Does epicardial adipose tissue volume provide information about the presence and localization of coronary artery disease?

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ABSTRACT

Objective: This study is important for the determination of branches and segments of the first atherosclerotic coronary artery. The objective was to examine the role of epicardial adipose tissue (EAT) volume in estimating the presence and localization of plaque of coronary arteries.
Methods: Our study is a retrospective study, consisting of 50 male (mean age: 45.5±12 yrs) and 58 female (mean age: 52.5±11.6 yrs). A total of 108 consecutive patients underwent coronary computerized tomography (CT) angiography. Each coronary artery segment was assessed for the presence of atherosclerotic plaque. According to the plaque-involved vessel, patients were grouped as without plaque; plaque-involved left anterior descending artery (LAD), right coronary artery (RCA), or circumflex artery (Cx); and mixed (two or more vessels).
Results: The differences in mean values between the two groups were compared using the independent samples t test. Mann-Whitney U test was used for the comparison of continuous variables among groups. While EAT volume was found to be higher in the group with plaque, the difference between the two groups was statistically significant (88.6±9.2 cm³, 67.4±7.2 cm³, respectively, p=0.001). EAT volume was 67.3±7.1 cm³ in the without plaque group, 97.7±22.8 cm³ in LAD, 79.7±10.1 cm³ in RCA, 70.7±8.9 cm³ in Cx, and 101.9±18.6 cm³ in mixed vessels. In the intragroup comparison, the EAT volume of plaque-involved LAD and mixed vessels was significantly higher than in the other groups. The EAT volume of plaque-involved RCA was significantly higher (p=0.015) than in plaque-involved Cx.
Conclusion: Increased EAT volume is directly proportional to the presence of coronary artery plaques, especially in LAD and with more than one artery. *(Anatol J Cardiol 2015; 15: 355-9)*
Keywords: epicardial adipose tissue, multidetector computerized tomography angiography, coroner artery disease, left anterior descending

Introduction

Epicardial adipose tissue (EAT) is fat tissue limited within the pericardial cavity (1). Its near relation to the coronary arteries has been considered to be possibly relevant to the increased incidence of arteriosclerotic coronary artery disease (CAD). EAT releases some pro-atherogenic mediators that can directly affect the development and progression of CAD through a local paracrine effect (2-5). Previous research has shown a connection between EAT and the risk of subclinical atherosclerosis (6) and CAD (7). Also, the relationship between EAT with plaque types and degree of coronary artery stenosis has been investigated (8). The relationship between central obesity and cardiovascular disease is known, and vascular risk factors are known to increase with increasing EAT.

The hypothesis is that increased EAT serves as an inflammatory organ that affects the function of the adjacent vessels, because the adventitia is the origin of vascular inflammation and atherogenesis. However, none of the investigators examined the relationship between the plaque-involved location of coronary atherosclerosis and EAT. Different clinical study shown that EAT affects vascular structure. For example, the affected proximal segment of LAD and the distal segment of RCA show great differences clinically in CAD pathologies. LAD obstruction of this place would endanger a large portion of the myocardium, placing the patient at risk for severe left ventricular dysfunction or death (9-12).

The objective was to examine the role of EAT volume in estimating the presence and localization of plaque in coronary arteries.

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Methods

Study population

Our study is a retrospective study, consisting of 50 male (mean age: 45.5±12 yrs) and 58 female (mean age: 52.5±11.6 yrs). One hundred eight patients who performed multidetector computerized tomography (MDCT) coronary angiography and were admitted to our cardiology department between September 2012 and May 2013 were involved in this study. The indications for MDCT coronary angiography were angina pectoris, symptoms suggestive of coronary artery disease, atypical chest pain, scanning for coronary artery disease, and angiography. We did not perform MDCT angiography for patients with continued arrhythmia, known allergic reaction to contrast agent, deteriorated renal function (creatinine 1.2 mg/dL), pregnancy, respiratory insufficiency, poor clinical condition, left ventricular ejection fraction less than 30%, known history of bronchial asthma, Raynaud syndrome, and atrioventricular conduction block for which use of an alpha-blocker was contraindicated. Patients with coronary stent or bypass grafts were also excluded from the study. The procedures used were in accordance with the recommendations found in the Helsinki Declaration, and we obtained approval from the local ethics committee.

