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Original article

Effect of epicardial adipose tissue on diastolic functions and left atrial dimension in untreated hypertensive patients with normal systolic function

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ABSTRACT

Background: Adipose tissue is the source of many adipokines affecting the cardiovascular system either locally or systemically. Although hypertension is one of the most important factors in diastolic dysfunction (DD), the exact cause of this relationship is unknown. There is no specific study in the current literature regarding the association of epicardial adipose tissue (EAT) with left ventricular DD in patients with essential hypertension.
Methods: The present study was cross-sectional and observational, including 127 patients with untreated hypertension who underwent a complete transthoracic echocardiographic examination as well as measurements of EAT and diastolic parameters.
Results: EAT was significantly correlated with left atrial dimension, DD parameters, and left ventricular (LV) mass as well as age and blood pressure measurements. EAT was also correlated with Framingham risk score ($p < 0.001$). Age and EAT were significantly increased in patients with high grades of DD compared to those with low values ($p < 0.001$ and $p = 0.001$, respectively). Linear regression analyses revealed EAT as an independent predictor of all DD parameters. The area under the curve values of EAT were similar to age and higher than those of LV mass and mean BP for both the presence of DD and grade two DD.
Conclusion: Based on our findings, increased EAT may be associated with diastolic dysfunction and left atrial dilatation due to local or systemic effects in untreated hypertensive patients. This relationship is independent of and stronger than abdominal obesity, implicating the clinical importance of measuring EAT thickness.

Introduction

Evaluation of diastolic function in every patient undergoing echocardiography is important clinically [1]. Diastolic dysfunction, as seen in patients with hypertension (HT), diabetes mellitus, and ageing, increases the risk of heart failure and cardiovascular mortality, even if in at an asymptomatic or preclinical stage [2]. Although identifiable by Doppler echocardiography, there is no definitive treatment for diastolic dysfunction. Pathophysiological research implicates an active fibrotic process, which might lead to new therapeutic options in future [3,4].

Obesity is one of the most important features of diastolic dysfunction. Adipose tissue is the source of many adipokines affecting the cardiovascular system either locally or systemically [5]. Fat, mainly accumulated in subcutaneous tissue, is also deposited around visceral organs in the abdominal or thoracic region [6]. Fat is accumulated in three different localizations around the heart: cellular, epicardial, and pericardial. Epicardial fat is located between myocardium and visceral layer of pericardium. Pericardial fat is located between the visceral and parietal layers of pericardium [7]. Epicardial adipose tissue (EAT) thickness measured by echocardiography has a good correlation with abdominal adiposity measured by computed tomography (CT) and magnetic resonance imaging (MRI) [8,9]. Konishi et al. demonstrated a significant correlation between pericardial fat and diastolic dysfunction in patients with normal systolic function [10].

Although HT is one of the most important factors in diastolic dysfunction, the exact cause of this relationship is still unknown [11]. An increased epicardial fat mass may deteriorate cardiac function either locally or systemically by passive or active effects. There is no specific study in the current literature regarding the association of EAT with left ventricular diastolic dysfunction in patients with essential HT. Therefore, we planned this study in order to clarify this relation.

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Methods

Patient population and study protocol

The present study was cross-sectional and observational, including 127 patients with untreated HT who underwent a complete transthoracic echocardiographic examination as well as measurements of EAT and diastolic parameters. All data were prospectively collected. Resting blood pressure (BP) values were obtained at a physician's office and echocardiography room by traditional auscultatory method using a sphygmomanometer. Patients were advised to refrain from smoking or consumption of coffee or tea, and physical exercise, 30 min prior to the measurement. Before measurement, patients were seated to rest for 5 min. Two separate measurements were averaged to determine office blood pressure.

