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Epicardial fat volume correlates with severity of coronary artery disease in nonobese patients

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Objective **It has been reported that epicardial adipose tissue could locally modulate the coronary artery functions through secretion of proinflammatory and anti-inflammatory cytokines. Epicardial fat tissue is further implicated in the pathogenesis of coronary artery disease (CAD) because of its proximity to the adventitia of the major epicardial coronary arteries. We investigated the relationship between epicardial fat volume (EFV) and severity of CAD in nonobese patients using 64-slice multidetector computed tomography (MDCT).**

Methods **One hundred and forty nonobese patients (BMI <25 kg/m^2) were enrolled. EFV and visceral fat area were measured by MDCT. Patients were classified according to the plaque components (noncalcified, mixed and calcified) and severity of CAD. Inflammatory biomarkers were also measured, and compared with each CT parameter.**

Results **EFV was significantly correlated with the extent or severity of CAD. Patients with noncalcified or mixed plaque had a greater EFV than those with calcified plaque. Log-transferred high sensitivity C-reactive protein (CRP) was significantly correlated with EFV ($r = 0.24$, $P = 0.04$). Adiponectin level was significantly inversely correlated with visceral fat area ($r = 0.38$, $P = 0.0001$).**

Conclusion **Increased EFV is associated with more severe CAD and noncalcified or mixed coronary plaques in nonobese patients.**

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Keywords: coronary artery disease, epicardial fat, inflammatory biomarker, nonobese patients, plaque component

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Introduction

Metabolic syndrome consists of visceral fat accumulation, insulin resistance, lipid profile abnormality and hypertension. It is well known that the metabolic syndrome is associated with the development of coronary artery disease (CAD).[1–3] This syndrome is considered to be caused by insulin resistance and imbalance of adipose-derived cytokines. Epicardial adipose tissue surrounding the heart is one of the thoracic visceral adipose tissues, and produces adipokines, as does abdominal visceral adipose tissue. Reportedly, epicardial adipose tissue may locally modulate coronary artery atherosclerosis through secretion of proinflammatory and anti-inflammatory cytokines, indicating that epicardial adipose tissue may play a key role in the development of CAD.[4–6] However, as many obese patients, who generally have rich abdominal and epicardial adipose tissue, were enrolled in the above-mentioned previous studies, the relationship between epicardial adipose tissue and CAD may be substantially affected by both adipose tissues. Some reports suggested that epicardial fat volume (EFV) was related to BMI or body weight change.[7,8] Alternatively, the relationship between epicardial adipose tissue itself and CAD still remains unclear.

Sixty-four-slice multidetector computed tomography (MDCT) is a noninvasive diagnostic modality that allows assessment not only of coronary artery stenosis and intracoronary plaque components, but also of quantitative EFV.

In this study, we investigated the potential relationship between epicardial fat volume and coronary plaque morphology or the extent or severity of CAD in nonobese patients using 64-slice MDCT.

Methods

Study population

From April 2007 until September 2009, MDCT was performed for the evaluation of chest discomfort in 264 consecutive patients with known or suspected CAD, who attended Nagoya University Hospital. Because the prevalence of conventional cardiovascular risk factors (e.g. hypertension, etc.) increases in Japanese with BMI[9] of above 25 kg/m^2, nonobese patients were defined as those with a BMI of less than 25 kg/m^2 according to the criteria of the Japan Society for the Study of Obesity. Consequently, 86 patients with a BMI of above 25 kg/m^2 were excluded. Thirty patients

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were excluded who had histories of cardiac surgery and/or coronary stenting. Seven patients with coronary artery calcification (CAC) score more than 600, which precludes an accurate evaluation of coronary lumen morphology in the subsequent computed tomography (CT) angiography, were also excluded.[10] Finally, 140 nonobese patients (mean age 66 years, 88 men) were enrolled in this study.

The study complied with the Declaration of Helsinki and was approved by the Ethics Review Board of Nagoya University School of Medicine, and informed consent was obtained from all patients before enrollment in the study.

