

Relationship between indexed epicardial fat volume and coronary plaque volume assessed by cardiac multidetector CT

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Abstract

We explored whether baseline indexed epicardial fat volume (EFVi) and serial changes in EFVi were associated with increase in coronary plaque volume as assessed by multidetector computed tomography.

We retrospectively reviewed 87 patients with coronary artery plaque, identified during either baseline or follow-up cardiac computed tomography (CT) examinations. Each plaque volume was measured in volumetric units using a semiautomatic software tool. EFVi was quantified by calculating the total volume of epicardial tissue of CT density -190 to -30 HU, indexed to the body surface area. Clinical cardiovascular risk factors were extracted by medical record review at the time of the cardiac CT examinations. The relationship between EFVi and coronary plaque volume was explored by regression analysis.

Although the EFVi did not change significantly from baseline to the time of the follow-up CT (65.7 ± 21.8 vs 66.0 ± 21.8 cm³/m², $P=0.620$), the plaque volumes were increased significantly on the follow-up CT scans. The annual change in EFVi was not accompanied by a parallel change in coronary plaque volume ($P=0.096-0.500$). On univariate analysis, smoking, hypercholesterolemia, 10-year coronary heart disease risk, obesity, and baseline EFVi predicted rapid increases in lipid-rich and fibrous plaque volumes. On multivariate analysis, baseline EFVi (odds ratio=1.029, $P=0.016$) was an independent predictor of a rapid increase in lipid-rich plaque volume.

EFVi was shown to be an independent predictor of a rapid increase in lipid-rich plaque volume. However, changes in EFVi were not associated with parallel changes in coronary plaque volume.

Abbreviations: BMI = body mass index, CAC = coronary artery calcium, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, CHD = coronary heart disease, CV = cardiovascular, EFV = epicardial fat volume, EFVi = indexed epicardial fat volume, ICC = intraclass correlation coefficient, MDCT = multidetector computed tomography.

Keywords: cardiovascular risk factors, coronary artery plaque, coronary computed tomography angiography, epicardial fat

1. Introduction

Epicardial fat is the adipose tissue around the heart constrained by the visceral pericardium.^[1] Epicardial fat directly surrounding the major epicardial coronary arteries is a rich source of free fatty acids and numerous bioactive adipocytokines that play important roles in the development of atherosclerosis.^[2-5] Recently, due to advances in temporal and spatial resolution, multidetector computed tomography (MDCT) has emerged as a noninvasive diagnostic modality that allows for simultaneous assessment of coronary artery calcium (CAC), coronary artery stenosis and coronary plaque, and epicardial fat volume (EFV) without

increased radiation exposure or cost. Several studies using MDCT have shown a relationship between EFV and CAC,^[6-9] the presence of coronary plaque,^[10-12] plaque composition,^[13-15] and plaque vulnerability.^[15-17] However, it is unknown whether elevated EFV is associated with a greater likelihood of developing atherosclerosis over time, and whether increases in EFV are accompanied by a parallel increase in coronary plaque volume. The relationship between serial changes in EFV and coronary plaque volume has not yet been investigated; therefore, the aim of the present study was to determine whether baseline indexed EFV (EFVi) and serial changes in EFVi are related to increase in coronary plaque volume as assessed by MDCT.

2. Methods

2.1. Patients and clinical risk factors

We reviewed the cardiac computed tomography (CT) patient data set from April 2007 to December 2014, retrospectively, and there were 237 patients who underwent MDCT examination more than once. After excluding patients who underwent coronary artery bypass graft ($n=48$) and percutaneous coronary angioplasty ($n=5$), we reviewed the MDCT data of the remaining 184 patients. We also excluded patients ($n=63$) who had no coronary artery plaques detected by CT and those ($n=34$) who underwent cardiac CT using a different tube voltage. As a result, this study ultimately examined data of 87 patients.

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This study was approved by the Ajou Institutional Review Board, in which there was no need to take informed consent due to the retrospective design.

