The impact of epicardial fat volume on coronary plaque vulnerability: insight from optical coherence tomography analysis

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Aims
Epicardial fat volume (EFV) has been implicated in coronary artery disease. Relationship between EFV and coronary plaque vulnerability has not been elucidated. The aim of this study was to investigate the association of EFV with coronary plaque vulnerability by using optical coherence tomography (OCT).

Methods and results
We enrolled 117 patients who underwent multislice computed tomography (MSCT) and OCT. EFV was quantified on MSCT. Patients were categorized according to tertiles of EFV: low tertile, EFV ≤ 104.1 cm³; mid-tertile, 104.1 cm³ ≤ EFV ≤ 130.7 cm³; high tertile, EFV > 130.7 cm³. A total of 180 vessels and 221 plaques were assessed with OCT to detect a thin-capped fibroatheroma (TCFA). TCFA was defined as a plaque with necrotic lipid pools ≥ 2 quadrants and minimum fibrous cap thickness measuring < 65 μm. Patients with low computed tomographic attenuation and positive remodelling were frequently observed and patients with OCT-derived TCFA were more common in the high tertile EFV. EFV was associated with a maximal lipid arc (103.4 ± 28.2 cm² in 0 quadrant, 120.2 ± 35.2 cm² in 1–2 quadrants, and 131.5 ± 41.1 cm² in > 2 quadrants; P = 0.01) and inversely correlated with a minimum fibrous cap thickness of the patients (r = 0.400, P < 0.01). In multivariate analysis, the high tertile of EFV remained an independent predictor for patients with OCT-derived TCFA [odds ratio (OR) 2.92; 95% confidence interval (CI) 1.13–7.55; P = 0.027] and acute coronary syndrome (ACS) patients (OR 2.89; 95% CI 1.14–7.29; P = 0.025).

Conclusion
EFV was associated with coronary plaque vulnerability and high EFV was an independent predictor of ACS in patients with coronary artery disease.

Keywords
Epicardial fat volume • Plaque vulnerability • Optical coherence tomography • Multislice computed tomography

Introduction
It has been suggested that vulnerable plaque characterized by a thin fibrous cap, large lipid pool, and macrophage infiltration is the precursor lesion of plaque rupture, which can result in acute coronary syndrome (ACS).1,2 Assessing the coronary plaque vulnerability could be useful for better risk stratification in patients with known or suspected coronary artery disease. Epicardial fat is known to be a rich source of free fatty acid and inflammatory cytokines,3,4 and epicardial fat volume (EFV), which can be quantified by using the ECG-gated computed tomography (CT) with good reproducibility,5 has been implicated in coronary artery disease, coronary plaque characteristics, and risk of future adverse cardiovascular outcomes.6–13 However, a relationship between EFV and coronary plaque vulnerability has not been fully elucidated.

Recently, intravascular optical coherence tomography (OCT) has emerged as an imaging method for plaque characterization in vivo with a high resolution of ~10–20 μm.14 A histology-controlled study has shown that OCT can detect a thin-capped fibroatheroma (TCFA), which possesses a thin fibrous cap and large lipid pools15 and that OCT can serve as a useful modality to assess vulnerable plaque.16

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The aim of this study was to investigate the association of EFV measured on 64-slice multislice CT (MSCT) with coronary plaque vulnerability by analysing the plaque characteristics with OCT.

Methods

Study population

Between March 2008 and May 2010, percutaneous coronary intervention was performed in 2560 patients in our institute. Of these, 210 haemodynamically stable patients with simple lesions (AHA/ACC type A or B1) underwent OCT examination for evaluation of coronary plaque characteristics. OCT was performed for the vessels with percent diameter stenosis ≥50% by visual estimate in invasive coronary angiography. In these patients, 117 consecutive patients who underwent MSCT within 30 days before OCT examination were enrolled in this study. Patients with ST elevation myocardial infarction and/or coronary artery bypass graft surgery were not enrolled (Figure 1). MSCT was not performed if patients had renal insufficiency (serum creatinine >1.5 mg/dL), allergy to contrast media, atrial fibrillation or other rhythm irregularities, or the inability to perform breath-holding. The research protocol was approved by the institutional review board and all patients provided written informed consent.

