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Increased Epicardial Adipose Tissue Thickness Is Correlated with Ascending Aortic Diameter

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Epicardial adipose tissue (EAT), localized beneath the visceral pericardium, is a metabolically active endocrine and paracrine organ with possible interactions within the heart. Recent studies identified possible roles of uric acid (UA)-induced oxidative stress and increased inflammatory status in the pathogenesis of ascending aortic dilatation. The aim of this study was to investigate whether EAT is an independent factor for ascending aortic dilatation. The patients were evaluated by a complete transthoracic echocardiographic examination including measurements of EAT and aortic dimensions. Serum levels of UA and C-reactive protein and EAT thicknesses were compared in 38 patients with dilated ascending aorta (DAA) (the diameter ≥ 37 mm) vs. 107 subjects with normal aortic diameter (AD) of < 37 mm. EAT thickness was significantly higher in DAA group compared to normal AD group (8.3 ± 2.7 vs. 5.4 ± 2.2 mm, $p < 0.001$) as well as age (53 ± 10 vs. 48 ± 9 years, $p = 0.004$), the presence of hypertension (54% vs. 30%, $p = 0.009$) and UA levels (6.0 ± 1.4 vs. 5.2 ± 1.1 mg/dL, $p < 0.001$). There was a strong correlation between EAT thickness and ascending aortic diameter ($r = 0.521$, $p < 0.001$). In multiple logistic regression analysis, EAT thickness (OR: 1.429, $p = 0.006$), body mass index (OR: 1.169, $p = 0.014$) and UA levels (OR: 1.727, $p = 0.023$) were independently correlated to ascending aortic dilatation. We therefore propose that increased EAT thickness is an independent predictor of ascending aortic dilation.

Keywords: ascending aortic dilatation; C-reactive protein; epicardial fat pad; epicardial adipose tissue; uric acid
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Visceral adipose tissue, a metabolically active endocrine and paracrine organ, secretes many pro-inflammatory and pro-atherogenic cytokines (Mazurek et al. 2003). Epicardial adipose tissue (EAT), localized beneath the visceral pericardium, is a special type of visceral fat depot, which is more closely related to visceral fat rather than total body fat (Marchington et al. 1989).

The physiological, biochemical, and biomolecular properties of epicardial adipose tissue and the possible paracrine interactions within the heart have been described in previous studies (Taguchi et al. 2001; Iacobellis et al. 2005a). EAT exists, mainly in the atrioventricular and interventricular groove along the major coronary arteries and branches, to a lesser extent in the atrium, right ventricle and the left ventricular free wall, and shows extension to the apex (Sacks and Fain 2007). The embryological origin of EAT is similar to intra-abdominal visceral adipose tissue (Marchington et al. 1989).

Previous studies indicated EAT as a stronger risk factor for coronary artery disease (CAD) than adipose tissues located in other parts of the body and EAT may have an important role in the development of CAD (Taguchi et al. 2001; Gorter et al. 2008; Rosito et al. 2008).

The pathogenesis of ascending aortic aneurysm (AscAA) involves several factors with locally or systemic effects. Alterations of the extracellular matrix are considered as a key element in the pathogenesis of aortic disease. EAT may have a causative role for ascending aortic dilation either with an active local paracrine role and passive thermogenic effect in this process or systemic endocrine effects on vasculature.

Recent studies identified possible roles of uric acid (UA) induced oxidative stress and increased inflammatory status in the pathogenesis of AscAA (Medina et al. 2010; Sen et al. 2009; Esen et al. 2011; Vlachopoulos et al. 2011). We hypothesized that cardiac adipose tissue may be involved in ascending aortic dilatation due to local or systemic effects. Therefore, in this study, we aimed to investigate whether EAT, serum UA and C-reactive protein (CRP) levels are independently related to ascending aortic dilatation.

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Methods

Patient population and Study Protocol

The present study was cross-sectional and observational, including 145 patients who underwent a complete transthoracic echocardiographic examination as well as measurements of EAT and aortic dimensions. Ascending aortic dilatation was defined as maximum diameter ≥ 37 mm. 38 patients with dilated ascending aorta (DAA group) were compared to 107 subjects with normal aortic diameter (Normal AD group; < 37 mm).