Patients with previous coronary artery disease (CAD) (17 patients), diabetes mellitus (20 patients), left ventricular systolic dysfunction (14 patients), secondary HT (2 patients, renal artery stenosis), moderate-severe valve disease (15 patients; 10 aortic stenosis, 5 mitral insufficiency), atrial fibrillation (18 patients), symptoms of CAD and equivalent findings on exercise electrocardiography and perfusion scan, or 24-h rhythm electrocardiography (20 patients; 15 positive exercise tests and 5 positive single photon emission computed tomography scans), and patients previously treated for HT (22 patients) were excluded.

Baseline characteristics of the patients were recorded. HT was defined as the documentation of blood pressure more than 140/90 mmHg. Patients who were using tobacco products on admission and those who had quit smoking within the last year were considered as smokers.

The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the local ethics committee.

Routine measurements

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least 8 h. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods. Serum C-reactive protein (CRP) was analyzed using a nephelometric technique (Beckman Coulter Image 800, Fullerton, CA, USA; normal range 0–0.8 mg/dL). Body mass index (BMI) was determined by the following formula: BMI = weight (kg)/height^2 (m).

Echocardiography

Patients were imaged in the left lateral decubitus position with commercially available systems with a GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5–3.5 MHz transducer. Diastolic parameters were measured according to guidelines by the American Society of Echocardiography [1]. Early (E) and late mitral inflow (A) velocities, lateral and medial mitral annular velocities (Em, Am), isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), ejection time (ET), deceleration time (DT), and Tei index (also known as myocardial performance index) [MPI = (IVRT + IVCT)/ET] were calculated according to relevant guidelines [1]. Left ventricular ejection fraction was measured by Simpson's method [12]. Maximum and minimum left atrial (LA) volumes were measured by the method of discs from the apical four-chamber view at end-systole and end-diastole [13]. End-systolic measurements were obtained from the frame preceding mitral valve opening.

Left ventricular mass (LV mass, in g) was calculated according to the following formula: $1.04 \times [(\text{LVEDD} + \text{IVSD} + \text{PWD})^3 - \text{LVEDD}^3] - 13.6$ (diameter in cm) [14], where LVEDD = left ventricular end-diastolic dimension; IVSD, interventricular septal thickness at diastole; PWD, posterior wall thickness at diastole.

Evaluation of epicardial adipose tissue

EAT was evaluated on the free wall of right ventricle from the parasternal long-axis view, using aortic annulus as an anatomic reference (Fig. 1). We preferred the area above the right ventricle to measure EAT thickness, because this area is known to have the thickest EAT layer. EAT, identified as an echo-free space between the visceral pericardial layer and myocardium on 2-dimensional echocardiography, was measured perpendicularly in front of the right ventricular free wall at end-diastole [8,15]. We magnified each still image for better visualization and accurate measurement

