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Epicardial adipose tissue thickness is a predictor for plaque vulnerability in patients with significant coronary artery disease

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ABSTRACT

The aim of this study is to assess the relationship of epicardial adipose tissue (EAT) and plaque vulnerability.

We consecutively enrolled 82 patients with coronary artery disease (CAD). A symptom-related vessel was imaged by virtual histology intravascular ultrasound (VH-IVUS). In 60 out of 82 patients, all three vessels were studied by VH-IVUS. EAT thickness was measured by echocardiography. All patients were divided into thick ($\geq$3.5 mm) and thin EAT groups ($<$3.5 mm). VH-IVUS parameters were compared according to the EAT group. To evaluate the independent effect of EAT thickness on plaque vulnerability, a set of well-known CAD risk factors and EAT thickness were included in multiple linear regression models of VH-IVUS parameters which denotes plaque vulnerability.

In a symptom-related vessel analysis, the thick EAT group had significantly more thin-cap fibroatheromas (TCFAs). In a symptom-related vessel analysis among 62 patients with unstable angina out of 82 patients, the thick EAT group had significantly more thin-cap fibroatheromas (TCFAs). In all three vessels analysis, the thick EAT group was associated with significantly larger total plaque volume, higher total plaque volume index, higher mean plaque burden, higher plaque volume indexes of the necrotic core (NC), and more total number of TCFAs than the thin EAT group. By multivariate analysis, total TCFAs of a symptom-related vessel, both in total population and in patients with unstable angina, and plaque volume index of the NC of all three vessels were independent factors associated with thick EAT. In multiple linear regression models of VH-IVUS parameters which means plaque vulnerability, EAT thickness was one of the independent factors.

In the present study, the VH-IVUS parameters indicating vulnerable plaque were significantly related with the thickness of EAT.

1. Background

Epicardial adipose tissue (EAT) is true visceral fat deposited around the heart, particularly around coronary vessels and mediates atherosclerosis via expression of several bioactive molecules [1,2]. EAT quantification has been demonstrated to correlate with the severity of coronary artery disease (CAD) and the extent of coronary artery atherosclerosis [3–6]. Although EAT may serve as a source of inflammation that can influence CAD activity, there are limited data regarding the association of EAT with the type of atherosclerotic plaque.

We have reported that the thickness of EAT by echocardiography was significantly correlated with unstable presentation of CAD [3]. We hypothesized that the unstable presentation of CAD in patients with thick EAT might be related with plaque vulnerability. The aim of this study is to assess the relationship of EAT and plaque vulnerability using analysis of plaque components by virtual histology intravascular ultrasound (VH-IVUS) in patients with significant CAD.

2. Methods

We consecutively enrolled 82 patients with angiographically significant CAD, who received successful coronary stenting. The medical records of all patients were retrospectively reviewed after informed consent of studied patients. As we intended to investigate the relationship between the histologic characteristics of plaque and EAT, we enrolled patients with angiographically significant CAD regardless of clinical presentation. As clinically stable angina is not necessarily associated with histologically stable atherosclerotic

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plaques [7,8] and a marker of inflammation or immune activation is occasionally raised in patients with stable angina according to disease activity [9], we enrolled patients with both stable angina and unstable angina. However, as inflammation within vulnerable coronary plaque is more closely related to unstable angina [10], we also tried to investigate the relationship between the histologic characteristics of plaque and EAT in patients with unstable angina. Upon quantitative analysis of the coronary angiograms, significant CAD was considered to be the presence of stenosis, ≥50% in diameter, of a major epicardial vessel. Revascularization was decided to be clinically indicated if there was >70% diameter stenosis on coronary angiography or >50% stenosis together with a positive stress test or ischemic symptoms. We tried to exclude the acute systemic inflammatory effect to avoid confounding the role of EAT. We excluded patients from the study if they had any of the following: active inflammation (such as infection or systemic autoimmune disease, often related to increased EAT [11,12]), a history of prior revascularization, heart failure, cardiomyopathy or acute myocardial infarction. Myocardial infarction was defined when there is a detection of rise in cardiac biomarkers (preferably troponin), with at least one value above the 99th percentile of the upper reference limit [13].

A symptom-related vessel was imaged by VH-IVUS before stent implantation in all patients. Symptom-related vessel was defined as the vessel with maximal stenosis (usually >70% diameter stenosis) by angiographic findings. If not localizable to a single symptom-related vessel by angiographic findings, symptom-related vessel was defined according to pre-interventional IVUS findings in patients with multivessel disease. If there were several minimum lumen area (MLA) sites, the MLA site with the largest external elastic membrane cross sectional area was chosen as a symptom-related lesion. A 20 MHz, 2.9 Fr IVUS imaging catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, California, USA) was advanced as far distally as possible into the coronary artery after intracoronary administration of 100–200 μg nitroglycerine. Imaging was performed, paying attention to cover any evident atherosclerosis. Automated pullback was performed at a speed of 0.5 mm/s. During pull-back, the raw radiofrequency data were captured at the peak of the *R* waves for the reconstruction of a color-coded map by a VH data recorder (Volcano Corporation, Rancho Cordova, California, USA). Manual contour tracing of the lumen and the media-adventitia interface was performed by an experienced analyst who was unaware of the patients' information. Volumetric data were generated using pcVH software (version 2.1, Volcano Corporation, Rancho Cordova, California, USA). The total plaque volume was automatically determined by the software, and the summation of measured cross sectional areas in all frames of the pullback region was based on Simpson's rule. In 60 patients among the study population, all three major epicardial arteries were studied by VH-IVUS.