Exclusion criteria were concomitant CAD, bicuspid aortic valve, rheumatic aortic valve disease, Marfan syndrome, Ehlers-Danlos syndrome and other connective tissue disorders, infectious and inflammatory conditions. To limit possible effects of confounding factors and to form a uniform subgroup, the patients with AscAA having an aortic dilatation ≥ 45 mm were also excluded from study.

Baseline characteristics of the patient were recorded. Hypertension (HT) was defined as the active use of antihypertensive drugs or documentation of blood pressure more than 140/90 mmHg. Diabetes mellitus was defined as fasting plasma glucose levels over 126 mg/dl or glucose level over 200 mg/dl at any measurement or active use antidiabetic treatment. Patients who were using tobacco products on admission and those quitted smoking within the last year were considered as smokers. The family history for CAD was defined as a history of CAD or sudden death in a first-degree relative before the age of 55 years in men and 65 years in women.

The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the Ethics Committee of Rize University, Faculty of Medicine.

Routine measurements

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least 8 hours. 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 CRP was analyzed using a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range 0-0.8 mg/dL).

Serum uric acid levels were evaluated using enzymatic colorimetric method (the uricase-peroxidase method) by clinical chemistry auto-analyzer (Aeroset, Abbott Laboratory, Abbott Park, IL, USA). Body mass index (BMI) was determined by the following formula: BMI = weight (kg)/height^2 (m). The estimated glomerular filtration rate was calculated by Cockcroft-Gault formula: (140 − age) × (weight, in kg) × (0.85 *if female*)/72 × serum creatinine (in mg/dL).

Echocardiography

All patients underwent complete transthoracic examination including two dimensional, color flow and pulsed doppler, tissue doppler imaging as well as epicardial fat thickness measurement with a GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5-3.5 MHz transducer. All examinations were performed by an experienced cardiologist, unaware of patient's clinical information. The intra-observer correlation coefficient was 0.96.

Evaluation of epicardial fat pad: Epicardial fat thickness 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 of above the right ventricle to measure EAT thickness, because this area is known to have the thickest EAT layer. Epicardial fat thickness, identified as an echo-free space between the pericardial layers on 2-dimensional echocardiography, was measured perpendicularly in front of the right ventricular free wall at end-diastole (Iacobellis et al. 2003a, 2003b). We magnified each still image for better visualization and accurate measurement 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.

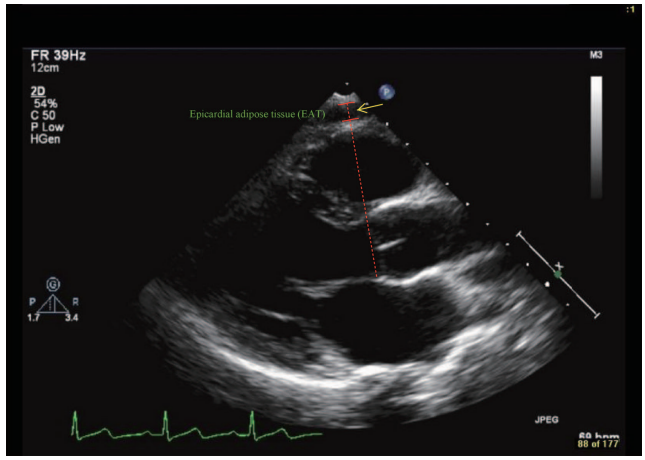

Fig. 1. The measurement of epicardial fat thickness by echocardiography.
EAT was evaluated on the free wall of right ventricle from the parasternal long-axis view, using aortic annulus as an anatomic reference. EAT, identified as an echo-free space between the pericardial layers on 2-dimensional echocardiography, was measured perpendicularly, ahead of the right ventricular free wall, at the end of diastole, for three cardiac cycles.

Measurement of ascending aortic diameter: Parasternal long-axis view was used to visualize the aortic root and proximal ascending aorta. The aortic diameter was measured between the inner edges of the aortic lumen perpendicular to the long axis 2 cm above the sinotubular junction at end-diastole in views showing the largest aortic diameters.