Data collection

Demographic documents were between September 2012 and May 2013 retrospectively on all patients through our PACS archive. The clinical information and the risk factors that were current for CAD (hypertension, dyslipidemia, diabetes, age, and gender) were acquired from hospital information records. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or current antihypertensive treatment. Hyperlipidemia was defined as total cholesterol ≥200 mg/dL, LDL-cholesterol ≥130 mg/dL, or present use of lipid-lowering agents (8). Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL or currently hypoglycemic treatment. A familial history of early CAD was defined as a first-degree relative with a background of myocardial infarction, coronary revascularization, or sudden death at a young age (men <55 years; women <65 years) (4).

Multidetector CT imaging protocol

All scans were obtained on a 256-slice CT scanner (SOMATOM® Definition Flash, Siemens Healthcare, Forchheim, Germany). Oral beta-blockers (metoprolol 50 or 100 mg) were given 1 hour before scanning in order to maintain heart rates at 70 beats/min and to increase image resolution. Primarily, an antero-posterior scout image (120 kV, 50 mAs) was first achieved to define the borders of the heart. Then, patients were scanned without contrast agent to evaluate the calcium score from the carina level to the diaphragm. In the image reconstruction of the calcium score, quantification was made at a slice thickness of 3 mm. After the coronary artery calcification (CAC) acquisition, coronary CT angiography (CCTA) imaging was done. Ninety milliliters of iodinated contrast agent (Omnipaque 350, Amersham Health, Cork, Ireland) was administered intravenously at 5 mL/s, followed by 60 mL saline at 4 mL/s. The whole heart was scanned for 8 s to cover one cardiac cycle during breath-holding without electrocardiographic (ECG) gating. A CT scan for both scanners was obtained with a tube current, tube voltage, and slice thickness of 300 mA, 120 kV, and 0.6 mm, respectively, and the gantry rotation time was 0.4 s.

Coronary artery calcium scoring

Each region of calcification of the coronary arteries was scored by an expert investigator who was blinded to the clinical variables, CCTA results, and EAT volume analyses, using semiautomatic software available on a workstation (Syngo Ca Score, Siemens Medical Solutions, Forchheim, Germany). CAC was agreed on if a minimum of three adjacent pixels with an attenuation of ≥130 Hounsfield units (HU) were identified along the way of a coronary artery. The calcium score was calculated using the Agatston method (13).

Plaque evaluation

The MDCT datasets were evaluated by two independent investigators who were blinded to EAT volume measurements using a dedicated cardiac workstation (Syngo.via, Siemens Medical Solutions, Forchheim, Germany). Axial source, multiplanar reconstruction, maximum intensity projection, and volume-rendered images were used for the assessment of the coronary arteries.

A modified American Heart Association classification that separated the coronary arterial system into 16 segments was used in the evaluation of the coronary arteries. Each coronary artery segment was assessed for the presence of atherosclerotic plaque. According to the plaque-involved vessel, patients were grouped as (a) without plaque or (b) with plaque: left anterior descending artery (LAD), right coronary artery (RCA), left circumflex (LCX), and more than one artery.

Epicardial adipose tissue volume measurement

EAT volumes were measured semi-automatically using a dedicated workstation (Myrian 1.12 3D Workstation, XP Liver, Intrasense, France). This method has been used with high performance for 3 years for measuring volumes of the donor in liver transplantation. Our experiences in terms of good image quality and the accuracy of the measurements are successful. Epicardial fat was defined on contrast-enhanced CT as a hypodense border near the myocardium and restricted by the pericardium. The reader was required to manually trace a region of interest. The visceral pericardium was drawn manually from the mid-left atrium to the left ventricular apex. All extra-pericardial tissue was excluded. This effectively excluded the myocardium, coronary arteries, coronary calcium, the aorta, and blood pool. Hounsfield units from -250 to -30 were identified to separate adipose tissue within the total selected volume (Fig. 1).

