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# The different association of epicardial fat with coronary plaque in patients with acute coronary syndrome and patients with stable angina pectoris: Analysis using integrated backscatter intravascular ultrasound

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ABSTRACT

*Objectives:* We assessed the hypothesis that the epicardial fat is associated with coronary lipid plaque.
*Background:* Epicardial fat volume (EFV) is increased in patients with acute coronary syndrome (ACS), and lipid-rich plaques have been associated with acute coronary events.
*Methods:* We enrolled 112 individuals who underwent percutaneous coronary intervention (PCI) (66 with ACS; 46 with stable angina pectoris [SAP]) and classified plaque components using integrated backscatter intravascular ultrasound as calcified, fibrous, or lipid. Possible effects of PCI on plaque data were minimized by assessing 10-mm vessel lengths proximal to the culprit lesions. Total plaque volume and percentage volumes of individual plaque components were calculated. EFV and abdominal visceral fat area were measured using 64-slice computed tomography.
*Results:* ACS patients had significantly higher EFV than did SAP patients (118 ± 44 vs.101 ± 41 mL, $p = 0.019$). In ACS patients, EFV was correlated with total plaque volume and percentage of lipid plaque ($r = 0.27$ and 0.31, respectively; $p < 0.05$). Moreover, an independent interaction between EFV and lipid-rich plaque (odds ratio, 1.04; 95% confidence interval, 1.00–1.07) were revealed. In contrast, in SAP patients, EFV was positively correlated with body mass index and abdominal visceral fat area but not with plaque characteristics.
*Conclusions:* EFV was associated with lipid-rich plaque in patients with ACS, whereas no correlation between EFV and coronary plaque profile was apparent in SAP patients. Epicardial fat may have a role in the development of lipid plaque, which contributes to the pathogenesis of ACS.


## 1. Introduction

Epicardial fat is the adipose tissue located under the visceral layer of the pericardium. It is considered an important factor in the development of cardiovascular disease because of its proximity to coronary arteries. Accumulating evidence links epicardial fat to the development of coronary atherosclerosis through several paracrine mechanisms, such as the local release of inflammatory mediators that trigger the atherosclerotic process, and other systemic effects [1,2]. Prior studies have demonstrated increased epicardial fat volume (EFV) in patients with coronary atherosclerosis [3–6] and that this relationship remains unchanged even if limited to patients with acute coronary syndrome (ACS) [7,8]. A previous study using integrated backscatter intravascular ultrasound (IB-IVUS) has reported associations between lipid-rich plaque and acute coronary events [9], and EFV was reported to be an independent predictor of

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the presence of plaque with a non-calcified component [10]. In another study, virtual-histology intravascular ultrasound parameters indicating vulnerable plaque were significantly related to the thickness of epicardial adipose tissue [11]. Therefore, we suspected that the amount of epicardial fat is associated with coronary lipid plaque. Moreover, the differential effect of epicardial fat on coronary plaque in patients with ACS or stable angina pectoris (SAP) has not been fully clarified. The purpose of this study was to evaluate the relationship between EFV and coronary plaque characteristics in patients with ACS and SAP using IB-IVUS.

## 2. Methods

### 2.1. Patients and study design

This study was a prospectively planned observational study for non-target coronary lesions in patients with ischemic heart disease who have undergone percutaneous coronary intervention (PCI) using IVUS. From July 2010 to July 2011, we enrolled a total of 112 consecutive Japanese patients who underwent PCI and IB-IVUS, including 66 patients with ACS and 46 patients with SAP. Patients with diminished renal function ($n = 14$) or with atrial fibrillation ($n = 13$) were excluded because cardiac CT examination was inappropriate in their cases. Patients who did not wish to participate in the study ($n = 8$) were also excluded. None of the patients had obstructive sleep apnoea syndrome or psoriasis, which plays a role in influencing both cardiovascular and epicardial fat conditions [12,13].