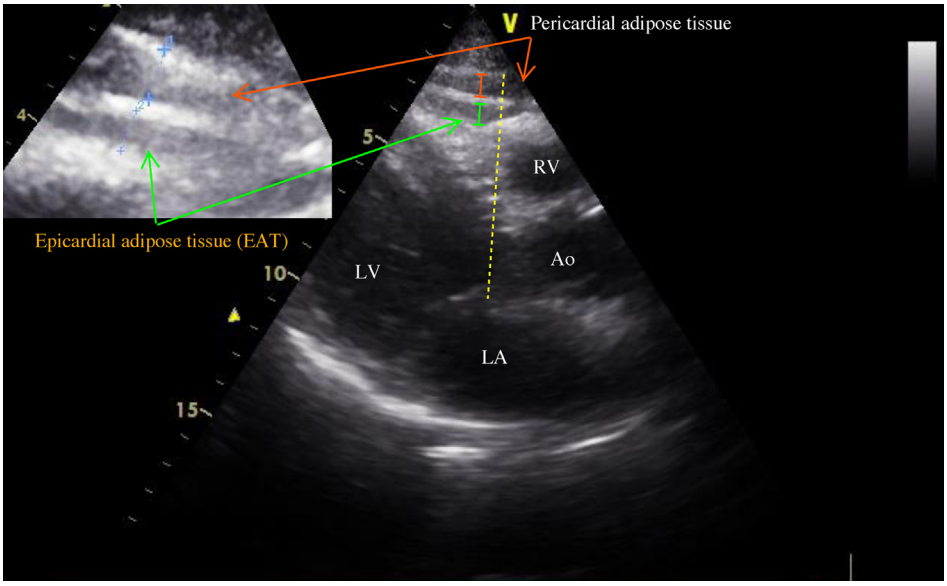

Fig. 1. Measurement of epicardial fat thickness by echocardiography. EAT, identified as an echo-free space between the myocardium and visceral pericardium from the parasternal long-axis view on 2-dimensional echocardiography, was measured perpendicularly in front of the right ventricular free wall at end-diastole. LV, left ventricle; LA, left atrium; RV, right ventricle; Ao, aorta.

of EAT thickness and measured the thickest point of EAT in each cycle. To standardize the measuring axis, we used the aortic annulus as anatomical reference. The 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. The average value comprising three cardiac cycles of each echocardiographical view was used for the statistical analysis. EAT measurements were performed by a second reader to prevent a possible bias between EAT and extensive echocardiographic measurements. The intra-observer mean absolute difference in measurements of EAT was 0.3 ± 0.4 mm (coefficient of variation: 1.6%, intra-class correlation: 0.95).

Statistical analysis

Continuous variables were given as mean ± standard deviation; categorical variables were defined as percentages. Data were tested for normal distribution using the Kolmogorov–Smirnov test. The χ^2 test was used for the categorical variables among the groups. Mean values were compared by ANOVA. Linear regression analysis with Backward method was used for the multivariate analysis of independent variables which were included if they were significantly different in the univariate analyses. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (SPSS 20.0 for Windows, Chicago, IL, USA) was used for all statistical calculations.

Results

The clinical characteristics of the study population are detailed in Table 1. Age ($p = 0.001$), BMI ($p < 0.001$), waist circumference ($p < 0.001$), CRP ($p = 0.002$), and blood pressure measurements (systolic, $p < 0.001$; diastolic, $p = 0.007$) were significantly higher in the high EAT group compared to the low EAT group (>7 mm vs. <5 mm). Left atrial dimension and diastolic dysfunction parameters were significantly higher in patients with increased EAT (Table 1).

Table 1
Baseline characteristics of the study population.