The pretest probability of coronary artery disease (CAD) was estimated for each patient based on age, sex, and symptoms.^[18] Medical records were obtained by reviewing the electronic medical database, and cardiovascular (CV) risk factors were analyzed at the time of the cardiac CT examination. Body mass index (BMI) was calculated in each patient, and a BMI value of $\geq 25 \text{ kg/m}^2$ was deemed to be obese. Systolic blood pressure of $\geq 140 \text{ mmHg}$, diastolic blood pressure of $\geq 90 \text{ mmHg}$, or current use of an antihypertensive agent was considered hypertension. Current and previous smoking histories were reviewed. Total cholesterol of $\geq 200 \text{ mg/dL}$ was deemed to be hypercholesterolemia. A confirmed diagnosis of diabetes mellitus or current use of any antidiabetic medication was evaluated. Finally, the 10-year risk of coronary heart disease (CHD) was calculated using the Framingham Risk Score.^[19]

2.2. Cardiac CT examination and reconstruction

Cardiac CT examinations were performed using a Brilliance 64-slice CT scanner (Philips Medical Systems, Eindhoven, The Netherlands) from January 2009 to February 2011 or a Somatom Definition Flash dual-source 128-slice CT scanner (Siemens Healthcare, Forchheim, Germany) from March 2011 to April 2013.

Using the 64-slice CT scanner, nonenhanced imaging was performed using 120 kV and 55 mAs with prospective electrocardiogram (ECG) triggering to calculate calcium score and volume. Coronary computed tomography angiography (CCTA) was performed with retrospective ECG gating using the following parameters: detector collimation of $64 \times 0.625 \text{ mm}$, gantry rotation of 400 milliseconds, pitch of 0.2, tube voltage of 120 kV, and an effective tube current of 600 to 900 mA with ECG modulation. Contrast medium (80 mL, Iomeron 400; Bracco SPA, Milan, Italy) was administered intravenously, at a rate of 4.5 mL/s. Then, 40 mL of saline was administered.

Using the dual-source 128-slice CT scanner, nonenhanced imaging was performed using 120 kV and 80 mAs with tube current modulation. CCTA examinations were performed as described previously by our research group.^[20] A prospective ECG tube current modulation technique, based on the patient's BMI, and the Mindose[®] protocol (Siemens Healthcare) were used. Contrast medium was injected using a split-bolus technique: first, 60 to 80 mL of pure iodine-containing contrast material (Iomeron 400; Bracco SPA) was administered intravenously at 4.5 mL/s, based on the patient's body weight. Then, 40 mL of a 60%-to-40% mixture of contrast medium and saline was administered.

2.3. Cardiac CT image analysis

Cardiac CT images were assessed by a single observer with 15 years of experience in cardiac CT. For the CAC score, Agatston calcium scores were calculated using semiautomated software (EBW; Philips Medical Systems, Best, The Netherlands), which identified areas of at least 0.5 mm^2 and a density $\geq 130 \text{ HU}$ as calcification. The software also measured the corresponding calcified plaque volume.

To evaluate the coronary arteries, images at 75% R–R intervals were used primarily for image reconstruction. If there were severe motion artifacts, additional images at other cardiac

cycles were used to obtain a better-quality image. Maximum intensity projection, volume rendering, multiplanar reformation, and curved multiplanar reformation were routinely constructed using a commercial workstation (EBW, Philips Medical Systems). According to the American Heart Association classification, a 15-segment model was used. If the ramus intermedius was present, segment 16 was also used.^[21,22] Coronary segments with a diameter $>2.0 \text{ mm}$ were analyzed. However, if there were motion artifacts that lowered the image quality, nonevaluable segments were excluded from the analysis. Cardiac CT images were analyzed using a picture archiving and communication system. If an abnormal segment was identified, that coronary artery was evaluated using an Aquarius workstation (TeraRecon, San Mateo, CA) and the volume of noncalcified plaque was measured. Referring to previous studies,^[23–25] noncalcified plaques were divided into 2 categories based on the CT value (HU): low (0–49 HU; deemed a lipid-rich plaque) and intermediate attenuation compositions (50–129 HU; deemed a fibrous plaque). The plaques were color coded and the volume of each component was measured (Fig. 1). The color-coded area was adjusted manually, including the full thickness of the vessel wall, and surrounding tissues were excluded. The 2 curved multiplanar reconstruction images of the baseline and follow-up CT were displayed in parallel and then identical segments were compared side by side using the Aquarius workstation. The lesions were matched on baseline and follow-up images using adjacent anatomical landmarks. We also evaluated the intracoronary lumen density. The CT values of the proximal segments of the right coronary artery, left anterior descending artery, and left circumflex artery were measured and the mean intracoronary lumen density (HU) was calculated.