Cardiovascular risk factors and covariates were measured in a contemporaneous examination. Serum triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and fasting plasma glucose were measured in fasting morning samples and body mass index (BMI) was calculated. Diabetes mellitus was defined as fasting plasma glucose ≥200 mg/dL, treatment with a hypoglycaemic agent, or insulin usage. Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive treatment was used to define hypertension. Triglyceride ≥150 mg/dL, LDL cholesterol ≥140 mg/dL, HDL cholesterol ≤40 mg/dL, or treatment with a dyslipidaemia agent was used to define dyslipidaemia. Current smoking status was defined as smoking at least 1 cigarette per day for the past year. The ACS group included 46 ST-elevation myocardial infarction (STEMI) and 20 non-STEMI patients. Patients were diagnosed with STEMI or non-STEMI according to the following criteria: Patients with ischemic chest discomfort, ST-segment elevation on electrocardiogram, and elevation of troponin-T level were defined as STEMI. Patients with chest ischemic discomfort presenting without ST-segment elevation on electrocardiogram but with an elevated troponin-T level were defined as non-STEMI. Patients with predictable chest ischemic discomfort during or after physical exercise or emotional stress were suspected to have SAP. All SAP patients were diagnosed with myocardial ischemia using exercise treadmill test or stress myocardial scintigraphy.

The study complied with the Declaration of Helsinki and was approved by the ethics review board of Chubu Rosai Hospital. Written informed consent was obtained from all patients prior to enrolment in the study.

### 2.2. Cardiac CT scanning technique and image analysis

EFV was measured in all patients using 64-multislice computed tomography (MSCT) (LightSpeed®; GE Healthcare, Waukesha, Wisconsin). Patients with ACS underwent MSCT scanning during their hospitalization and patients with SAP performed MSCT as outpatient. Contrast medium was used on all patients to evaluate the coronary arteries at the same time.

MSCT analysis was performed as in a previous report [7]. EFV was defined as the total amount of adipose tissue between the surface of the heart and the visceral layer of the pericardium. Epicardial area was measured by tracing a single region of interest semi-automatically and epicardial fat on the section obtained at each level. A density range of −190 to −30 Hounsfield units was used to isolate the adipose tissue [14]. Volume analysis software (Advantage Workstation 4.2; GE Healthcare) was used to discern fat from other tissues (Supplementary Fig. 1). Two experienced analysts, who had not been informed of characteristics of the results, measured EFV from the images obtained of the heart. Interobserver variability for the quantification of EFV was <5.0%.

In addition to cardiac scans, abdominal scans were performed at the umbilicus level, which is approximately the level of lumbar 4 and 5. The visceral fat area was defined as intraperitoneal fat, with attenuation ranging from −190 to −30 Hounsfield units [15].

### 2.3. Coronary angiography and IVUS procedure

Before performance of coronary angiography, patients were administered an intracoronary 0.5 mg of isosorbide dinitrate to prevent coronary spasm. Furthermore, 5000 to 10,000 IU of heparin was administered before PCI. The IVUS procedure was performed on all patients. However, the coronary artery was not analyzed when the IVUS catheter could not cross the lesion, when chronic total occlusion occurred, and when the lesion was too distal in the target coronary artery for the catheter to reach.

A personal computer equipped with custom software (IB-IVUS; YD, Nara, Japan) was connected to the IVUS imaging system (View-it, TERUMO, Tokyo, Japan) to obtain radiofrequency signal, signal trigger, and video image output.

We used a 40-MHz IVUS catheter. The tip of the IVUS catheter was placed in the coronary vessel and was then pulled back automatically at a rate of 0.5 mm/s. The radiofrequency signals were acquired at the top of the R-wave of the electrocardiogram after detection of a regular R–R interval. Off-line calculation of IB values for the acquired radiofrequency signals was performed by retrieval of the stored data. IB values for each histologic category were determined as described previously [16]. Each data set was stored digitally and assessed by a cardiologist blinded to the patient characteristics.

### 2.4. Definitions of analysis segment and IB-IVUS parameters

We evaluated the coronary plaque of non-culprit lesions, which we defined as lesions proximal to a stented area, with a length of 10 mm from the proximal edge of the stent. When the stented area was located in the left main trunk, just proximal to the right coronary artery, or the recorded IVUS image was less than 10 mm, we measured the lesions located in the segment 10 mm distal to the distal stent edge. Distal lesions were measured in 5 (7%) ACS patients and 2 (4%) SAP patients.

IB-IVUS analysis was performed as in a previous report [17]. IB values for each tissue component were calculated using a fast Fourier transform of the frequency component of the backscattered signal from a small volume of tissue. On the basis of previous studies [18], an IB value for each plaque component (lipid, fibrous, or calcified) was determined (supplementary Fig. 2). Color-coded maps were constructed for each 0.5-mm slice to illustrate the tissue characteristics of the lesion.

Total plaque volume, vessel diameter, vessel area, lumen area, and the percentage of each plaque component were automatically calculated using the IB-IVUS system. Twenty IB-IVUS images, each