Parameters ($N = 127$)	Epicardial fat pad thickness			*p*-Value
	<5 mm (36)	5–7 mm (42)	>7 mm (49)	
Age (years)	44 ± 7	50 ± 7	50 ± 9	0.001
Gender (male)	67%	67%	66%	0.981
BMI (kg/m^2)	28.8 ± 3.4	30.1 ± 3.3	33.6 ± 4.3	<0.001
Waist circumference (cm)	97.2 ± 9.6	101.6 ± 7.1	111.0 ± 9.1	<0.001
Smoking	48%	42%	55%	0.679
Hyperlipidemia	35%	38%	42%	0.797
Glucose (mg/dL)	93 ± 12	99 ± 17	99 ± 14	0.096
Creatinine (mg/dL)	0.86 ± 0.23	0.85 ± 0.13	0.81 ± 0.10	0.146
Total cholesterol (mg/dL)	205 ± 44	219 ± 35	227 ± 41	0.029
LDL (mg/dL)	128 ± 35	138 ± 33	145 ± 36	0.056
HDL (mg/dL)	45 ± 14	47 ± 11	45 ± 9	0.614
Triglyceride (mg/dL)	165 ± 89	171 ± 123	186 ± 109	0.611
CRP (mg/dL)	0.38 ± 0.41	0.46 ± 0.42	0.72 ± 0.57	0.002
Epicardial fat pad thickness (mm)	4.2 ± 0.8	6.2 ± 0.5	9.3 ± 1.7	<0.001
Systolic BP (mmHg)	146 ± 17	156 ± 13	161 ± 17	<0.001
Diastolic BP (mmHg)	92 ± 11	99 ± 7	99 ± 10	0.007
Mean BP (mmHg)	110 ± 12	118 ± 8	120 ± 11	<0.001
Echocardiography				
Left ventricular parameters				
Ejection fraction (%)	65 ± 4	65 ± 3	64 ± 5	0.068
LVEDD (mm)	45 ± 9	46 ± 4	47 ± 4	0.380
LVESD (mm)	28 ± 4	29 ± 6	30 ± 5	0.299
IVSD (mm)	11.5 ± 1.3	12.0 ± 1.8	13.4 ± 2.1	<0.001
PWD (mm)	10.6 ± 1.3	11.3 ± 1.4	12.3 ± 1.6	<0.001
LV mass (g)	211 ± 69	234 ± 59	279 ± 82	<0.001
Doppler echocardiography				
Mitral E velocity (cm/s)	71 ± 16	70 ± 18	63 ± 16	0.064
Mitral A velocity (cm/s)	73 ± 16	80 ± 18	87 ± 16	0.002
E/A ratio	1.02 ± 0.34	0.91 ± 0.31	0.74 ± 0.20	<0.001
DT (ms)	208 ± 32	230 ± 58	232 ± 38	0.061
IVRT (ms)	82 ± 13	92 ± 18	100 ± 19	0.001
IVCT (ms)	34 ± 25	29 ± 40	48 ± 22	0.022
LVET (ms)	271 ± 23	264 ± 30	269 ± 28	0.537
MPI	0.42 ± 0.11	0.48 ± 0.19	0.55 ± 0.14	0.004
Left atrial parameters				
LA diameter (mm)	34.7 ± 3.3	36.3 ± 4.4	39.1 ± 3.4	<0.001
LA volume				
Maximum	53 ± 12	58 ± 16	67 ± 17	0.001
Minimum	21 ± 6	26 ± 10	31 ± 11	0.011
Tissue Doppler parameters				
Sm: lateral/septal	9.3 ± 1.9/7.9 ± 1.1	10.0 ± 2.6/7.9 ± 1.5	8.7 ± 1.7/7.1 ± 1.4	0.015/0.020
Em (cm/s): lateral/septal	10.6 ± 2.6/8.1 ± 2.4	9.8 ± 2.9/6.6 ± 1.8	8.6 ± 2.6/6.1 ± 1.4	0.005/<0.001
Am (cm/s): lateral/septal	10.1 ± 2.6/9.8 ± 2.3	11.1 ± 3.0/10.0 ± 2.2	10.5 ± 2.8/9.9 ± 2.1	0.375/0.941
Em/Am ratio: lateral/septal	1.1 ± 0.5/0.9 ± 0.4	1.0 ± 0.4/0.7 ± 0.2	0.9 ± 0.4/0.6 ± 0.2	0.032/0.001
E/Em ratio: lateral/septal	6.8 ± 1.7/9.2 ± 2.7	7.6 ± 2.6/11.0 ± 2.7	8.0 ± 2.5/10.7 ± 2.9	0.162/0.044

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; BP, blood pressure; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVSD, interventricular septal diameter; PWD, posterior wall diameter; A, atrial (late) peak mitral velocity obtained from pulsed Doppler; Am, late diastolic mitral annular velocity obtained from tissue Doppler; E, early peak mitral velocity obtained from pulsed Doppler; Em, early diastolic mitral annular velocity obtained from tissue Doppler; ET, ejection time; DT, deceleration time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle; MPI, myocardial performance index; LA, left atrium.

EAT significantly correlated to left atrial dimension, diastolic dysfunction parameters, and left ventricular mass (LV mass) as well as age and BP measurements (Tables 2 and 3). EAT also correlated to Framingham risk score ($p < 0.001$). Age and EAT were significantly increased in patients with high degrees of diastolic dysfunction group compared to the low group ($p < 0.001$ and $p = 0.001$, respectively) (Table 4). Linear regression analyses revealed EAT as an independent predictor of all diastolic dysfunction parameters (Table 5).