Patients were classified as ACS or stable angina pectoris (SAP). Non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP) were diagnosed as ACS. NSTEMI was defined as continuous chest pain and an abnormal level of cardiac enzyme (creatinine kinase MB or troponin-I) and no ST-segment elevation [0.1 mV in more than two contiguous electrocardiographic (ECG) leads]. UAP was diagnosed as a progressive crescendo ECG pattern or angina at rest without an abnormal cardiac enzyme. SAP was defined as no change in the frequency, duration, or intensity of angina symptoms within 6 weeks before intervention.

Definition of risk factors and Framingham’s risk score

Hypertension was defined as a systolic blood pressure (BP) of >140 mmHg and/or a diastolic BP of >90 mmHg or the current treatment with antihypertensive medication. Hyperlipidaemia was determined to be present if total cholesterol >220 mg/dL or if lipid-lowering therapy was being used. Diabetes was regarded to be present if fasting blood glucose ≥126 mg/dL, postprandial blood glucose ≥200 mg/dL, haemoglobin A1c ≥6.5%, and/or the need for oral hypoglycaemic agents or insulin. Smoking was defined as current or previous smoking. The Framingham risk score was assessed based on the six coronary risk factors: gender, age, total cholesterol, HDL-cholesterol, systolic BP, and smoking habit.

Scan protocol and data acquisition of multislice computed tomography

MSCT was performed with a 64-slice scanner (SOMATOM Sensation 64, Siemens Medical Solutions, Forchheim, Germany). Before MSCT angiography, a non-contrast CT was acquired to measure calcium score according to the Agatston method. Prospective ECG triggering (55% of R-R interval) was used and slice thickness was 3.0 mm. When the patient heart rate was >60 bpm, a β-blocker (metoprolol 20–60 mg orally or 1–2 mg propranolol iv or both) was administered before the scan. A bolus of contrast media (Omnipaque, 350 mg iodine/mL or iopamidol, 370 mg iodine/mL) was iv injected, followed by 30 mL of normal saline. The start delay was automatically defined using bolus tracking software equipped in the scanner. The region of interest (ROI) was placed within the ascending aorta and the scan was started when the CT density levels reached 120 Hounsfield units (HU) higher than the baseline CT density. The scan was performed between the tracheal bifurcation and diaphragm with the following parameters: collimation width 64 × 0.6 mm, rotation time 330 ms, tube voltage 120 kV, maximum effective tube current 800 mA, table feed 11.5 mm/rotation, and pitch 0.2.

Figure 1 Flowchart of patient enrolment. AHA, American Heart Association; CABG, coronary artery bypass graft; CAG, coronary angiography; MSCT, multislice computed tomography; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.
reconstruction was retrospectively gated to an ECG, and the optimal cardiac phase showing the minimum motion artefact was individually determined. CT images were reconstructed using a smooth kernel (B25f) with a slice thickness of 0.75 mm (increment 0.4 mm). CT data sets were transferred to an offline workstation (Aquarius NetStation, Terarecon Inc., San Mateo, CA, USA) for image analysis. The optimal display image setting was adjusted in each patient, at a window between 600 and 900 HU, and at a level between 40 and 250 HU.

Quantification of epicardial fat volume with CT

EFV was measured three-dimensionally with the contrast-enhanced data sets. Epicardial fat was defined as adipose tissue within the visceral epicardium. The layer of the epicardium was manually traced and a three-dimensional image of the heart was constructed. Next, EFV was quantified by calculating the total volume of the tissue whose CT density ranged from −250 to −40 HU within the epicardium by using the workstation (Figure 2). Patients were categorized according to tertiles of EFV: low tertile (EFV ≤ 104.1 cm³, n = 39); mid-tertile (104.1 cm³ < EFV ≤ 130.7 cm³, n = 39), high tertile (EFV > 130.7 cm³, n = 39).

Data analysis of multislice computed tomography angiography

Based on the modified AHA classification, coronary arteries were divided into 17 segments and segments with a diameter >2.0 mm were analysed. Coronary plaques were identified based on cross-sectional images and multiplanar reconstruction images. Plaque images were analysed as described previously. Briefly, calcification was defined as structures with a CT density of 130 HU or more within the plaque. For each plaque, three cross-sectional slices were evaluated. In each slice, five rounded ROIs of 0.2 mm² were randomly placed within the target plaque and one ROI in the centre of the lumen. The lowest CT density values (HU) of each ROI were measured and averaged. In the cases of plaques with calcium deposition, ROIs were placed on the non-calcified area. The outer vessel area was manually traced at the site of maximal luminal narrowing and the reference segment without a detectable plaque proximal to the lesion by cross-sectional images. The remodelling index was defined as the ratio of the outer vessel area of the lesion to the outer vessel area of the proximal reference site. The presence of low CT attenuation (CT density value of the plaque <30 HU) and positive remodelling (remodelling index >1.10) was evaluated, which are considered to be CT findings associated with plaque vulnerability resulting in ACS with high possibility.