Sixty-four-slice multidetector computed tomography scanning

CT angiography was performed with a 64-slice MDCT scanner (Aquillion64, Toshiba, Japan). β-Adrenergic antagonist (atenolol 25–50 mg; Tenormin, Astra-Zeneca, London, UK) was orally administered 30 min before scanning. In the presence of contraindications for a β-adrenergic antagonist or an unsatisfactory lowering of heart rate with atenolol, the scan was performed at the higher heart rate. In fact, the heart rate control (<65 beats/min) was achieved in most patients during CT scan. Nitroglycerin spray (Nitroglycerin, Myocor, Toa-Eiyo, Tokyo, Japan) was administered for all patients just before scanning. Before administration of contrast agent, nonenhance CT scanning was performed for the evaluation of CAC score and EFV measurement. A bolus of 70 ml of contrast agent (Iohexol 350 mg/cm^3; Omnipaque, Daiichi-Sankyo, Tokyo, Japan) was injected intravenously at a rate of 3.5 ml/s and followed by a 20 ml saline flush at the same injection rate. The data were acquired with a radiograph beam collimation width of 32 mm (0.5 mm slice thickness × 64 rows) and with a spatial resolution in *x*-axis, *y*-axis and *z*-axis of 0.35 mm, a gantry rotation of 400 ms, a helical pitch of 11.2–13.2, an electric current of 350–450 mA, and a tube voltage of 120–135 kV (depending on patient size). When the signal in the ascending aorta achieved the predefined threshold of 150 Hounsfield units, the scan was initiated automatically and the entire volume of the heart was acquired during one breath-hold with simultaneous recording of the electrocardiographic tracking. Axial images were reconstructed with the use of a multisector reconstruction algorithm. Using retrospective ECG gating, images were routinely reconstructed at 75% of the R–R intervals of cardiac cycle in the mid-diastolic phase. If motion artifacts were present in these reconstructions, evaluable images were selected at the optimal electrocardiographic phase. The reconstructed image data of CT was transferred to a computer workstation (Zio M900, Amin, Tokyo, Japan) for postprocessing. Both cross-sectional and curved multiplanar reformation images were analyzed by software at the workstation. The software detected both plaques and vessel walls on CT imaging.

Coronary artery analysis

Coronary plaques were classified as calcified, mixed or noncalcified as follows. Calcified plaques are higher density plaques compared with the contrast-enhanced vessel lumen; noncalcified plaques are lower density plaques compared with the density of the contrast-enhanced vessel lumen; and mixed plaques are plaques with noncalcified and small calcified elements (<0.5 mm) within a single plaque.[11] Obstructive plaques were defined as plaques with more than 50% in diameter of luminal narrowing. Patients were classified into four groups according to the severity and extent of CAD as follows: patients without coronary plaque, patients with nonobstructive plaque; patients with obstructive plaque in a single vessel; and patients with obstructive plaques in multivessel and/or left main coronary artery. Furthermore, the number of coronary vessels in each patient was assessed. Left main coronary artery was graded as two-vessel disease. CAC score was calculated with dedicated software at a workstation and expressed as Agatston score.[12]

Measurement of epicardial fat volume and visceral fat area

EFV was defined as the total amount of adipose tissue between the surface of the heart and the visceral layer of the pericardium. On cross-sectional slices (3 mm thickness) from cardiac base to apex, the border of epicardium is semi-automatically traced. A density range from −190 to −30 Hounsfield units was assigned as adipose tissue. EFV was calculated as the sum of the each epicardial fat area using commercially available software at the workstation (Zio M900, Amin, Japan) (Fig. 1). Both visceral fat area and total fat area were also measured in the same way. On a cross-sectional slice at the umbilical level, the visceral fat area was calculated by tracing the abdominal cavity. Total fat area was defined as the visceral fat area and the subcutaneous fat area at the umbilical level and calculated by tracing body surface.