VH-IVUS analysis classified the color-coded tissue into four major components as green (fibrous), yellow-green (fibrofatty), white (dense calcium), and red (necrotic core) [14–16]. Four plaque components were defined as follows: 1) fibrous: areas of densely packed collagen, 2) fibrofatty: fibrous tissue with lipid interspersed in collagen, 3) dense calcium: calcium deposits without adjacent necrosis, and 4) necrotic core: necrotic regions consisting of cholesterol clefts, foam cells, and microcalcifications [15]. Each plaque component was measured in every recorded frame. The total plaque volume of a symptom-related vessel was obtained, and the mean plaque burden was calculated as the total plaque volume of a symptom-related vessel divided by the total vessel volume of a symptom-related vessel × 100. A plaque volume index of a symptom-related vessel was calculated as total plaque volume of a symptom-related vessel divided by vessel length. The plaque volume index of each plaque component was calculated. Each plaque component was also expressed as a percentage of the total plaque volume. Thin-cap fibroatheroma (TCFA) was defined as a necrotic core ≥10% of plaque area without evident overlying fibrous tissue in the presence of ≥40% plaque burden in at least three consecutive frames [16]. The numbers of TCFAs were calculated in a symptom-related vessel. Also, total plaque volume, mean plaque burden and plaque volume indexes, percentage of each plaque component and the numbers of TCFAs were obtained in 60 patients by analyzing all three major epicardial arteries.

Two-dimensional transthoracic echocardiography was performed within 1 week, either after or before undergoing VH-IVUS. Recordings of three cycles of the two-dimensional parasternal long-axis were obtained. We enlarged images for better visualization and accurate measurement of EAT thickness. EAT thickness was measured on the free wall of the right ventricle (RV) in the still image of a two-dimensional echocardiography at end diastole on the parasternal long-axis view. We preferred the area above the RV to measure EAT thickness, as this area is recognized as having the thickest EAT layer. In addition, the parasternal long-axis view allows the most accurate measurement of EAT thickness with optimal cursor beam orientation. The anterior echo-lucent space between the linear echo-dense parietal pericardium and the RV epicardium was considered to be EAT. We measured the thickest point of EAT in each cycle. The average value of the EAT thickness was calculated.

All patients were divided into two groups: thick EAT group, EAT ≥3.5 mm ($n = 37$) and thin EAT group, EAT <3.5 mm ($n = 45$). The median value of EAT thickness in patients with unstable presentation of CAD was 3.5 mm in our previous studies [3,17]. We chose 3.5 mm, the median value of EAT thickness in patients with significant CAD, derived from these previous studies, as the cut off value, instead of the median value of EAT thickness in the present study population. While the present study population consists of relatively small number, more than 500 patients were enrolled in our previous studies. The cut off value, 3.5 mm, derived from these studies might be a more reasonable standard than the median EAT value of the present study. We compared the characteristics of patients in the thick EAT group to those in the thin EAT group. VH-IVUS analyses were compared according to the EAT groups (Fig. 1). Volumetric VH-IVUS analyses and the total number of TCFA of symptom-related vessel of all study populations were compared according to the EAT groups. Volumetric VH-IVUS analyses and the total number of TCFAs of symptom-related vessel of patients with unstable angina were compared according to the EAT groups (thick EAT group = 28, thin EAT group = 34). Volumetric VH-IVUS analyses and the total number of TCFAs of all three major epicardial arteries of 60 patients were compared according to the EAT groups (thick EAT group = 21, thin EAT group = 39).

The SPSS 13.0 (SPSS inc., Chicago, Illinois, USA) statistical software package was used for all calculations. Data are shown as the mean ± standard deviation for continuous variables and as percentages for categorical variables. Comparisons were conducted by unpaired Student's *t* test. Multiple stepwise logistic regression analysis was performed to assess independent VH-IVUS parameters that were related to thick EAT. To evaluate the independent effect of EAT thickness on plaque vulnerability, a set of well-known CAD risk factors and EAT thickness were included in multiple linear regression models of VH-IVUS parameters which denotes plaque vulnerability. A p value < 0.05 was considered statistically significant.

3. Results

The median and mean ± standard deviation EAT thickness of the study population were 2.8 mm and 3.4 ± 2.2 mm, respectively. The