The area under the curve values of EAT were similar to age and higher than those of LV mass and mean BP for both the presence of diastolic dysfunction and grade two diastolic dysfunction (Table 6).

Discussion

We have revealed that echocardiographically measured EAT related significantly to left ventricular diastolic dysfunction and increased left atrial volume, independent of blood pressure, LV mass, and other risk factors, in a group of patients with essential hypertension and normal left ventricular systolic function without preexisting diabetes mellitus and CAD. To the best of our knowledge, this is the first study documenting this association.

The echocardiographic measurement of EAT, an objective, noninvasive, readily available, and certainly less expensive measure of visceral fat than MRI or CT, offers a more sensitive and specific index of true visceral fat content by avoiding the possible confounding effect of subcutaneous abdominal fat [16].

The embryological source of EAT is similar to abdominal visceral adiposity [17]. Fat is accumulated in different localizations around the heart. Pericardial fat is located between the visceral and parietal layers of pericardium whereas epicardial fat is between myocardium and visceral layer of pericardium [7]. EAT is a special fat depot which is related to visceral fat rather than total adiposity and shares the same microcirculation with myocardial tissue [17]. EAT is located mainly in periaortic, atrioventricular, and interventricular sulcus along with main coronary arteries. Coronary arteries are embedded within EAT and have the same metabolic milieu. This adipose tissue envelops tunica intima, media, and adventitia as tunica adiposa through the entire length of coronary arteries and all vasculature [18,19].

EAT is a stronger predictor of CAD than visceral adipose tissues located in other parts of the body [20–22]. Moreover, increased EAT was associated with poor coronary flow reserve even in patients with angiographically normal coronary arteries [23,24]. In a recent study, Mahfouz et al. demonstrated a strong relationship between impaired endothelial coronary flow reserve and left ventricular diastolic dysfunction [25]. Moreover, Sasaki and coworkers reported a positive association between coronary blood flow and isovolumic

Table 2
Correlations of EAT with Framingham risk score, demographic, metabolic, and echocardiographic study parameters.

Variables	Epicardial fat pad thickness (mm)
Age (years)	$r = 0.296$, $p = 0.001$
BMI (kg/m^2)	$r = 0.467$, $p < 0.001$
Waist circumference (cm)	$r = 0.582$, $p < 0.001$
Mean BP (mmHg)	$r = 0.374$, $p < 0.001$
Systolic BP (mmHg)	$r = 0.372$, $p < 0.001$
Diastolic BP (mmHg)	$r = 0.256$, $p = 0.009$
Metabolic syndrome parameters	
CRP (mg/dL)	$r = 0.435$, $p < 0.001$
Glucose (mg/dL)	$r = 0.216$, $p = 0.021$
Creatinine (mg/dL)	$r = 0.045$, $p = 0.636$
Uric acid (mg/dL)	$r = 0.259$, $p = 0.008$
LDL (mg/dL)	$r = 0.236$, $p = 0.003$
HDL (mg/dL)	$r = -0.157$, $p = 0.108$
Triglyceride (mg/dL)	$r = 0.156$, $p = 0.053$
Echocardiography	
LA diameter (mm)	$r = 0.500$, $p < 0.001$
LV mass (g)	$r = 0.519$, $p < 0.001$
Framingham risk score	$r = 0.414$, $p < 0.001$

BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LA, left atrium; LV, left ventricle; EAT, epicardial adipose tissue.

Table 4
The relationship of EAT and other study parameters with degree of diastolic dysfunction.

Parameters	Diastolic dysfunction grade[a]			p-Value
	Normal	Grade I	Grade II	
Age (years)	41 ± 8	50 ± 8	52 ± 8	<0.001
BMI (kg/m^2)	30 ± 4	32 ± 5	32 ± 4	0.118
Waist circumference (cm)	100 ± 10	106 ± 11	106 ± 10	0.136
EAT (mm)	5.4 ± 1.8	7.2 ± 2.4	7.7 ± 2.3	0.001
LV mass (g)	213 ± 64	253 ± 79	249 ± 63	0.108
CRP (mg/dL)	0.36 ± 0.20	0.65 ± 0.54	0.62 ± 0.62	0.208
Mean BP (mmHg)	116 ± 12	114 ± 14	118 ± 9	0.276

BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; LV, left ventricle; EAT, epicardial adipose tissue.