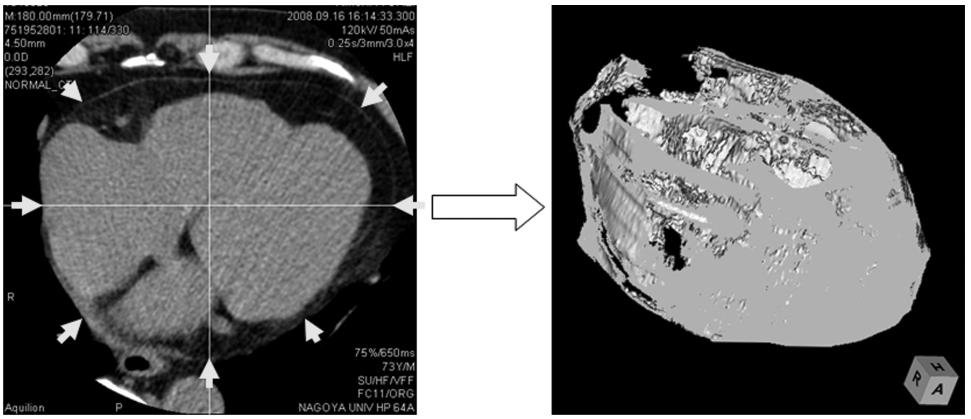
Laboratory measurements

Blood sampling was performed to measure biochemical and inflammatory markers. Peripheral venous blood was obtained under standardized conditions at the time of the CT scan. Plasma was isolated from the blood and stored at 4°C until analysis. Biochemical markers linked to the conventional cardiovascular risk factors and inflammatory biomarkers are as follows: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, hemoglobin A1c (HbA1c), creatinine, uric acid, adiponectin, interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP).

Cardiovascular risk factors

The conventional cardiovascular risk factors were compiled by personal interview and laboratory data. Diabetes was diagnosed as the fasting plasma glucose level of at

Fig. 1



Measurement of epicardial fat volume. On cross-sectional slices from cardiac base to apex, the border of epicardium is semiautomatically traced. A density range from −190 to −30 Hounsfield units (HU) was assigned as adipose tissue. Epicardial fat volume (EFV) was calculated as the sum of each epicardial fat area by the workstation software (Zio M900).

least 126 mg/dl, random glucose level of at least 200 mg/dl or HbA1c at least 6.5%, or a history of treatment with antidiabetic agents. Hypertension was diagnosed as SBP at least 140 mmHg or DBP at least 90 mmHg, or a history of treatment with antihypertensive agents. Dyslipidemia was diagnosed as LDL-C level of at least 140 mg/dl, HDL-C level of 40 mg/dl or less, or triglyceride at least 150 mg/dl, or a history of treatment with lipid-lowering agents.

Table 1 Patient characteristics

Age (years)	66 ± 10
Sex (male/female)	88/52
Body weight (kg)	56.2 ± 9.1
Waist circumference (cm)	82.3 ± 7.8
BMI (kg/m^2)	21.7 ± 2.3
Coronary risk factors	
Diabetes mellitus	31 (22%)
Hypertension	75 (53%)
Dyslipidemia	62 (44%)
Current smoking	32 (22%)
Family history of coronary artery disease	31 (22%)
Medication	
Antiplatelet	33 (23%)
ACE-I/ARB	45 (32%)
Calcium channel blocker	44 (31%)
Statin	30 (22%)
Biochemical and inflammatory markers	
Triglyceride (mg/dl)	131.0 ± 88.6
HDL−C (mg/dl)	54.4 ± 17.5
LDL−C (mg/dl)	116.7 ± 26.2
Hemoglobin A1c (%)	5.9 ± 1.2
Creatinine (mg/dl)	0.8 ± 0.4
Uric acid (mg/dl)	6.3 ± 1.2
Adiponectin (μg/ml)	12.4 ± 6.4
IL-6 (pg/ml)	2.9 ± 5.4
hs-CRP (mg/dl)	0.17 ± 0.29
Parameters of CT imaging	
Epicardial fat volume (ml)	93.0 ± 35.6
Visceral fat area (cm^2)	121.4 ± 82.3
Total fat area (cm^2)	260.3 ± 121.2
CAC score	196.1 ± 418.2

Data are indicated as mean ± SD or number (%). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAC, coronary artery calcium; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol.