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Table 1. Basic features and frequency of cardiovascular risk factors of study patients with (+) or without (-) plaque in CCTA

	All patients (n=108)			
	All	**(+) plaque**	**(-) plaque**	***P***
N (%)	108 (100)	72 (66.7)	36 (33.3)	-
Male	50 (46.3)	34 (31.4)	16 (14.8)	0.787
Age, years	51.6±11	55.4±10.6	44.1±7.5	0.001*
Diabetes	14 (13)	14 (13)	0 (0)	0.002*
Hypertension	93 (86.1)	66 (61.1)	27 (25)	0.018*
Dyslipidemia	44 (40.7)	44 (40.7)	0 (0)	0.001*
CAC score	53.4±138	80±163	0.14±0.8	0.001*
EAT volume, cm³	81.6±20.4	88.6±21.2	67.4±7.2	0.001*

Continuous variables are expressed as mean±standard deviation, and categorical values are expressed as absolute (percentage) values. CAC - coronary artery calcification; EAT - epicardial adipose tissue.
* significant

Statistical analysis

Descriptive data are presented as absolute and relative frequencies (percentage). Continuous data are given as mean value±standard deviation. Risk factors for coronary artery disease were compared between patients with and without plaque. The differences in mean values between the two groups were compared using the independent-samples t-test. Comparisons of categorical variables between the two groups were achieved using the chi-square test. Mann-Whitney U test was used for the comparison of continuous variables among groups. To detect the optimal EAT value that was predictive of the presence of plaque in the coronary artery, the area under the receiver operating characteristic (ROC) curve was used for each potential cut-off, and the SE and 95% confidence interval (CI) were calculated. All statistical analyses were done using SPSS 15.0 for Windows (SPSS, Inc., Chicago, Illinois). A two-tailed p value of 0.05 was agreed on as statistically significant.

Results

On the CCTA, while patients with plaque were seen in 72 (66.7%) of the 108 cases, patients without plaque were detected in 36 (33.3%) of the cases. Of the cases with plaque, 34 (31.4%) were males and 38 (35.1%) were females, while 16 (14.8%) of the cases without plaque were males and 20 (18.5%) were females. The mean age of the cases with plaque (55.4±10.6) was significantly higher when compared to those without plaque (44.1±7.5) (p=0.001). The frequency of diabetes mellitus, hypertension, and dyslipidemia was significantly higher in cases with plaque than without plaque (p=0.002, 0.018, and 0.001, respectively). The basic features of the patients with plaque and without plaque detected on CCTA and the frequency of the cardiovascular risk factors are given in Table 1.

While EAT volume was found to be higher in the group with plaque, the difference between the two groups was statistically significant (88.6±9.2 cm³, 67.4±7.2 cm³, respectively, p=0.001). The frequency of diabetes mellitus, age, and dyslipidemia was

significantly higher in cases with increased EAT volume (p=0.001, 0.001, and 0.001, respectively). The outcomes of the ROC analysis showed that the cut-off value for EAT volume was 72.5 cm³ and that the area under the curve was 0.880 in patients with plaque. The sensitivity and specificity of EAT volume ≥72.5 cm³ in predicting the presence of plaque in coronary artery were, respectively, calculated as 83.3% and 86.1%.

While CAC score was found to be higher in the group with plaque, the difference between the two groups was statistically significant (80±163 and 0.14±0.8, respectively, p=0.001). The frequency of diabetes mellitus, hypertension, age, and dyslipidemia was significantly higher in cases with CAC score >0 (p=0.001, 0.005, 0.001, and 0.001, respectively).

According to the plaque-involved vessel, patients were grouped as (a) without plaque or (b) with plaque: left anterior descending artery (LAD), right coronary artery (RCA), left circumflex (LCX), and more than one artery. The percentages for these groups were, respectively, 34.3%, 27.8%, 14.8%, 13%, and 10.2%. EAT volume was significant in predicting the plaque-involved vessels (p=0.001). EAT volume was 67.4±7.2 cm³ in those without plaque, 97.7±22.8 cm³ in LAD, 79.7±10.1 cm³ in RCA, 70.7±8.9 cm³ in Cx, and 101.9±18.6 cm³ with more than one artery. In the intragroup comparison, EAT volume of the plaque-involved LAD and with more than one artery was significantly higher when compared to other groups (Table 2). However, the difference in EAT volume between the plaque-involved LAD and plaque-involved more than one artery was not statistically significant (p>0.459). EAT volume of the plaque-involved RCA was significantly higher (p=0.015) than in plaque-involved Cx.