EFV was assessed by 2 observers with 3- or 10-year experience in cardiac CT. The observers were blinded to the patients' clinical histories, CAC scores, and CCTA results. Epicardial fat was defined as the adipose tissue between the surface of the myocardium and the visceral layer of the pericardium. The border of the epicardium was traced semiautomatically. The superior boundary of epicardial fat was set at the center of the right pulmonary artery,^[26] and the inferior extent was indicated by the end of the pericardial sac.^[24–27] The Aquarius software automatically constructed a 3-dimensional image of the epicardium (Fig. 2).^[28,29] EFV was quantified by calculating the total volume of the tissue in which the CT density ranged from -190 to -30 HU within the epicardium.^[7,8,14,16,17,27] EFV was reported in cubic centimeters and indexed (EFVi) to body surface area.^[30]

2.4. Statistical analysis

The Excel 2010 software (Microsoft Corp, Redmond, WA) was used for data collection. Continuous measures are presented as means \pm standard deviations. Comparisons of data between baseline and follow-up were performed using the χ^2 test for categorical data and the paired *t* test for continuous variables. Interobserver agreement was estimated using the intraclass correlation coefficient (ICC). Relationships between clinical variables, EFVi, and plaque volume were explored by regression analysis. Annual changes in plaque volume and EFVi were calculated for each plaque by subtracting the values measured at baseline CT from the values measured at follow-up. Then, the difference value was divided by the time elapsed between the 2 CT scans. Annual change values in the highest tertile for each plaque volume were considered to indicate rapid increases in plaque

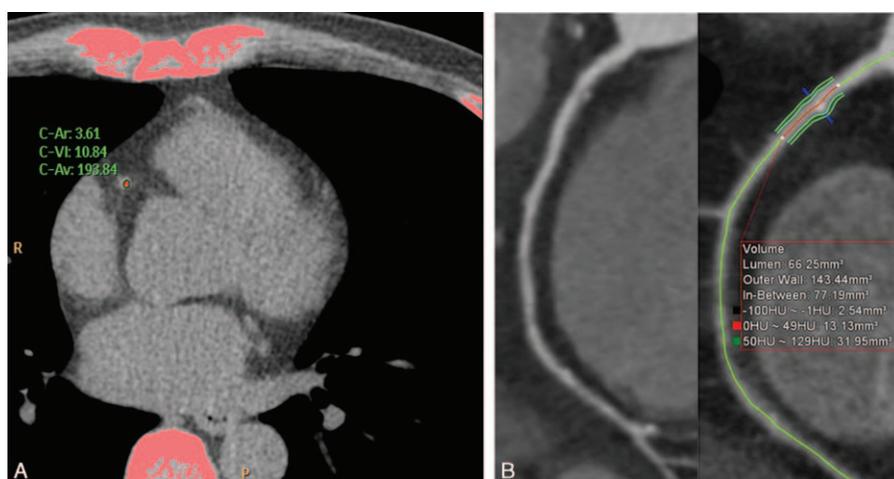


Figure 1. A 54-year-old male patient with low pretest probability underwent calcium score CT (A) and coronary CT angiography (B). (A) The semiautomated software was used to identify an area of at least 0.5 mm^2 with a density $\geq 130\text{ HU}$ as calcified plaque, and then to measure the coronary calcium score and volume. The calcified plaque volume of the patient was 13.61 mm^3 . (B) Noncalcified plaque volume was measured on coronary CT angiography. Noncalcified plaque was color-coded according to CT value (HU) and classified into low attenuation plaque ($0\text{--}49\text{ HU}$; designated as lipid-rich plaque) and intermediate attenuation plaque ($50\text{--}129\text{ HU}$; designated as fibrous plaque). Lipid-rich and fibrous plaque volumes of the patient were 13.13 and 31.95 mm^3 , respectively. CT = computed tomography.

volume. Logistic regression analysis was used to determine whether baseline clinical variables and EFVi were predictors of rapid increase in plaque volume. Variables that achieved significance in the univariate analysis were included in a stepwise logistic regression analysis. Statistical analyses were performed using MedCalc (version 13.1.2.0; MedCalc Software, Maria-kerke, Belgium). A P value <0.05 was considered to indicate statistical significance.

