ORIGINAL ARTICLE

Increased Epicardial Adipose Tissue is Associated with the Extent of Aortic Dissection

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Abstract

Background: **Epicardial adipose tissue (EAT) is a biologically active organ that has endocrine and paracrine functions. Endothelial dysfunction, systemic, and local inflammatory response, due to bio-active molecules produced by EAT, may affect aortic dissection propagation and extent. We investigated the association between EAT thickness and the extent of aortic dissection.**

Methods: **We retrospectively enrolled 78 patients with aortic dissection diagnosed by thoracoabdominal Computerized Tomography (CT). EAT was measured from the thickest part of the perpendicular plane between the pericardium and free wall of the right ventricle using CT. Aortic dissection length was measured from the beginning to the end of the dissection flap at sagittal images.**

Results: **We included 78 patients with the mean age of 63.9 ± 11.7 and 57 (73.5%) patients were male. Dissection length was correlated positively with EAT ($r = 0.409$, $p < 0.001$), body mass index ($r = 0.408$, $p = 0.018$), and admission systolic blood pressure ($r = 0.830$, $p = 0.026$) whereas an inverse correlation existed between age and dissection length ($r = -0.318$, $p = 0.005$). Multivariate analysis identified age and EAT as independent predictors of dissection length.**

Conclusion: **Increased EAT was independently associated with the extent of aortic dissection. We think that either paracrine and endocrine functions of EAT might have contributed to the extent of aortic dissection.**

Keywords: Epicardial adipose tissue (EAT), Aortic dissection, Hypertension

Introduction

Aortic dissection is a life-threatening condition with a mortality rate of 1 to 2% per hour after onset of symptoms in untreated patients. Due to the separation of aortic media into two layers, aortic dissection requires surgery urgently.[1,2] Dissection may propagate along the entire aortic tree due to high pressure within the vessel wall, and inside the false-lumen.[3]

The histopathology of aortic aneurysm and dissection involves loss of small muscle cells and elastin fibers resulting in medial degeneration, and aortic wall softening.[4,5] High aortic wall tension due to acute or chronic pressure load enhances aneurysm formation and the extent of dissection.[2] The severity of the aortic wall degeneration may be associated with the propagation of aortic dissection. The direct and indirect factors related with aortic medial degeneration remain a subject of research.[5]

Epicardial adipose tissue (EAT) is an adipose layer located between myocardium and visceral pericardium that nearly covers the entire heart. Although the gold standard quantification method of EAT is magnetic resonance imaging, it may also be measured by transthoracic echocardiography and computerized tomography (CT).[6] EAT is not an inert

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structure but is a highly active endocrine organ with anabolic and erosive activities through secretion of adipokines, fibrocytes, growth factors, and cytokines. The endocrine activity of EAT may result in both systemic and local inflammatory response, and endothelial dysfunction.[7]

We hypothesized that increased EAT thickness may indirectly facilitate aortic medial degeneration, dissection propagation, and induce more extensive aortic dissection. We aimed to investigate the association between EAT thickness with the extent of aortic dissection by measuring the dissection length.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CRP	C-reactive protein
CT	Computerized Tomography
EAT	Epicardial adipose tissue
ED	Endothelial dysfunction
HT	Hypertension

Methods

Study Population

In this retrospective cohort study, we included 78 patients with aortic dissection, who were diagnosed at the emergency department clinic of our hospital between January 2010 and August 2018.

All patients who were admitted to the emergency department with chest pain radiating to shoulder, back, or arms, patients with back pain, or patients complaining of an abrupt onset severe tearing chest pain underwent transthoracic echocardiography. Regardless of flap presence by echocardiography, contrast enhanced thoracoabdominal CT was performed to diagnose aortic dissection in the event of suspicious complaints and/or pulse asymmetry at physical examination. An informed consent form was taken from all patients before CT.

The detailed past medical history and medication of patients were acquired using hospital and electronic medical records. Patients with unavailable CT or medical records, left ventricular dysfunction, connective tissue disease, moderate-severe valvular disease, obstructive sleep apnea syndrome, chronic liver or renal failure, and patients with malignancy were excluded from the study. Patients who previously had aortic dissection or operation for any other aortic diseases were excluded from the study.