[a] Diastolic function was graded using echocardiographic Doppler variables designated as normal, grade I (impaired relaxation pattern), grade II (pseudo-normal pattern).

Table 3
Correlations of diastolic function parameters and LA with EAT and other study parameters.

Variables	E/A ratio	IVRT	MPI	DT	LA
Age (years)	$r = -0.466$, $p < 0.001$	$r = 0.219$, $p = 0.028$	$r = 0.009$, $p = 0.926$	$r = 0.382$, $p < 0.001$	$r = 0.158$, $p = 0.083$
BMI (kg/m^2)	$r = -0.153$, $p = 0.102$	$r = 0.112$, $p = 0.269$	$r = 0.134$, $p = 0.172$	$r = -0.042$, $p = 0.652$	$r = 0.270$, $p = 0.003$
Waist circumference (cm)	$r = -0.287$, $p = 0.004$	$r = 0.228$, $p = 0.037$	$r = 0.244$, $p = 0.020$	$r = 0.137$, $p = 0.180$	$r = 0.391$, $p < 0.001$
Epicardial fat pad thickness (mm)	$r = -0.430$, $p < 0.001$	$r = 0.418$, $p < 0.001$	$r = 0.401$, $p < 0.001$	$r = 0.291$, $p = 0.001$	$r = 0.500$, $p < 0.001$
LV mass (g)	$r = -0.302$, $p = 0.001$	$r = 0.389$, $p < 0.001$	$r = 0.266$, $p = 0.006$	$r = 0.224$, $p = 0.015$	$r = 0.641$, $p < 0.001$
CRP (mg/dL)	$r = -0.297$, $p = 0.003$	$r = 0.076$, $p = 0.491$	$r = 0.158$, $p = 0.132$	$r = 0.080$, $p = 0.432$	$r = 0.076$, $p = 0.446$
Systolic BP (mmHg)	$r = -0.172$, $p = 0.073$	$r = -0.021$, $p = 0.844$	$r = -0.036$, $p = 0.719$	$r = 0.027$, $p = 0.779$	$r = 0.273$, $p = 0.003$
Diastolic BP (mmHg)	$r = -0.137$, $p = 0.153$	$r = 0.176$, $p = 0.090$	$r = 0.124$, $p = 0.215$	$r = 0.119$, $p = 0.216$	$r = 0.269$, $p = 0.004$
Mean BP (mmHg)	$r = -0.160$, $p = 0.095$	$r = 0.086$, $p = 0.409$	$r = 0.037$, $p = 0.714$	$r = 0.083$, $p = 0.389$	$r = 0.303$, $p = 0.001$
Framingham risk score	$r = -0.473$, $p < 0.001$	$r = 0.342$, $p = 0.001$	$r = 0.070$, $p = 0.504$	$r = 0.483$, $p < 0.001$	$r = 0.404$, $p < 0.001$
Metabolic parameters					
Glucose (mg/dL)	$r = -0.158$, $p = 0.099$	$r = 0.056$, $p = 0.592$	$r = 0.125$, $p = 0.214$	$r = 0.218$, $p = 0.022$	$r = 0.105$, $p = 0.270$
Creatinine (mg/dL)	$r = -0.131$, $p = 0.171$	$r = 0.129$, $p = 0.216$	$r = 0.157$, $p = 0.118$	$r = 0.209$, $p = 0.028$	$r = 0.108$, $p = 0.255$
Uric acid (mg/dL)	$r = -0.018$, $p = 0.854$	$r = 0.073$, $p = 0.486$	$r = 0.171$, $p = 0.092$	$r = 0.023$, $p = 0.810$	$r = 0.126$, $p = 0.189$
HDL (mg/dL)	$r = 0.007$, $p = 0.944$	$r = -0.194$, $p = 0.064$	$r = -0.123$, $p = 0.227$	$r = -0.113$, $p = 0.242$	$r = -0.250$, $p = 0.008$
LDL (mg/dL)	$r = -0.313$, $p = 0.001$	$r = -0.063$, $p = 0.555$	$r = 0.035$, $p = 0.735$	$r = 0.179$, $p = 0.066$	$r = -0.129$, $p = 0.180$
Triglyceride (mg/dL)	$r = -0.045$, $p = 0.668$	$r = 0.082$, $p = 0.467$	$r = 0.208$, $p = 0.056$	$r = 0.034$, $p = 0.750$	$r = 0.138$, $p = 0.181$

BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LA, left atrium; LV, left ventricle; EAT, epicardial adipose tissue; IVRT, isovolumic relaxation time; MPI, myocardial performance index; DT, deceleration time.

Table 5
Linear regression analyses were used for prediction of E/A ratio, IVRT, MPI and LA diameter.

Dependent variables Independent variables	E/A ratio Beta, *p* value	IVRT Beta, *p* value	MPI Beta, *p* value	LA Beta, *p* value
Age (years)	β: −0.362, $p < 0.001$	–	β: −0.195, $p = 0.058$	–
Epicardial fat pad thickness (mm)	β: −0.332, $p < 0.001$	β: 0.247, $p = 0.045$	β: 0.404, $p < 0.001$	β: 0.195, $p = 0.023$
LV mass (g)	–	β: 0.286, $p = 0.021$	–	β: 0.527, $p < 0.001$
CRP (mg/dL)	β: −0.169, $p = 0.051$	–	–	–
Mean BP (mmHg)	–	–	–	–

BMI, body mass index; CRP, C-reactive protein; EAT, epicardial adipose tissue; BP, blood pressure; CRP, C-reactive protein; LA, left atrium; LV, left ventricle; IVRT, isovolumic relaxation time; MPI, myocardial performance index.

Table 6
Receiver-operating characteristic curves for the sensitivity and the specificity of age, EAT, LV mass, and mean blood pressure to detect the presence of DD and grade 2 DD.

Parameters	AUC	SE	*p*	95% CI
Presence of DD				
Age	0.838	0.052	0.000	0.736–0.940
EAT	0.749	0.066	0.001	0.621–0.878
LV mass	0.647	0.076	0.058	0.497–0.796
Mean BP	0.515	0.076	0.842	0.366–0.665
Presence of grade 2 DD				
Age	0.678	0.054	0.002	0.573–0.784
EAT	0.630	0.057	0.026	0.519–0.741
LV mass	0.586	0.058	0.139	0.473–0.700
Mean BP	0.580	0.058	0.168	0.468–0.693

AUC, area under the curve; SE, standard error; CI, confidence interval; DD, diastolic dysfunction; BP, blood pressure; LV, left ventricle; EAT, epicardial adipose tissue; IVRT, isovolumic relaxation time; MPI, myocardial performance index; DT, deceleration time; DD, diastolic dysfunction.

relaxation time [26]. In this report, myocardial ischemia was closely related to left ventricular systolic and diastolic dysfunction in patients with hypertension. Therefore, we may speculate that increased EAT may deteriorate diastolic function by decreasing coronary flow reserve due to secreted mediators which may affect myocardial tissue and coronary arteries either by endocrine effect or by direct diffusion via vasa vasorum or by passive perivascular compressive and thermogenic effects even before clinically evident ischemia. In our study, since we found a moderate independent correlation between EAT and diastolic dysfunction parameters, we think that EAT may be a contributor rather than an absolute cause.