Statistical analysis

Continuous variables were given as mean ± S.D.; 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 univariate analysis of the categorical variables. All tests of significance were two-tailed. Mean values were compared by ANOVA followed by the Tukey honestly significant difference test among different groups. Logistic and linear regression with Enter method was used for multivariate analysis. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (SPSS for windows, version 15.0, Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

The clinical characteristics of the study population are detailed in Table 1. EAT thickness was significantly higher (8.3 ± 2.7 vs. 5.4 ± 2.2 mm, $p < 0.001$) as well as age (53 ± 10 vs. 48 ± 9 yrs., $p = 0.004$), the presence of HT (54% vs. 30%, $p = 0.009$) and UA levels (6.0 ± 1.4 vs. 5.2 ± 1.1 mg/dl, $p < 0.001$) in DAA group compared to normal AD group. Ascending aortic diameter ($p < 0.001$), CRP ($p = 0.003$), body mass index (BMI, $p < 0.001$), waist circumference ($p < 0.001$) and age ($p = 0.003$) were significantly elevated in patients with an increased EAT thickness (Table 2). There was a strong correlation between EAT thickness and ascending aortic diameter ($r = 0.521$, $p < 0.001$) (Fig. 2). In addition, EAT correlated to CRP ($r = 0.294$, $p = 0.001$) and UA ($r = 0.257$, $p = 0.002$) levels. Ascending aortic diameter was associated with CRP ($r = 0.208$, $p = 0.016$) and UA ($r = 0.269$, $p = 0.001$). There was a weak correla-

Table 1. Baseline characteristics of the study population.

Parameters ($N = 145$)	Normal AD (107)	Dilated AA† (38)	*P* value
Ascending aortic diameter (mm)	32 ± 3	39 ± 2	< 0.001
Age (yrs)	48 ± 9	53 ± 10	0.004
Gender (male)	81% (87)	87% (33)	NS
Height (m)	1.71 ± 0.07	1.72 ± 0.08	NS
Weight (kg)	83 ± 14	96 ± 15	< 0.001
BMI (kg/m^2)	28 ± 4	32 ± 4	< 0.001
Waist circumference (cm)	99.6 ± 12.8	109.4 ± 8.6	< 0.001
Hypertension	30% (32)	55% (21)	0.009
Diabetes mellitus	9% (10)	3% (1)	NS
Smoking	57% (61)	53% (20)	NS
Hyperlipidemia	45% (48)	32% (12)	NS
Family history of CAD	31% (33)	21% (8)	NS
Glucose (mg/dL)	99.6 ± 26.4	96.5 ± 20.1	NS
Creatinine (mg/dL)	0.87 ± 0.14	0.90 ± 0.13	NS
eGFR (ml/dk)	122 ± 28	130 ± 32	NS
Uric acid (mg/dL)	5.2 ± 1.1	6.0 ± 1.4	< 0.001
Total cholesterol (mg/dL)	204 ± 41	192 ± 42	NS
LDL (mg/dL)	130 ± 34	122 ± 34	NS
HDL (mg/dL)	42 ± 12	41 ± 9	NS
Triglyceride (mg/dL)	172 ± 111	145 ± 59	NS
CRP (mg/dL)	0.42 ± 0.47	0.55 ± 0.44	NS
Epicardial fat pad thickness (mm)	5.4 ± 2.2	8.3 ± 2.7	< 0.001

Normal AD, Normal aortic diameter; Dilated AA, dilated ascending aorta; BMI, Body mass index; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; CRP, C-reactive protein; BMI, body mass index; CAD, coronary artery disease †A dilated aorta was defined as an ascending aorta with a diameter greater than or equal 37mm. eGFR, estimated glomerular filtration rate

Table 2. The association of epicardial fat tissue thickness with AAD, CRP and BMI.

	Epicardial fat pad tissue thickness			
EAT	< 4 mm	4-7 mm	> 7 mm	*P* value
Age (yrs)	46 ± 9	48 ± 9	53 ± 10†,‡	0.003
AAD (mm)	31 ± 3	34 ± 3†	36 ± 4†,‡	< 0.001
CRP (mg/dL)	0.36 ± 0.29	0.35 ± 0.26	0.65 ± 0.67†,‡	0.003
BMI (kg/m^2)	28 ± 6	29 ± 3	32 ± 4†,‡	< 0.001
Waist circumference (cm)	94 ± 15	101 ± 9†	109 ± 11†,‡	< 0.001
Uric acid (mg/dL)	4.6 ± 1.0	5.6 ± 1.1†	5.7 ± 1.3†	< 0.001
eGFR (ml/dk)	125 ± 35	121 ± 25	128 ± 31	NS

BMI, Body mass index; CRP, C-reactive protein; EAT, epicardial adipose tissue; AAD, Ascending aortic diameter; eGFR, estimated glomerular filtration rate; †When compared with < 4 mm, $p < 0.05$; ‡When compared with <4-7 mm.