Demographic variables

The baseline characteristics of the patients were recorded. Hypertension (HT) was defined as the documentation of blood pressure more than 140/90 mmHg or use of antihypertensive medication. Diabetes mellitus (DM) was described as fasting blood glucose levels above 126 mg/dL or individuals on antidiabetic therapy or blood glucose level above 200 mg/dL at any time. Hypercholesterolemia was acknowledged as the presence of either low-density lipoprotein (LDL) cholesterol level over 159 mg/dL or total cholesterol level over 199 mg/dL or individuals on antihyperlipidemic therapy. Individuals who were still smoking and former smokers who quitted smoking within 3 months were considered as current smokers. Body mass index (BMI) was calculated by the following formula: BMI = weight (kg)/height 2 (m). The missing data were obtained by contacting the patients by telephone. Laboratory data including complete blood count, total and direct bilirubin, C-reactive protein (CRP), serum glucose, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were obtained in all patients.

Computerized Tomography

Thoracoabdominal CT acquisitions were performed using non-ionic contrast medium by Alexion 16 detector CT (Toshiba Medical Systems, Japan) machine in the supine position from lung apex to pubic symphysis during breath-holding following deep inspiration [Omnipaque (iohexol) 300 mg/ml, GE Healthcare, Cork, Ireland], using the parameters of 120 kV, 125 mA, 16 × 1.5 mm collimation and 3 mm thickness, and 512 × 512 matrix. A specialized cardiovascular radiologist assessed axial views at the mediastinal window (70 HU, 500 HU). The images were transferred to a workstation to measure epicardial adipose tissue thickness, abdominal circumference, and dissection length.

EAT thickness was measured at axial plane perpendicularly from the pericardium to right ventricular free wall, at the thickest region (Fig. 1). Abdominal circumference was calculated at the umbilical plane using axial images by following skin lines with curved linear measurement technique (Fig. 2).

Following detection of the initial and the end of aortic dissection at axial and coronal planes, dissection length was measured at maximum intensity projection sagittal images using the curved linear measurement technique from the initial part to the end of the dissection (Fig. 3).

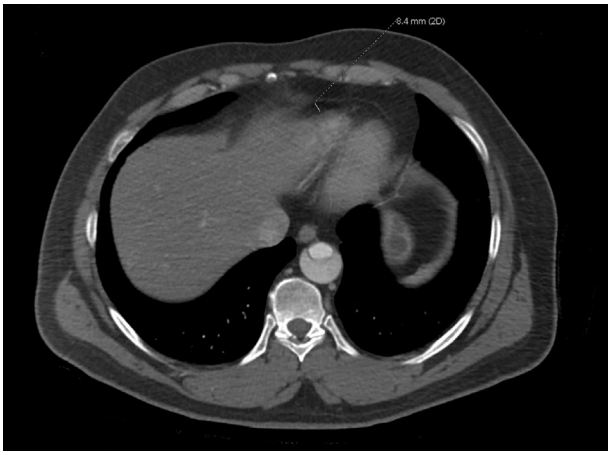

Fig. 1. Measurement of EAT. Epicardial adipose tissue thickness was measured at axial plane perpendicularly from the pericardium to right ventricular free wall, at the thickest region.

Statistical Analysis

The Statistical Package for the Social Sciences 21.0 statistical software program (SSPS Inc, Chicago, Illinois) was used for the statistical analysis. Kolmogorov Smirnov test was used to check normality of continuous variables. Continuous variables were expressed as the mean ± standard deviation. Categorical variables are presented as percentages. Pearson and Spearmen correlation analysis were used where appropriate. Linear and logistic regression analyses were 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 $p < 0.05$.

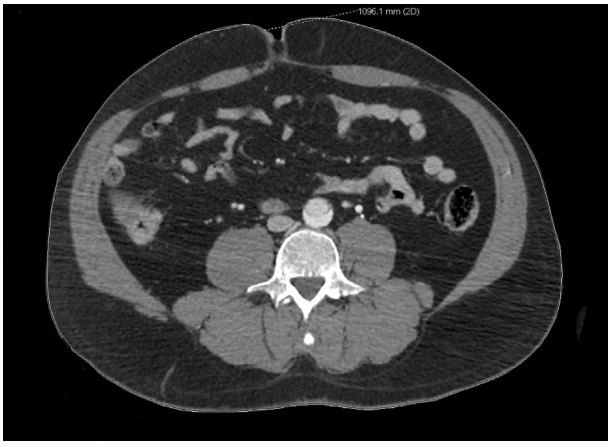

Fig. 2. Abdominal circumference was calculated at umbilical plane using axial images, following skin lines with curved linear measurement technique.