Discussion

The current study of the association of EAT with CAD has given some significant outcomes. First, the frequency of traditional cardiovascular risk factors (diabetes mellitus, hypertension, and dyslipidemia) was significantly higher in cases with plaque than in cases without plaques. Second, the frequency of diabetes mellitus, age, and dyslipidemia was significantly higher in cases with increased EAT volume. Third, EAT volume ≥72.5 cm³ moderately predicted the presence of plaque in coronary arteries. Fourth, the frequency of diabetes mellitus, hypertension, age, and dyslipidemia was significantly higher in cases with CAC score >0. Fifth, significant relationships were found between the localization of plaque-involved vessels and EAT volume.

The introduction of non-invasive methods for the identification of CAD and the globalized use of MDCT, which allows the simultaneous assessment of CAD and high-resolution volumetric quantification of EAT, without "window" or acquisition plane limitations, facilitated the study of this suggested association. Volumetric quantification of EAT using cardiac CT has been shown to have superior reproducibility compared to thickness and area measurements (14, 15). CCTA is a method used to accurately detect, quantify, and characterize coronary artery plaque that may be applied to predict clinical outcomes in patients with suspected CAD (16). Also, 256-slice CTCA is feasi-
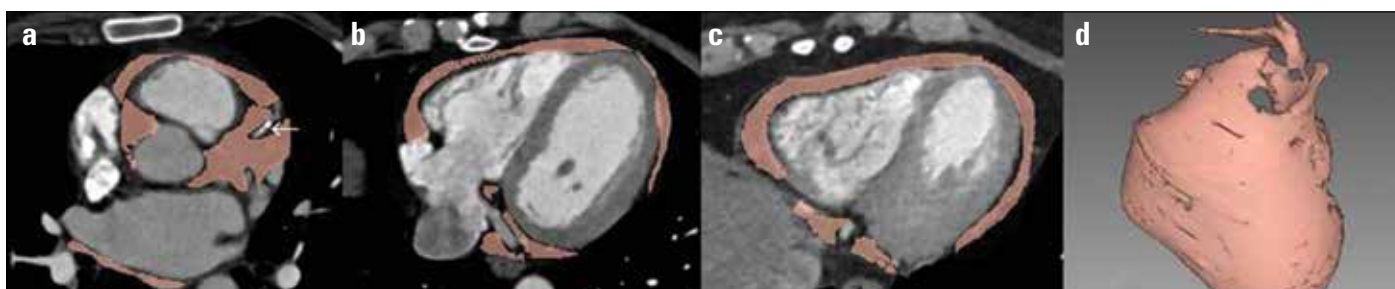
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Figure 1. a-d. Demonstration of semi-automated detection of epicardial adipose tissue on axial images of a 40-year-old male, with the pink painted regions representing epicardial adipose tissue (a, b, and c) and 3D reconstruction (d). Calcified plaques were observed in the proximal segment of the LAD (A) (white arrow)

Table 2. The comparison with Mann-Whitney U test of EAT volume in the plaque-involved vessel

	Localization			
	LAD	**RCA**	**Cx**	**More than one artery**
LAD	-	0.009[a]	0.001	0.459
RCA	0.009[a]	-	0.015[a]	0.005[a]
Cx	0.001[a]	0.015[a]	-	0.001[a]
More than one artery	0.459	0.005[a]	0.001[a]	-

Mann-Whitney U-test ([a]p value ≤0.05 was accepted as statistically significant)

ble in obese patients and allows the preservation of image quality while maintaining a low rate of non-assessable segments (17). Iterative reconstruction has emerged as an exciting new tool in cardiac CT, affording opportunities for dose reduction and improvements in image quality (18). In our study, 256-slice MDCT and a dedicated workstation (Myrian 1.12 3D Workstation, XP Liver, Intrasense, France) for measuring EAT volume were used. Therefore, volumetric measurements of our study were more accurate and precise compared with other studies. In terms of radiation exposure, our patients received less radiation, owing to 256-slice MDCT.