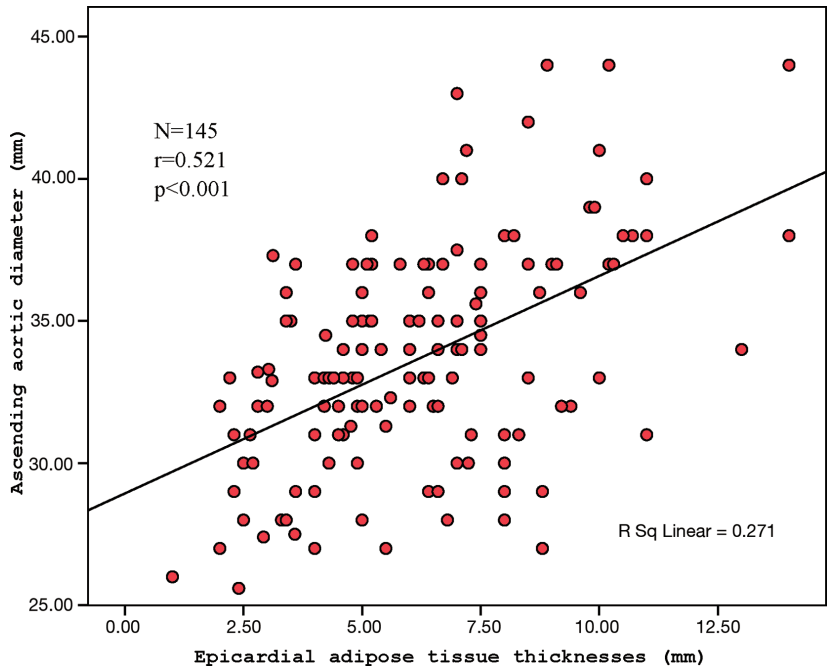

Fig. 2. The correlation between epicardial adipose tissue thickness and ascending aortic diameter.

tion between CRP and UA ($r = 0.181$, $p = 0.041$).

Multiple logistic regression analysis revealed EAT thickness (OR: 1.429, 95% CI: 1.108-1.843, $p = 0.006$), BMI (OR: 1.169, 95% CI: 1.032-1.324, $p = 0.014$), and UA levels (OR: 1.727, 95% CI: 1.078-2.766, $p = 0.023$) as the independent predictors of ascending aortic dilatation (Table 3).

Discussion

In the present study, we found significantly higher EAT thickness in patients with dilated ascending aorta compared to patients with normal aortic diameter. To our knowledge, this is the first study displaying an independent relationship between EAT thickness and ascending aortic diameter.

The pathogenesis of AscAA involves many factors. Elastin degradation may lead to initial dilation and changes in the collagen structure predispose the aneurysm to rupture. Alterations of the extracellular matrix are considered as a key element in the pathogenesis of aortic disease.

AscAA is an uncommon but highly lethal condition (Clouse et al. 1998). In contrast to aneurysms of the descending aorta, AscAAs are not commonly due to atherosclerosis (Lilly 1997). Most AscAAs have unknown etiology and are classified as idiopathic (Kirsch et al. 2006). However, a recent study revealed aortic root dimension as a predictor of incident congestive heart failure, stroke, cardiovascular disease mortality, and all-cause mortality as well (Gardin et al. 2006). Furthermore, aortic root dilatation, more frequently observed in hypertensive than normotensive individuals, correlates to cardiac and extracardiac target organ damage in hypertensive patients (Kim et al. 1996; Cuspidi et al. 2006). Therefore, AscAA seems to be related to atherosclerotic risk factors as well as cardiovascular end-points. However, in our study, despite the fact that HT was more prevalent in patients with aortic dilatation, HT was not a predictor of aortic dilatation independent of age, CRP, BMI, UA and EAT.