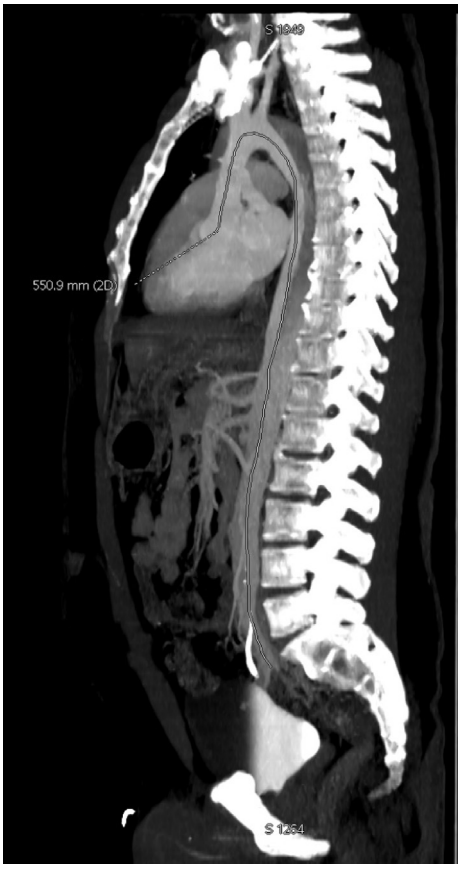

Fig. 3. Dissection length was measured at maximum intensity projection sagittal images using curved linear measurement from the beginning to the end of dissection.

Results

Baseline Characteristics

Our study included 78 patients with a mean age of 63.9 ± 11.7. The majority (73.5%) of our patients were male. The mean dissection length was 40.9 ± 18.2. Mean BMI was 29.31 ± 4.29, mean EAT was 8.5 ± 0.87 mm, and mean admission systolic blood pressure was 156.2 ± 41.2 mmHg.

We stratified our patients according to De Bakey classification: 35 patients (44.8%) had type 1, 12 patients (15.3%) had type 2, and 31 patients (39.7%) had type 3 aortic dissection. Type 1 dissection was more common and had longer dissection length than types 2 and 3 statistically ($r = -0.304$, $p = 0.007$). Meanwhile by Stanford classification, 47 patients (60.3%) had type A and 31 patients (39.7%) had type B. Dissection length was numerically longer in type A classification than type B, which did not reach statistical significance ($r = -0.054$, $p = 0.642$).

Our patients were predominantly hypertensive (79.4%), however, the prevalence of DM, hyperlipidemia, and coronary artery disease was low. Only 39.7% of patients were active smokers. Serum CRP ($p = 0.818$), white blood cell count ($p = 0.111$), neutrophil count ($p = 0.187$), and lymphocyte count ($p = 0.619$) were not related with dissection length suggesting aortic dissection was not related with an acute inflammatory process. The remaining patient characteristics are detailed in Table 1.

Correlation analysis

Dissection length correlated positively with EAT ($r = 0.409$, $p < 0.001$) (Table 2), BMI ($r = 0.408$, $p = 0.018$), and admission systolic blood pressure ($r = 0.830$, $p = 0.026$), whereas a negative correlation existed between age and dissection length ($r = -0.318$, $p = 0.005$). Unlike admission systolic BP, admission diastolic BP ($p = 0.445$) and the abdominal circumference ($p = 0.151$) was not related with EAT.

Table 1. Basic characteristics of patients.