Optical coherence tomography image acquisition

OCT imaging was performed using an OCT imaging system (M2 OCT systemR, LightLab Imaging, Westford, MA, USA) with the occlusion-flushing balloon catheter (HeliosR, LightLab Imaging) as reported previously. The coronary artery was cannulated with a 6–8 Fr guide catheter under fluoroscopic guidance. Following intracoronary injection of 100–200 μg nitroglycerine, baseline coronary angiography was performed and the occlusion-flushing balloon catheter was advanced proximal to the lesion under guidance of a 0.014 in. angioplasty wire. The guide wire was then exchanged for the OCT imaging wire, which was introduced distal to the lesion, at least two-thirds of the way up each artery explored. During image acquisition, lactated Ringer’s solution was continuously flushed through the wire lumen of the occlusion catheter at a rate of 0.5–1.0 mL/s by a power injector, and the balloon was inflated to 0.4–0.6 atmospheres until blood flow was fully occluded. In cases with a lesion at an ostial segment, a non-occlusive continuous flushing technique was used. Dextran-40 and lactated Ringer’s solution (Low Molecular Dextran L, Otsuka Pharmaceutical Factory, Tokushima, Japan) was infused through the guiding catheter at an infusion rate between 3 and 4.5 mL/s by a power injector to remove the blood from the vessel. Motorized pullback OCT imaging was performed at a pullback rate of 1.0 mm/s throughout the lesion. Images were acquired at 15 frames/s and digitally archived.

Optical coherence tomography image analysis

Plaques at OCT were defined as structures without normal coronary morphology (three-layer appearance) within the vessel wall. Plaques in the same artery were considered to be separate if normal coronary morphology >5 mm between plaques was observed. The components of the plaque were classified as lipid, fibrous, and fibrocalcific using previously established criteria for plaque characterization. Necrotic lipid pools of the plaque were quantified as the number of

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**Figure 2** Quantification of epicardial fat volume (A, axial plane; B, coronal plane; C, sagittal plane). Region of interest was placed within the visceral epicardium and volume of adipose tissue (from −250 to −30 HU) was calculated. Areas of epicardial fat are shaded in green.
quadrants. Fibrous cap thickness was measured at the thinnest section of the distance from the coronary artery lumen to the inner border of the lipid pool. OCT-derived TCFA was defined as a plaque with necrotic lipid pools present in ≥2 quadrants within a plaque and fibrous cap thickness < 65 μm.16

**Inter- and intraobserver variability**

In 30 randomly selected patients, CT and OCT images were analysed by two independent observers, respectively. All MSCT angiography images were analysed by two independent observers. In the case of observer readings differing, a consensus reading was performed and used in the final analysis. To assess intraobserver variability, image analysis was repeated at least 2 weeks later by a single reader. An interand intraobserver agreement was good for the measurement of EFV (r = 0.95, P < 0.01 and r = 0.96, P < 0.01) in CT analysis. For OCT analysis, there was a good inter- and intraobserver agreement in fibrous cap thickness (r = 0.94, P < 0.01 and r = 0.93, P < 0.01) and TCFA (κ = 0.85 and 0.90).

**Statistical analysis**

Quantitative variables are described as mean ± SD. Discrete variables are presented as numbers and percentages. A one-way ANOVA test was used to compare the quantitative variables while χ² tests were performed on the discrete variables. A receiver operating characteristic (ROC) curve was generated to identify the optimal cut-off mean EFV to detect patients with OCT derived-TCFA and ACS patients. Correlation between the minimum fibrous cap thickness of the patient and EFV was estimated using Pearson’s correlation coefficient. Logistic regression was performed to identify potential predictors of patients with OCT-derived TCFA and ACS patients. The covariates in the univariate analysis included the high tertile of EFV, clinical presentation of ACS, and conventional coronary risk factors [male gender,