Although the pathogenesis of AscAAs remains unclear, the pathogenesis of aneurysmal disease appears to be associated with defects or deficiencies in structural proteins like elastin and collagen (Baxter et al. 1994). Collagen, in polymeric form, is a significant component of the media and surrounding fibrous adventitia. Collagen is the most abundant structural protein within the aorta, providing most of the tensile strength in the connective tissue (Oxlund and Andreassen 1980). In abdominal aortic aneurysms, collagen and massive elastic destruction are possibly mediated by the action of inflammatory cell derived matrix metalloproteinases. In our opinion, this pathogenesis is also valid in AscAA except congenital collagen tissue disorder induced dilatations, characterized with an accumulation of mucoid material (likely proteoglycans), elastic fiber-delicate and localized fragmentation (Shah 1997).

Until recently, magnetic resonance imaging (MRI) had been accepted as a gold standard for measuring epicardial fat thickness. In 2003, Iacobellis and coworkers measured epicardial fat using echocardiography for the first time (Iacobellis et al. 2003a, 2003b). They revealed an excellent correlation, compared to gold standard abdominal and epicardial fat measurements using MRI. Echocardiographically measured epicardial fat may provide a highly reliable measure of true visceral fat content, avoiding the possible confounding effect of increased subcutaneous abdominal

Table 3. Logistic and linear regression analyses were used for prediction of dilated ascending aorta.

Logistic regression analysis	Dependent variable: Dilated ascending aorta (≥ 37 mm)	
Independent variables	†*P* value	Odds Ratio (95%CI)
Age (yrs)	0.450	1.023 (0.964-1.086)
HT, +	0.436	1.581 (0.499-5.015)
Epicardial fat pad thickness (mm)	0.006	1.429 (1.108-1.843)
CRP (mg/dl)	0.359	0.419 (0.065-2.689)
BMI (kg/m^2)	0.014	1.169 (1.032-1.324)
Waist circumference (cm)*	0.091	1.046 (0.993-1.102)
Uric acid (mg/dL)	0.023	1.727 (1.078-2.766)
Constant	0.001	0.000
R^2	0.429	
Linear regression analysis	Dependent variable: Ascending aortic diameter (mm)	
Independent variables	†*P* value	Beta (standardized)
Age (yrs)	0.263	0.100
HT, +	0.549	0.053
Epicardial fat pad thickness (mm)	<0.001	0.337
CRP (mg/dL)	0.640	−0.038
BMI (kg/m^2)	0.027	0.195
Waist circumference (cm)*	0.153	0.134
Uric acid (mg/dL)	0.054	0.161
Constant	<0.001	—
R^2	0.313	

BMI, Body mass index; CRP, C-reactive protein; EAT, epicardial adipose tissue; AAD, Ascending aortic diamete; HT, hypertension.

†Logistic and linear regression with Enter method was used for multivariate analysis. CI, Confidence Interval.

fat (Iacobellis et al. 2005a).

Obesity is an important risk factor for atherosclerotic cardiovascular disease. Visceral adipose tissue, the fat deposited around the internal organs, may be a more important marker for cardiovascular disease rather than total body adiposity (Peiris et al. 1989; Visscher et al. 2001; Doll et al. 2002). EAT is a true visceral fat tissue, given the previous reports indicating a strong correlation between epicardial adipose tissue and abdominal visceral fat deposits (Iacobellis et al. 2003b). This finding is justified according to the common embryogenesis pathway; that is, epicardial fat and intra-abdominal fat seem to be originally brown adipose tissue in infancy. This adipose depot is now recognized as a source of variable bioactive molecules, such as adiponectin (Iacobellis et al. 2005b), tumor necrosis factor-alfa, monocyte chemotactic factor-1, interleukine-1 beta, interleukine-6 (Mazurek et al. 2003) and inflammatory cytokines which might affect coronary artery (Hirata et al. 2011a, 2011b). In fact, some epicardial fat-related cytokines, such as adiponectin, resistin, and free fatty acids, have been linked to hypertension, coronary artery disease, endothelial dysfunction, and sympathetic over activity (Bruun et al. 2003). Previous studies demonstrated impaired endothelium-dependent vasodilation with response to changes in adiponectin and resistin levels, suggesting adiponectin as a link between adipose tissue and vasculature (Tan et al. 2004; Dick et al. 2006). Elevated plasma fatty acid concentrations may also stimulate cardiac autonomic nervous system activity through an increase in plasma catecholamine concentrations. These data suggest that EAT may have an active role in the development of cardiovascular disorders rather than being an innocent bystander (Manzella et al. 2001). These biochemical properties of EAT suggest a possible causative role for aortic dilatation as a cardiovascular risk factor.