Statistical analysis

All values are presented as mean ± SD or number (percentage). Differences between study groups were analyzed by an ANOVA test. The potential correlation of volume measurements by the two methods was examined with a Spearman's correlation coefficient by rank test. A cut-off value of EFV related to obstructive coronary artery plaque was determined by receiver operating characteristic analysis. A P value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS version 17 (SPSS Inc., Chicago, Illinois, USA).

Results

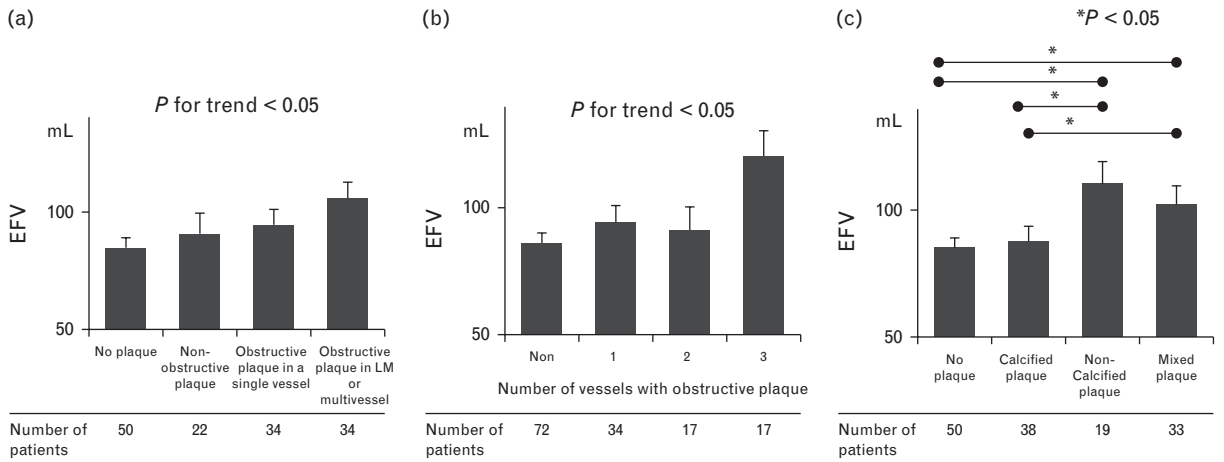
Patient characteristics

Sixty-four-slice MDCT was successfully performed in all 140 patients and adequate image quality was obtained from all patients. Patient characteristics are shown in Table 1. The mean BMI was 21.7 ± 2.3 kg/m^2. The mean EFV was 93.0 ± 35.6 ml. The mean visceral fat area and total fat area at the umbilical level were 121.4 ± 82.3, and 260.3 ± 121.2 cm^2, respectively. The mean CAC score was 196.1 ± 418.2.

Relationships between epicardial fat volume and coronary artery disease

EFV of the patients without plaque ($n = 50$), with non-obstructive plaque ($n = 22$), with obstructive plaque in a single vessel ($n = 34$) and with obstructive plaque in left main or multiple vessels ($n = 34$) were 85.0 ± 4.2, 91.0 ± 8.8, 94.8 ± 6.8 and 105.7 ± 7.3 ml, respectively. Increased EFV significantly correlated with the severity

Fig. 2



Relationships between epicardial fat volume and severity or extent of coronary artery disease or plaque morphology. Increased epicardial fat volume (EFV) was significantly correlated with the severity or extent of coronary artery disease (CAD). The number of vessels with obstructive plaques was increased in proportion to EFV. Patients with noncalcified or mixed plaques had a greater EFV compared to those without plaque or with calcified plaque.