3. Results

The baseline patient characteristics are listed in Table 1. The mean age of the study population was 54.8 ± 7.9 years at the baseline examination and 56.5 ± 7.9 years at the follow-up examination. The mean interval between the baseline and the follow-up CT was 25.5 ± 15.7 months. The study included 69 (79.3%) males.

The ICC for interobserver agreement was 0.975 (95% confidence interval: 0.962, 0.984) for baseline EFV and 0.970 (95% confidence interval: 0.954, 0.980) for follow-up EFV. Both baseline and follow-up EFVi were positively correlated with age and BMI (Table 2). With the exception of lipid-rich plaque volume on follow-up CT, no index of plaque volume was correlated with EFVi. Comparisons between the baseline and follow-up examination results are provided in Table 3. CAC score and coronary plaque volumes increased significantly ($P = 0.010$ to <0.001) on follow-up CT. The mean annual change values were $4.1 \pm 26.8\text{ mm}^3/\text{y}$ for lipid-rich plaque, $5.9 \pm 26.8\text{ mm}^3/\text{y}$ for fibrous plaque, and $15.1 \pm 27.0\text{ mm}^3/\text{y}$ for calcified plaque volume. However, EFV (116.0 ± 37.5 vs $116.6 \pm 37.4\text{ cm}^3$, $P = 0.604$) and EFVi (65.7 ± 21.8 vs $66.0 \pm 21.8\text{ cm}^3/\text{m}^2$, $P = 0.620$) change values between baseline and follow-up CT were not significant. The mean intracoronary lumen density was not

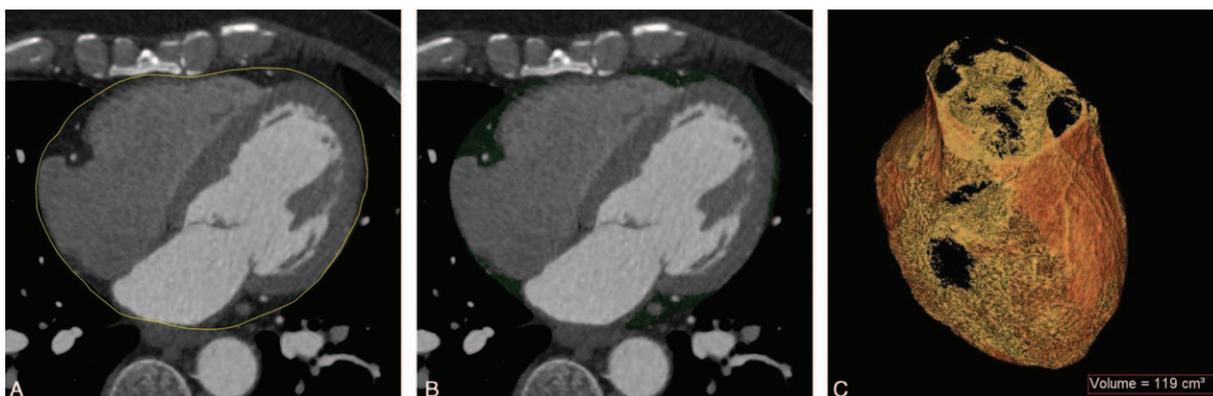


Figure 2. A 50-year-old male patient with low pretest probability. Epicardial fat was defined as the adipose tissue between the surface of the myocardium and the visceral layer of the pericardium. (A) The border of the epicardium (yellow line) was traced semiautomatically. (B) EFV was quantified by calculating the total volume of the tissue (green color) showing a CT density of -190 to -30 HU within the epicardium. (C) The computer software constructed a 3-dimensional image of the epicardial fat automatically, with the data reported in cubic centimeters. The EFV of the patient was 119 cm^3 , and that indexed to body surface area (EFVi; 1.91 m^2) was $62.3\text{ m}^3/\text{m}^2$. CT = computed tomography, EFV = epicardial fat volume, EFVi = indexed epicardial fat volume.

Table 1
Baseline clinical characteristics of the patients (n=87).