EAT is a source of several pro-inflammatory and pro-atherogenic cytokines [27–29]. Our results showed a positive correlation between CRP levels and EAT. Previous studies demonstrated hypertension-like changes in myocardial tissue cultures with interleukin 6 (IL-6) and transforming growth factor-β, cytokines secreted from EAT [30,31]. Additionally, mediators secreted from EAT may influence collagen metabolism negatively by stimulating local inflammation [32]. We think that EAT may enhance myocardial hypertrophy, myocardial fibrosis, and perivascular fibrosis. Although our study was not designed to investigate this issue, autopsy and echocardiographic findings in previous studies demonstrated a strong association between EAT and left ventricular hypertrophy [33,34]. Our analyses also showed a significant elevation in thicknesses of interventricular septum and posterior wall with increasing EAT, thus supporting our theory.

Moreover, recent studies also documented that EAT is also associated with diastolic dysfunction, non-dipper status, increased left atrial size and lower ejection fraction, arterial stiffness, higher coronary calcium score, and reduced regional systolic motion in various populations. Pathological changes within myocardium and perivascular area may cause diastolic dysfunction due to either impaired coronary flow reserve or myocardial stiffness [35–37].

We also revealed a significant association between EAT and left atrial volumes. The left atrium has a central role that involves collecting blood during systole and augmenting left ventricular filling during diastole [38]. Left ventricular diastolic dysfunction may lead to left atrial pressure overload, which, if chronically maintained, may end in left atrial remodeling and enlargement [39]. Left atrial diameter is independently associated with all-cause mortality and ischemic stroke [40]. Since we excluded patients with moderate-severe valvular disease, diastolic dysfunction is likely to be the cause of left atrial enlargement that appears in association with increased EAT [41].

Nelson et al. demonstrated a positive correlation between EAT and Framingham risk score. They also revealed higher carotid plaque burden in patients with EAT thickness >5.0 mm, compared to patients with EAT thickness <5.0 mm [42]. We also investigated this relationship between EAT and Framingham risk score and confirmed it in our study. We also found similar correlations to left atrial diameter and diastolic dysfunction parameters. We believe that EAT is not only a marker but also a factor for metabolic and structural changes in myocardium and human body. Although EAT may not be the sole cause of diastolic dysfunction, it may be an important contributor to it.

Study limitations

Our study has several limitations. Currently, MRI and non-contrast cardiac CT [43] are the gold standard diagnostic methods for assessing epicardial fat. By measuring epicardial fat thickness and volumes, these methods provide more accurate assessment. Although epicardial fat is readily visualized with high-speed CT and MRI, widespread use of these methods for assessment of EAT is not practical. Echocardiography provides an objective, noninvasive, readily available method and is certainly less expensive than MRI or CT for measuring epicardial fat.

The relatively low number in the study population may be a limitation for interpretation of our results. We implemented specific patient criteria to avoid potential confounders. In addition, we specifically included untreated hypertensive patients in the early stage of HT rather than patients with long-standing HT. This and the low sample size of the current study might have resulted in low correlations among study parameters.

Another limitation is that our study had a cross-sectional longitudinal study design and a cohort study might provide information for causality. The measurement of EAT and diastolic function parameters by echocardiography may be a limitation because it can facilitate an unconscious bias. To overcome this limitation, two different sonographers blinded for the study details performed measurements of EAT and extensive diastolic parameters separately.

Currently there is no gold standard method for determining diastolic dysfunction. Therefore, we evaluated several diastolic parameters with extensive echocardiography parameters.

Conclusion

In conclusion, an increased EAT thickness related to diastolic dysfunction and left atrial enlargement in patients with essential HT. Based on our findings, increased EAT may be associated with diastolic dysfunction and left atrial dilatation due to local or systemic effects in untreated hypertensive patients. This relationship is independent of and stronger than abdominal obesity, implicating the clinical importance of measuring EAT thickness. Although there is currently no treatment option for lowering EAT thickness, patients with thinner EAT seem to have a lower risk of diastolic dysfunction and a better prognosis.

Conflict of interest

All authors of this study have no conflict of interest regarding this paper.

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