or extent of CAD (Fig. 2a). EFV of the patients without obstructive plaque ($n = 72$), with 1 vessel of obstructive plaque ($n = 34$), with 2 vessels ($n = 17$) and with 3 vessels ($n = 17$) were 86.5 ± 3.9, 94.8 ± 6.8, 91.7 ± 9.2 and 121.0 ± 10.3 ml, respectively. The number of vessels with obstructive plaque increased in proportion to EFV (Fig. 2b). EFV of the patients without plaque ($n = 50$), with calcified plaque ($n = 38$), with noncalcified plaque ($n = 19$) and with mixed plaque ($n = 33$) were 85.0 ± 4.2, 87.6 ± 5.9, 110.4 ± 8.6 and 102.3 ± 7.1 ml, respectively. Patients with noncalcified or mixed plaque had a greater EFV than those without plaque or with calcified plaque (Fig. 2c). There was no relationship between EFV and CAC score. A cut-off value of EFV related to obstructive coronary artery plaque was 85.8 ml with a sensitivity of 63.8%, a specificity of 51.4% and area under the curve of 0.576.

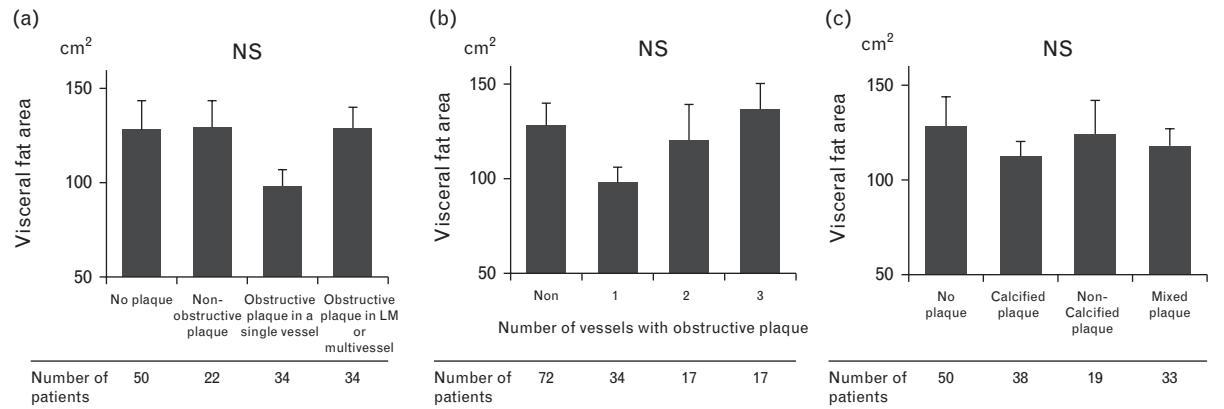
Relationships between visceral fat area and coronary artery disease

No significant correlation was found between the visceral fat area and the extent or severity of CAD (Fig. 3a), the number of vessels with obstructive plaque (Fig. 3b), or plaque component (Fig. 3c). There was no relationship between visceral fat area and CAC score.

Correlations between epicardial fat volume or visceral fat area and biochemical or inflammatory biomarkers