Several studies have shown a connection between EAT and the risk of subclinical atherosclerosis (6) and CAD (7). According to previous studies (15, 19), EAT volume was associated with other indirect measures of cardiovascular risk, such as systolic and diastolic blood pressure, fasting blood glucose levels, and lipid profile. Our study found that the frequency of traditional cardiovascular risk factors (diabetes mellitus, hypertension, and dyslipidemia) was significantly higher in cases with plaque than in cases without plaques. The frequency of diabetes mellitus, age, and dyslipidemia was significantly higher in cases with increased EAT volume. EAT volume moderately predicted the presence of plaque in coronary arteries.

Bettencourt et al. (20) identified no important independent connection of EAT volume with the degree of coronary artery stenosis. This study showed that EAT may have a significant role in the early inflammatory stage of the coronary atherosclerotic development process but not on plaque progression to important stenosis. In another study, the relationship between EAT, mea-

sured by dual-source MDCT, and descending thoracic aorta (DTA) atherosclerosis was assessed in additional; this patients with critical coronary atherosclerosis, DTA atherosclerosis had a significant relationship with EAT. So that study demonstrated that atherosclerotic plaque burden of DTA was associated with EAT thickness among patients with suspected CAD (21). Djaberi et al. (22) studied the relation between epicardial adipose tissue (EAT) volume and coronary atherosclerosis using MDCT, and they found that mean EAT volume in patients with normal coronary arteries was significantly smaller than in those with atherosclerosis. However, EAT did not significantly increase with increasing extent or severity of atherosclerosis. In this study, in patients with obstructive atherosclerosis, no significant difference was detected in mean EAT volume between patients with single-vessel atherosclerosis and those with left main coronary artery and/or multi-vessel atherosclerosis. ROC analysis resulted in a sensitivity and specificity of 72% and 70%, respectively, with an EAT cut-off volume of 77 mL, for predicting coronary atherosclerosis (22). Konishia et al. (23) found that EAT volume was higher in patients with non-stenotic plaques and those with significantly stenotic plaques than in those without plaques. However, there was no difference in the EAT of patients with non-stenotic and significantly stenotic coronary plaques. Moreover, this study also showed that EAT was higher in patients with coronary plaques. Similar to this study, we found that increased EAT volume was directly proportional to the presence of coronary artery plaques. In addition, we demonstrated that EAT volume in those with plaque-involved LAD and more than one artery was significantly higher in according to other groups.

Proximal LAD stenosis is valued by cardiologists and cardiac surgeons because of its severe reverse influence on morbidity and mortality. The anterior part of the interventricular septum and the anterior wall of the left heart ventricle create 40% of the left ventricle myocardium (24). The LAD supplies all of this part and much more in cases when it wraps around the apex (25). Therefore, it is easy to understand why proximal LAD disease can be a high-risk lesion.

In our study, EAT volume was significant in predicting plaque-involved vessels. However, the link between EAT volume in those with plaque-involved LAD and more than one artery was not statistically significant. EAT volume in plaque-involved RCA was significantly higher than in plaque-involved Cx.

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Study limitations

Our study has several limitations. First, this was a single-center study, and the sample size was small. Second, it has a retrospective study design. Third, in the present study, we neither measured waist and hip circumference nor the volume of intra-abdominal visceral fat by CT, which have been closely associated with cardiovascular cases. Thus, we were not able to assess the association of EAT with proxies of visceral adipose tissue accumulation. Finally, the serum levels of several serological markers of inflammation, cellular, and endothelial activation and adipocytokines that influence EAT in the development of coronary atherosclerosis were not measured.

Conclusion

Increased EAT volume is directly proportional to the presence of coronary artery plaques, especially in LAD and having more than one artery. This information can be used as predictors in terms of CAD.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - N.Ç.; Design - N.Ç., M.K.; Supervision - B.P., Y.K.; Resource - N.Ç., M.K.; Materials - Ü.B., H.O.; Data collection &/or processing - L.K., Ü.B.; Analysis &/or interpretation - N.Ç.; Literature search - N.Ç.; Writing - N.Ç.; Critical review - N.Ç.; Other - N.Ç.

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