Characteristics	Values
Age, y	54.8 ± 7.9
Male/female	69/18
Agatston calcium score, n (%)	
0	31 (35.6)
1–10	17 (19.5)
10–100	25 (28.7)
100–400	14 (16.1)
Symptom, n (%)	
Atypical chest pain	17 (19.5)
Nonanginal pain	14 (16.1)
Asymptomatic	56 (64.4)
Pretest probability, n (%)	
Intermediates	30 (34.5)
Low	55 (63.2)
Very low	2 (2.3)

Values are means ± standard deviations or n (%).

significantly different (424.5 ± 58.1 vs 430.3 ± 78.8 HU, *P* = 0.811) between baseline and follow-up CT examinations.

The mean annual changes in EFV and EFVi were 0.8 ± 8.0 cm³/y and 0.5 ± 4.8 cm³/m²/y, respectively. The annual change in EFVi was not accompanied by a parallel change in coronary plaque volume (*P* = 0.286 for lipid-rich plaque, 0.500 for fibrous plaque, and 0.096 for calcified plaque) (Fig. 3). The mean annual change values in plaque volume in the highest tertile were 32.4 ± 17.9 mm³/y for lipid-rich plaque, 32.6 ± 18.5 mm³/y for fibrous plaque, and 39.5 ± 35.3 mm³/y for calcified plaque (Table 4).

On univariate analysis, predictors of rapid increases in lipid-rich and fibrous plaque volumes were smoking, hypercholesterolemia, 10-year CHD risk, obesity, and baseline EFVi (Table 5). Diabetes mellitus was the only significant predictor of a rapid increase in calcified plaque volume. On multivariate analysis, 10-year CHD risk was an independent predictor of rapid increases in lipid-rich (odds ratio [OR] = 1.184, *P* = 0.002) and fibrous (OR = 1.413, *P* < 0.001) plaque volume. Baseline EFVi (OR = 1.029, *P* = 0.016) was an independent predictor of a rapid increase in lipid-rich plaque volume, but not fibrous plaque volume (Table 6).

Table 2
Correlations between clinical variables and indexed epicardial fat volume.

	Baseline EFVi		Follow-up EFVi	
	R ²	P	R ²	P
Age, y	0.165	<0.001*	0.155	<0.001*
Systolic BP, mm Hg	0.001	0.730	0.066	0.016*
Diastolic BP, mm Hg	0.013	0.289	0.010	0.363
Total cholesterol, mg/dL	0.001	0.748	<0.001	0.862
HDL cholesterol, mg/dL	<0.001	0.974	<0.001	0.859
10-y CHD risk, %	0.019	0.199	0.055	0.029*
BMI, g/m ²	0.076	0.010*	0.053	0.033*
Agatston calcium score	0.001	0.754	<0.001	0.997
Noncalcified plaque volume, mm ³	<0.001	0.905	0.027	0.129
Lipid-rich plaque volume, mm ³	0.011	0.324	0.052	0.033*
Fibrous plaque volume, mm ³	0.004	0.583	0.008	0.397
Calcified plaque volume, mm ³	0.002	0.706	<0.001	0.977

BMI = body mass index, BP = blood pressure, CHD = coronary heart disease, EFVi = indexed epicardial fat volume, HDL = high-density lipoprotein.

* Statistically significant (*P* < 0.05).

Table 3
Serial change in clinical variables and computed tomography measurements.

	Baseline	Follow-up	P
Age, y	54.8 ± 7.9	56.5 ± 7.9	<0.001*
Systolic BP, mm Hg	125.6 ± 13.0	126.6 ± 16.1	0.559
Smoking	35	34	0.870
DM	27	27	1.000
Total cholesterol, mg/dL	179.0 ± 35.4	181.4 ± 31.6	0.504
HDL cholesterol, mg/dL	46.6 ± 9.0	45.4 ± 9.0	0.253
10-y risk, %	10.4 ± 5.7	11.5 ± 6.1	0.057
BMI, g/m ²	25.1 ± 3.3	25.2 ± 3.3	0.364
Agatston calcium score	42.6 ± 79.4	74.1 ± 117.5	<0.001*
Calcified plaque volume, mm ³	41.8 ± 69.8	68.7 ± 100.5	<0.001*
Noncalcified plaque volume, mm ³	111.2 ± 93.4	142.0 ± 105.5	0.004*
Lipid-rich plaque volume, mm ³	48.2 ± 41.6	62.4 ± 52.1	0.010*
Fibrous plaque volume, mm ³	63.0 ± 54.3	79.6 ± 58.5	0.003*
EFV, cm ³	116.0 ± 37.5	116.6 ± 37.4	0.604
EFVi, cm ³ /m ²	65.7 ± 21.8	66.0 ± 21.8	0.620
Intracoronary lumen density, HU	424.5 ± 58.1	430.3 ± 78.8	0.811

BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, EFV = epicardial fat volume, EFVi = indexed epicardial fat volume, HDL = high-density lipoprotein.

* Statistically significant (*P* < 0.05).

4. Discussion

Epicardial fat tissue produces several different hormones, adipokines, and vasoactive substances.^[2] The development of coronary atherosclerosis is linked to EFV.^[3–5] Several previous studies reported a relationship between EFV and coronary plaque or CAD.^[10–12,29] Djaber et al^[10] reported that EFV is a significant predictor of coronary atherosclerosis after adjusting for CV risk factors. Sarin et al^[11] and Iwasaki et al^[12] showed that higher EFV (>100 mL) was associated with the presence and severity of CAD. Bastarrika et al^[29] showed that patients with significant coronary artery stenosis had significantly greater EFV than those without significant CAD. However, there have been no previous studies on the relationship between EFV and coronary plaque volume. To the best of our knowledge, the present study is the first to assess this relationship.

First, we investigated the relationship between EFVi and coronary plaque volume and found that EFVi was correlated

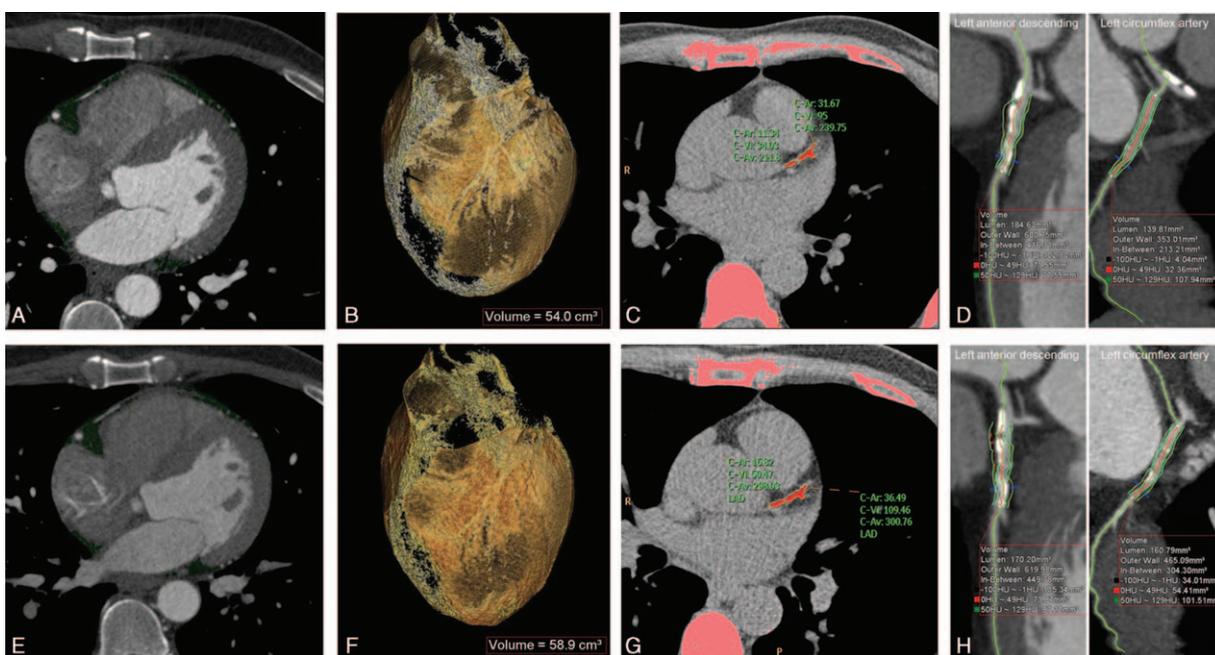


Figure 3. A 43-year-old male patient with an intermediate pretest probability underwent baseline cardiac CT (A–D). The baseline EFV was 54.0 cm³ (A, B), calcified plaque volume was 380.1 mm² (C), and noncalcified plaque volume (D) was 289.4 mm² (lipid-rich plaque volume, 103.9 mm²; fibrous plaque volume, 185.5 mm²). After 31 months, follow-up CT images (E–H) showed no rapid annual change in EFV (Δ 1.9 cm³/y) or EFVi (Δ 1.0 cm³/m²/y). Although the calcified plaque volume (Δ 62.9 mm²/y) increased rapidly, the noncalcified plaque volume (lipid-rich plaque volume, Δ 9.4 mm²/y; fibrous plaque volume, Δ 1.2 mm²/y) did not. CT = computed tomography, EFV = epicardial fat volume, EFVi = indexed epicardial fat volume.

significantly and positively with age and BMI, which accords with previous reports of a strong association between EFV and obesity^[2] and BMI.