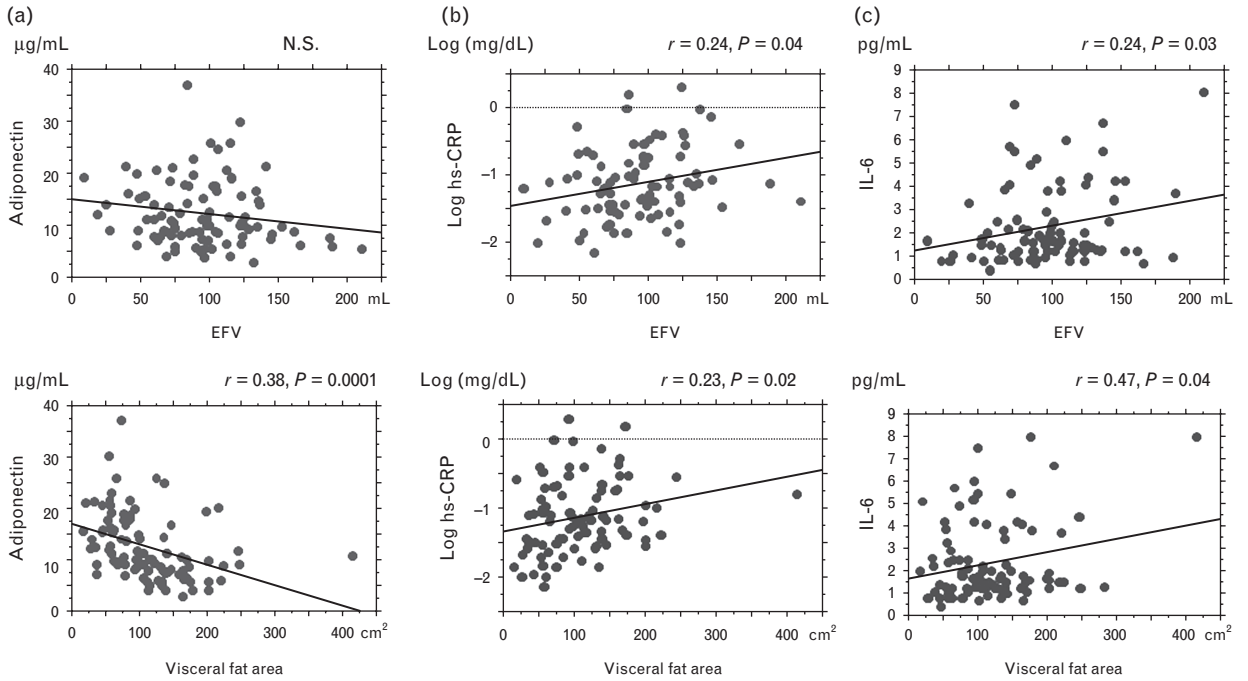
The adiponectin level did not significantly correlate with decreased EFV ($P = 0.12$), but was significantly inversely

Fig. 3



Relationships between visceral fat area and severity or extent of coronary artery disease or plaque morphology. No significant correlation was found between visceral fat area and extent or severity of coronary artery disease (CAD), the number of vessels with obstructive plaque or plaque component.

Fig. 4



Correlations between epicardial fat volume (EFV) visceral fat area and adipokines. Adiponectin level did not significantly correlate with decreased epicardial fat volume (EFV) ($P=0.12$), but significantly correlated with decreased visceral fat area ($r=0.38$, $P=0.0001$). Log-transferred hs-CRP significantly correlated with both EFV ($r=0.24$, $P=0.04$) and visceral fat area ($r=0.23$, $P=0.02$). Interleukin 6 (IL-6) significantly correlated with both EFV ($r=0.24$, $P=0.03$) and visceral fat area ($r=0.47$, $P=0.04$).

correlated with visceral fat area ($r=0.38$, $P=0.0001$) (Fig. 4a). The log-transferred hs-CRP significantly correlated with both EFV ($r=0.24$, $P=0.04$) and visceral fat area ($r=0.23$, $P=0.02$) (Fig. 4b). IL-6 also significantly correlated with both EFV ($r=0.24$, $P=0.03$) and visceral fat area ($r=0.47$, $P=0.04$) (Fig. 4c). HDL-C significantly correlated with EFV ($r=0.26$, $P=0.01$), whereas LDL-C, triglyceride, total cholesterol and HbA1c did not.

Discussion

In the present study, patients with an increased EFV had more noncalcified or mixed plaque than those without it. In addition, they also had a greater number of obstructive plaque and diseased coronary vessels compared to those without it. EFV significantly correlated with plasma inflammatory cytokines, but not with the plasma adiponectin concentration.

Relation of epicardial fat with coronary artery disease

The development of coronary atherosclerosis is thought to be linked to the amount of pericardial fat. In particular, inflammatory cytokines or adipokines, which are secreted from pericardial fat, play a pivotal role in the development of coronary plaques.[5] A close relation of EFV with the severity or extent of coronary artery disease, or the plaque component has recently been demonstrated.[13,14] A significant correlation was seen between visceral and pericardial fat with the grade of obesity. However, which fat is more critical for the development of CAD is still unkown.[15] In a nonobese population, although a previous study has reported that patients with significant CAD show a greater EFV than those without it,[16] scant data are available about the relationship between EFV and plaque component or severity. In the present study, a significant correlation was seen between EFV and the severity of CAD or plaque component in nonobese patients, indicating that EFV plays a key role in the development of CAD even in individuals without visceral fat accumulation.