Endothelial function has great importance in predicting the clinical manifestations of established atherosclerotic lesions and further cardiovascular events (Celermajer et al. 1994). Epicardial fat seems to affect endothelial function and increase sympathetic system activity by paracrine influence. EAT related to endothelial dysfunction assessed by flow-mediated dilatation of the brachial artery, in patients with metabolic syndrome (MS) (Aydin et al. 2010). Furthermore, increased sympathetic activation and decreased vagal activity may markedly suppress endothelial function (Hijmering et al. 2002; Huang et al. 2004). Şengül and Duman (2011) reported that EAT was significantly associated with blunted heart rate recovery in patients with

MS. A recent study revealed a linear and negative correlation between aortic diameters and endothelium dependent vasodilation (Medina et al. 2010). Thus, EAT may accelerate aortic dilatation by endothelial dysfunction.

In recent studies, possible roles of UA-induced oxidative stress and increased inflammatory status in the pathogenesis of AscAAs have been demonstrated. Esen and coworkers proposed that UA is a marker of dilatation in the ascending aorta mediated by oxidative stress (Esen et al. 2011). A significant association between serum UA levels, aortic stiffness and arterial wave reflections was demonstrated (Vlachopoulos et al. 2011). Increased UA concentration has also been demonstrated in patients with coronary aneurysmal lesions (Sen et al. 2009). Tang and coworkers (2010) revealed an independent relationship between the aortic root dimensions and increased levels of serum UA in hypertensive patients without MS; same interaction was not valid in patients with MS. Despite the strong relationship between UA and MS, the lack of association between serum UA and aortic root dimensions in patients with MS could indicate that the observed association between UA and aortic root dimensions may not be solely attributed to MS-dependent mechanisms, implicating direct influence (Tang et al. 2010).

An interesting finding of our study is that, CRP was not significantly elevated in patients with dilated ascending aorta while being related to an increased epicardial fat pad thickness. The known relationship between atherosclerosis and CRP is still convincing with documented association between CRP and EAT; and the possible role of CRP on atherosclerosis appears to be invalid for ascending aortic dilatation. On the other hand, in multivariate analyses, UA and BMI remained significant in addition to EAT. Supporting evidence for possible causative role of CRP in ascending aorta dilatation is not available in the medical literature, consistent with the findings of the current study. Apart from ascending aorta, CRP and especially endothelial dysfunction have been associated with size of abdominal aortic aneurysms (Medina et al. 2010). Based on these data and our findings, increased epicardial and total visceral adipose tissue, UA and associated-endothelial dysfunction may be suggested as the mechanism of ascending aortic dilation.

The findings of the present study may support the notion that increased epicardial adipose tissue may lead to the ascending aortic dilatation. In our opinion, increased fat accumulation may have a critical role in this entity. Bioactive molecules from periaortic tissues may alter arterial homeostasis (Shimokawa et al. 1996; Miyata et al. 2000). Perivascular adipose tissue also releases factors that might profoundly modulate vascular function (Löhn et al. 2002).

Study limitations

Magnetic resonance imaging (MRI) is the gold standard diagnostic method for measuring epicardial fat thickness at the moment. Not using MRI in our research is a study limitation. Although epicardial fat is readily visualized with the high-speed computed tomography 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 computed tomography for measuring epicardial fat. Other inflammatory cytokines except CRP might be searched to clarify possible causative mediators. We did not investigate cardiac autonomic dysfunction and endothelial dysfunction, in our group of patients, the results of which could define pathophysiological interactions.

Conclusion

To the best of our knowledge, this is the first study displaying a significantly higher EAT thickness in patients with dilated ascending aorta. Based on our findings, increased epicardial adipose tissue may be suggested as a mechanism of ascending aortic dilation due to local or systemic effects. We believe that further studies are needed to clarify the role of adipose tissue in the pathogenesis of AscAAs. Specific roles of adipose tissue can provide new treatment modalities in clinical cardiovascular medicine.

Conflict of Interest

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

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