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**Notes:** ACS, acute coronary syndrome; BMI, body mass index; CAC, coronary artery calcium; DM, diabetes mellitus; EFV, epicardial fat volume; HL, hyperlipidaemia; HT, hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OCT, optical coherence tomography; TCFA, thin-capped fibroatheroma; TG, triglyceride.
diabetes, hypertension, age, body mass index (BMI), smoking, hyperlipidaemia] in identifying the patients with OCT-derived TCFA and high tertile of EFV and conventional risk factors in identifying ACS patients. Variables of patient characteristics with a P-value of < 0.10 in the univariate model were used in the multivariate model. The inter- and intraobserver agreement was assessed by linear regression analysis (continuous variables) and by the Kappa test (categorical variables). Statistical significance was defined as a P-value of < 0.05. SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

A total of 180 vessels in 117 patients were imaged and 244 plaques were detected by OCT. The total length of the coronary arteries assessed with OCT was 65±12 mm in the left anterior descending artery, 60±10 mm in the left circumflex artery, and 84±21 mm in the right coronary artery. Of 244 plaques, OCT imaging could not be obtained in 23 plaques because OCT imaging could not be obtained due to suboptimal image quality. Finally, 221 plaques were analysed. Based on OCT findings, 51 plaques were diagnosed as TCFA and 170 plaques as non-TCFA. At least one TCFA was present in 37 patients and TCFA was absent in 80 patients. An interval between MSCT and OCT was 9.8±8.8 days. Baseline patient characteristics stratified into EFV tertiles are presented in Table 1. Hypertension was more common and BMI was larger in the high-tertile group. Patients with low CT attenuation and positive remodelling were frequently observed and patients with OCT-derived TCFA were more common in the high-tertile group. ROC analysis provided the cut-off value of EFV for detecting patients with TCFA (126.7 cm³; area under the curve 0.721; sensitivity 0.68, specificity 0.71, positive predictive value 0.52, negative predictive value 0.83) and ACS patients (152.3 cm³; area under the curve 0.689; sensitivity 0.38, specificity 0.89, positive predictive value 0.57, negative predictive value 0.78). Twenty-eight patients had no necrotic lipid pool within plaques in OCT and the fibrous cap thickness of these patients could not be measured. In 89 patients where lesion fibrous cap thickness could be evaluated, EFV was inversely correlated with patients’ minimal fibrous cap thickness (r = −0.400, P < 0.01; Figure 3). Extension of the necrotic lipid pool (maximal lipid arc of the patient) was associated with larger EFV (Figure 4). Multivariate analysis identified ACS and the high tertile of EFV as independent predictors of TCFA (Table 2). In logistic regression analysis, the high tertile of EFV remained an independent predictor for ACS patients (Table 3). Figure 5 shows a representative case with OCT-derived TCFA and a large amount of epicardial fat.

Discussion

The main findings of our study were as follows. First, EFV was associated with low CT attenuation and positive vessel remodelling in MSCT and EFV was correlated with the extension of the necrotic lipid pool and inversely correlated with fibrous cap thickness in OCT. Secondly, high EFV was an independent predictor of the presence of OCT-derived TCFA. Finally, high EFV was an independent predictor for ACS patients. These findings indicate that EFV is related to plaque vulnerability in patients with coronary artery disease. To our knowledge, this is the first study investigating the relationship between EFV quantified with MSCT and plaque vulnerability assessed by OCT.

Epicardial fat volume and coronary plaque characteristics

Previous studies have shown that epicardial fat could serve as a mediator of coronary artery disease. Several studies have demonstrated that epicardial fat contributes not only to coronary atherosclerosis and myocardial ischaemia but also to coronary
plaque characteristics. Alexopoulos et al.\textsuperscript{10} showed that patients with plaque demonstrating calcification in \( \leq 50\% \) of the plaque area had larger EFV in their CT plaque analysis. Our results showed that low CT attenuation and positive remodelling were frequently observed in patients with high EFV. On the other hand, Greif et al.\textsuperscript{11} reported that no relationship was found between EFV and type of atherosclerosis evaluated by MSCT. This controversy in the role of EFV for plaque characterization may be due to limited spatial resolution of MSCT which cannot allow the accurate and reliable evaluation of plaque components. At this time, OCT is the only clinically available modality which has enough resolution to assess plaque configuration and fibrous cap thickness, which are the principal factors of plaque vulnerability. In the present study, EFV was the independent predictor of OCT-derived TCFA along with clinical presentation of ACS. Furthermore, EFV was associated with fibrous cap thickness and extension of necrotic lipid pools.