Coronary plaque morphology in multidetector computed tomography and coronary artery disease

It is clinically relevant that approximately 50% of patients with acute coronary syndrome had no prior significant coronary stenosis (<50% lumen stenosis).[17–19] The characteristics of plaque morphology in acute coronary syndrome are spotty calcification, low density, lipid-rich plaques and positive remodeling plaques.[20,21] Noncalcified lipid-rich plaque plays an important role in the development of acute coronary syndrome. Accordingly, the adequate management of patients with noncalcified plaque is essential. In the present study, the patients with noncalcified plaque have a greater EFV

than those without it, but there is no difference in visceral fat area between patients with and without noncalcified plaques. In patients with a greater EFV, even without obesity, cardiovascular risk factors should be strictly managed.

Relation of biomarkers and epicardial fat volume

High LDL-C as well as low HDL-C, high inflammatory markers, and low adiponectin are parameters well known to contribute to the development of CAD. Our results indicate a significant correlation between EFV and low HDL-C, high IL-6 or high-sensitivity CRP. However, adiponectin did not significantly correlate with EFV. The adiponectin levels are reportedly more reduced in obese patients compared with nonobese patients.[22] Although it is unclear why adiponectin was not associated with EFV, it may be due to the study design according to which only nonobese patients were enrolled in this study.

Clinical implications

The results of the present study have the following important implications. Nonobese patients with multiple coronary risk factors who have a greater EFV (probably more than 85.8 ml) and/or a higher CAC score on nonenhanced CT may be recommended for the subsequent coronary evaluation by enhanced MDCT. If patients have many low-density plaques or plaques with spotty calcification on enhanced MDCT, coronary risk factors must be carefully managed even though coronary atherosclerosis is not significant. Strong statins are recommended for such patients.[23,24] If patients have heavily calcified lesions in the coronary artery regardless of EFV or if patients have significant coronary stenosis, they warrant alternatives, for example, stress myocardial scintigraphy.[25] A recent study[26] demonstrated that epicardial adipose tissue volume predicts the prevalence of myocardial ischemia, indicating that patients showing a positive scintigraphic test need conventional invasive coronary angiography. Thus, the evaluation of coronary plaque morphology by MDCT provides important insights for further therapeutic strategies in nonobese patients.

Limitations

The limitations of the present study include its being conducted in a single center with a relatively small sample size.

Patients showing severe calcification in the coronary arteries were excluded. A high CAC score becomes a predictor for long-term adverse cardiac events [27,28] and patients with severe calcification (CAC score >600) have a high prevalence of significant coronary atherosclerosis.[29] On the contrary, some studies described the correlation between a high CAC score and rich EFV.[30–32] However, as we focused on the precise assessment of coronary artery morphologies, we excluded patients exhibiting unevaluable severe calcification. Accordingly, our exclusion criteria may affect the results, showing no relationship between EFV and CAC score.

This study does not aim to provide prognostic values. We already reported that patients with acute coronary syndrome had a large amount of EFV,[33] suggesting that increased EFV would promote plaque vulnerability. The nonobese patients with increased EFV must also be given careful follow-up and strict interventions for the coronary risk factors in order to prevent acute coronary events.

In addition, it is reported that epicardial adipose tissue thickness in the atrioventricular groove could be more strongly related to coronary artery atherosclerosis, rather than EFV.[34] We did not measure epicardial fat thickness, but it may also be a valuable marker of CAD in nonobese patients.

In conclusion, an increased EFV is associated with not only the extent or severity of CAD but also with noncalcified and mixed coronary plaque. Our results imply that subsequent enhanced MDCT is recommended if nonobese patients have increased EFV on nonenhanced CT. Then, coronary risk factors should be strictly managed if they have multiple low-density or spotty calcified plaques.

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