Variable	n = 78
Age (years)	63.9 ± 11.7
Gender (male) (%)	73.5
Hypertension (%)	79.4
Diabetes Mellitus (%)	11.5
Hyperlipidemia (%)	27.3
Smoking (%)	39.7
CAD (%)	6.4
Abdominal Circumference (cm)	101.5 ± 11.4
EAT (mm)	8.5 ± 0.87
Height (cm)	171.2 ± 4.9
Weight (kg)	85.1 ± 12.3
BMI (kg/m^2)	29.31 ± 4.29
Admission Pulse Count	93.11 ± 21.5
Admission Systolic BP (mmHg)	156.2 ± 41.2
Admission Diastolic BP (mmHg)	81.4 ± 22.3
Admission Glucose (mg/dL)	143.1 ± 73
Serum creatinine (mg/dL)	1.06 ± 0.41
CRP (mg/dL)	3.25 ± 4.32
WBC ($10^3/\mu L$)	10.9 ± 4.4
Neutrophil ($10^3/\mu L$)	7.7 ± 4.1
Lymphocyte ($10^3/\mu L$)	2.29 ± 1.2
Hemoglobin (gr/dL)	13.1 ± 1.7
DeBakey Class	
Tip I	35 (44.8)
Tip II	12 (15.4)
Tip III	31 (39.7)
Stanford Class	
Tip A	47 (60.3)
Tip B	31 (39.8)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CRP: c-reactive protein, EAT: epicardial adipose tissue, MPV: mean platelet volume, WBC: white blood cell.

Table 2. Correlations of study parameters with dissection length.

Variable	r	p (0.05)
Age (years)	−0.318	0.005
Gender (male) (%)	−0.023	0.841
Hypertension (%)	0.070	0.571
Diabetes Mellitus (%)	0.041	0.725
Hyperlipidemia (%)	−0.110	0.373
Smoking (%)	0.042	0.735
CAD (%)	0.061	0.599
Abdominal Circumference (cm)	0.164	0.151
EAT (mm)	**0.409**	**<0.001**
Height (cm)	0.075	0.679
Weight (kg)	**0.278**	**0.023**
BMI (kg/m^2)	**0.408**	**0.018**
Admission pulse count	−0.133	0.281
Admission Systolic BP (mmHg)	**0.830**	**0.026**
Admission Diastolic BP **(mmHg)**	−0.094	0.445
Admission Glucose (mg/dL)	−0.028	0.809
Serum creatinine (mg/dL)	0.170	0.141
CRP (mg/dL)	0.033	0.818
WBC ($10^3/\mu L$)	0.183	0.111
Neutrophil ($10^3/\mu L$)	0.154	0.187
Lymphocyte ($10^3/\mu L$)	0.058	0.619
Hemoglobin (gr/dL)	0.130	0.266
DeBakey Class.	−0.304	0.007
Stanford Class.	−0.054	0.642

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CRP: c-reactive protein, EAT: epicardial adipose tissue, MPV: mean platelet volume, WBC: white blood cell.

Multivariate analysis

We performed stepwise linear regression analysis using the significant variables in the univariate tests, in order to identify independent predictors for dissection extent. Age [$B = -0.399$, 95% confidence interval (CI) (−0.662)- (−0.017), $p = 0.004$)] and EAT ($B = 7.32$, 95% CI (2.993-11.66), $p = 0.001$) were independent predictors of dissection length (Table 3, Fig. 4).

Discussion

We found that age, admission systolic blood pressure, and EAT thickness were related to aortic dissection length. Moreover, we demonstrated EAT and age as independent predictors of aortic dissection extent. As far as we know, our study is the first to demonstrate the association of EAT with aortic dissection.

Even though the exact pathophysiological mechanism of aortic dissection is not exactly understood, loss of collagen and elastin seems to be very important in pathogenesis. Matrix metalloproteinases originating from inflammatory cells, extracellular matrix (ECM) degeneration and apoptosis of vascular smooth muscle cells (VSMC) also play a major role in the pathogenesis of aortic

Table 3. Stepwise Multivariate Linear Regression analyses to predict dissection length.

Variable	Beta	CI 95%	P Value
Age (years)	−0.339	−0.662-0.017	0.040
EAT (mm)	7.32	2.993-11.66	0.001

EAT; epicardial adipose tissue.

degeneration.[2–5] In addition, the balance shifts from production to destruction of ECM and VSMC with increasing age. We also discovered that age was associated with the extent of aortic dissection as demonstrated in a previous study.[22]

Obesity is closely associated with cardiovascular disease. There is growing evidence that visceral adiposity is more hazardous than total adiposity for cardiovascular risk.[7,8] EAT is the visceral adipose layer positioned between myocardium and visceral pericardium, which nearly surrounds the entire heart. EAT is localized particularly in the periaortic area, and interventricular, and atrioventricular sulcus. Since there is not any membrane between EAT and the neighboring tissues, there is constant interaction between these structures.[7,9] Previous data suggest that perivascular adipose tissue deeply affects vascular structure and hemostasis. These effects are thought to be the result of either paracrine, or the endocrine effect through vasa vasorum.[10]