### Epicardial fat as a predictor of acute coronary syndrome

Disruption of vulnerable plaque and subsequent thrombus formation is one of the key roles in the pathogenesis of ACS. ACS can suddenly arise in stable patients with a mild-to-moderate coronary stenosis.\textsuperscript{22} Thus, detection of clinically stable but high-risk patients with vulnerable plaque before rupture and the appropriate management of these patients is important. Our results showed that high EFV was an independent predictor of ACS, which indicates that large EFV was related to not only the plaque vulnerability speculated by OCT findings but also to the actual unstable clinical manifestation. The cut-off value to detect ACS patients (152.3 cm\(^3\)) with high specificity (0.89) may be useful to rule out ACS. In line with our study, previous studies reported that greater EFV associated with future cardiovascular events including myocardial infarction.\textsuperscript{12,13}
Role of epicardial fat in the pathophysiology of acute coronary syndromes

Several studies have reported the potential role of epicardial fat in the pathophysiology related to coronary atherogenesis. It has been suggested that epicardial adipose tissue itself supplies some pro-inflammatory signals such as interleukin-1β, interleukin-6, monocyte chemotactic, and tumour necrosis factor. On the other hand, epicardial fat has expression of adiponectin, which has anti-inflammatory and antiatherogenic cytokine. However, in the patients with coronary artery disease, levels of this vasoprotective agent were lower compared with the patients without CAD. Atherosclerotic lesions were absent in the intramyocardial segment in rabbits and in the human myocardial bridge where the coronary artery was covered by the myocardium, suggesting a plausible role of epicardial fat for atherogenesis. An autopsy study demonstrated that greater infiltration of macrophages was observed in the perivascular fat of coronary arteries containing large necrotic lipid pools compared with in the vessels with fibrocalcific plaques. With the close anatomical relationship and no fibrous fascial layer between epicardial fat and coronary adventitia, two hypothetical mechanisms of epicardial fat in the coronary atherogenesis can be speculated. One is the endocrine effect through adventitial vasa vasorum. Adipokines secreted by epicardial fat can transverse the vessel into its lumen and react with cells around the plaque. The other is the direct paracrine effect. Adipokines can diffuse in the interstitial fluid across the vascular wall and act towards atherogenesis. These mechanisms are postulated as ‘outside-to-inside’ cellular cross-talk.

Feasibility of multislice computed tomography for quantifying epicardial fat volume

Epicardial fat thickness can be measured by echocardiography and a relationship between epicardial fat thickness as assessed by echocardiography and coronary atherosclerosis has been suggested. However, it is difficult to distinguish epicardial adipose tissue from pericardial effusion in some cases with obese patients and patients with small amounts of epicardial fat, and the reproducibility was poor. In addition, two-dimensional echocardiography cannot quantify the total amount of epicardial fat. As another imaging modality to assess accurate EFV, cardiovascular magnetic resonance (CMR) has evolved recently. However, obtaining CMR images spends relatively more time and effort, and for the purpose of evaluating EFV, CMR is not feasible in routine clinical setting. On the other hand, MSCT can quantify the total volume of epicardial fat quickly and easily, regardless of body size, with high reproducibility as shown in our study. Furthermore, EFV...
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can be obtained as additional information at the same time with calcium scoring or CT coronary angiography to provide an incremental value for the evaluation of coronary artery disease.

**Clinical implication**

The results of our study suggest a relationship between EFV and unstable rupture-prone characteristics of coronary artery plaque and unstable clinical manifestation, which may indicate important diagnostic and therapeutic implication. Measuring EFV by MSCT can provide useful information for the risk stratification of patients with coronary artery disease and the selection of candidates who require aggressive plaque stabilization therapy such as lifestyle and/or pharmacological intervention to prevent cardiovascular events.

**Limitation**

The limitations of this study are as follows. First, our study was conducted with a relatively small size of patients with coronary artery disease. Due to selection bias, it is uncertain that our results can be applicable to general population. Secondly, this study was of cross-sectional design and causality is unclear. Thirdly, although OCT can depict the fibrous cap and lipid component clearly, it cannot visualize the entire plaque because of limited penetration depth (1–2 mm). Finally, the whole coronary tree was not explored with OCT, and plaques located at angiographically normal segments could have been missed.

**Conclusion**

EFV was associated with coronary plaque vulnerability and high EFV was an independent predictor of ACS in patients with coronary artery disease.

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