship between EFth and diastolic dysfunction has been shown in previous reports. Konishi et al. found that increased epicardial fat detected with computed tomography was associated with LV diastolic dysfunction, independent of other general risk factors such as age, sex, diabetes, HT, or abdominal obesity.[40] Cavalcante et al. demonstrated that EFT is an independent predictor of LV diastolic dysfunction in apparently healthy, overweight patients, even after accounting for other possible associated risk factors.[41] The present study determined that EFT is related to TD-MPI, which is likely to be more effective for analysis of global cardiac functions than systolic and diastolic measures alone in newly diagnosed hypertensive patients.

In addition, the present study demonstrated that TD-MPI was also significantly correlated with LVMI on multivariate linear regression analysis. Relationship between MPI and LVMI has been previously shown.[30] Increased LVMI is related to higher LV end-diastolic pressure and wall stresses, which result in decrease of subendocardial coronary blood flow and reduced tolerance to myocardial ischemia.[42] Increased myocardial ischemia may lead to myocardial scarring and LV dysfunction.

Additionally, association between TD-MPI and AD was shown in bivariate linear regression analysis in the present study, but this relationship could not have been shown strongly in multivariate linear regression analysis. Recently, Gür at el. demonstrated the relationship between MPI and AD in newly diagnosed hypertensive patients.[17]

Study limitations

A significant relationship between increased EFT thickness and TD-MPI was observed in the present study, but exact underlying mechanism responsible for this association could not be established. Secondly, epicardial fat could not be confirmed using standard computed tomography and magnetic resonance imaging, which accurately quantify epicardial fat volume better than echocardiography.[3] Although echocardiography is a relatively simple and inexpensive method, its accuracy and reproducibility should be further tested. In addition, as epicardial adipose tissue has a 3-dimensional distribution, 2D echocardiography may not completely assess total amount of epicardial adiposity.

TD-MPI, a useful imaging modality to assess global cardiac function, is associated with EFth in patients with newly diagnosed HT. EFth may be used as a predictor of impaired ventricular function in patients with normal LVEF and newly diagnosed HT.

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

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Keywords: Epicardial fat thickness; hypertension; hypertrophy; myocardial performance index.

Anahtar sözcükler: Epikardiyal yağ dokusu; hipertansiyon; hipertrofi; miyokardiyal performans indeksi.