EAT is a proinflammatory tissue that has high biological activity via the secretion of various agents such as Interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor α.[6] There is enough evidence that EAT is related to coronary artery disease, HT, endothelial dysfunction, diastolic dysfunction, and sympathetic stimulation due to systemic and local effects of these cytokines.[11–14] Moreover, EAT boosts cytokine secretion and macrophage infiltration in the periaortic adipose tissue that causes inflammation at the intima-media zone.[15-16] EAT was also associated with cardiac autonomic dysfunction due to increased free fatty acid, and catecholamine concentrations.[17] EAT may influence the whole aorta by the systemic endocrine function, independent of the region.[7,9] Systemic endocrine effects may occur via transmural inflammation at the intima-media section of descending aorta.[18,19] Ascending aorta, aortic arch, and thoracic aorta have varying smooth muscle cell, collagenous, and fibrous fiber content in their media. EAT may facilitate the propagation of aortic dissection by direct paracrine effect in addition to endocrine action at the intima-media level of ascending aorta and aortic arch. The inflammatory markers such as CRP, white blood cells, neutrophil, and lymphocyte counts were in the normal range and were not related to dissection length. However, we may speculate that active inflammation may not be important in the acute phase of dissection.

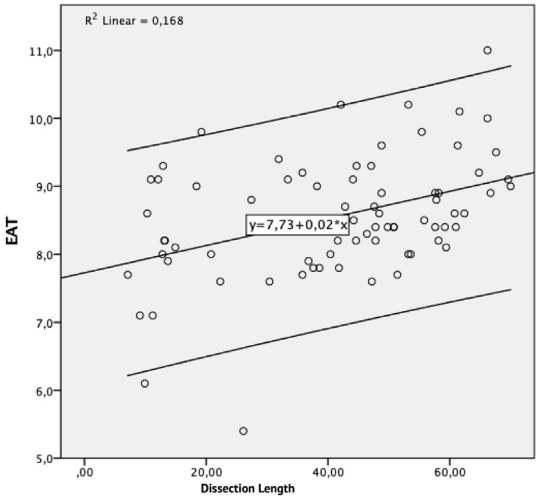

Fig. 4. Correlation plot of EAT and aortic dissection length.

HT is a major risk factor for aortic dissection due to shared etiologic factors including endothelial dysfunction, decreased elasticity of aortic wall, and vascular stiffness. Several studies revealed that EAT was related to hypertension.[20] Moreover, HT facilitates aortic dissection directly by exerting increased mechanical load at the aortic wall.[21] Accordingly, almost 80% of our patients had hypertension. We discovered a strong correlation between admission systolic blood pressure and dissection length in our study. We think that this result is not surprising and concurrent with the medical literature.

Our study has several limitations. First, our study includes a small number of subjects. Moreover, our study was retrospective in design. Since our study is cross-sectional, our results do not implicate causality. Although the epicardial adipose volume is the gold standard, a 16-slice detector CT was used at the emergency department which would not be enough for 3D reconstruction. Therefore we preferred to measure EAT thickness. We do not have data regarding inflammatory cytokines, which could explain the systemic inflammatory effect of EAT.

In conclusion, we documented that increased EAT is independently associated with aortic dissection length. We think that either paracrine or systemic effects of EAT might have caused that result.

Conflicts of interest

None declared.

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This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contribution

Conception and design of Study: Mustafa Cetin, Nadir Emlek. Design: Mustafa Cetin, Ahmet Seyda Yilmaz. Supervision of the research: Nadir Emlek, Mustafa Cetin. Funding for the research: Mustafa Cetin, Savas Ozer. Materials: Ahmet Seyda Yilmaz, Savas Ozer. Data collection: Mustafa Cetin, Nadir Emlek Ahmet Seyda Yilmaz, Savas Ozer. Analysis and interpretation of data: Mustafa Cetin, Hasan Gundogdu. Literature review: Murtaza Emre Durakoglugil, Nadir Emlek. Drafting of manuscript: Ahmet Seyda Yilmaz, Mustafa Cetin, Murtaza Emre Durakoglugil. Revising and editing the manuscript critically for important intellectual contents: Murtaza Emre Durakoglugil, Mustafa Cetin, Nadir Emlek.

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