^[31,32] However, with the exception of lipid-rich plaque volume on follow-up CT, no index of plaque volume was correlated with EFVi (Table 2). Second, we investigated serial changes in EFVi and coronary plaque volume, which could be helpful to determine the relationship between EFVi change and coronary plaque progression. The EFVi did not change significantly from baseline to the time of follow-up CT, although plaque volumes increased significantly on follow-up CT (Table 3). Therefore, the annual change in EFVi was not accompanied ($P = 0.096-0.500$) by a parallel change in any index of coronary plaque volume. Third, we investigated whether baseline characteristics, including EFVi, were predictors of rapid increase in plaque volume. In addition to smoking, hypercholesterolemia,

10-year CHD risk (Framingham Risk Score), and obesity, baseline EFVi was a predictor of rapid increases in lipid-rich and fibrous plaque volumes on univariate analysis (Table 5). After controlling for CV risk factors, baseline EFVi remained a significant independent predictor of a rapid increase in lipid-rich plaque volume (Table 6). However, baseline EFVi was not an independent predictor of a rapid increase in fibrous plaque volume.

CAC score measured by MDCT may reflect the overall burden of coronary atherosclerosis and may predict the risk of future CV events better than the Framingham Risk Score.^[33] An association between a high CAC score and large EFV has been reported by several studies.^[6-9] Gorter et al^[6] and Bettencourt et al^[9] observed that EFV was positively related to the CAC score. Ahmadi et al^[7] observed that EFV was higher in both males and

Table 4
Plaque and epicardial fat volume according to tertile group.

Measurements	Lowest tertile	Mid tertile	Highest tertile
Baseline lipid-rich plaque volume, mm ³	4.6 ± 4.7 (0.0–15.1)	42.4 ± 14.7 (17.5–62.9)	97.6 ± 23.5 (63.0–141.2)
Follow-up lipid-rich plaque volume, mm ³	9.0 ± 8.8 (0.0–28.3)	54.4 ± 14.8 (28.4–77.6)	123.8 ± 33.1 (79.3–194.1)
Lipid-rich plaque volume change, mm ³ /y	-20.9 ± 19.5 (-72.5 to -3.5)	0.8 ± 3.2 (-3.1 to 9.3)	32.4 ± 17.9 (12.3–76.3)
Baseline fibrous plaque volume, mm ³	5.7 ± 5.8 (0.0–22.2)	56.1 ± 21.3 (22.4–87.3)	127.2 ± 29.3 (87.6–188.6)
Follow-up fibrous plaque volume, mm ³	13.3 ± 13.5 (0.0–42.5)	78.9 ± 18.2 (43.2–106.2)	146.6 ± 28.1 (109.1–199.7)
Fibrous plaque volume change, mm ³ /y	-18.7 ± 21.9 (-85.4 to -1.2)	3.9 ± 4.9 (-0.7 to 13.5)	32.6 ± 18.5 (15.2–89.7)
Baseline calcified plaque volume, mm ³	0.0 ± 0.0 (0.0–0.0)	12.0 ± 9.7 (0.0–32.5)	113.5 ± 82.6 (37.3–342.3)
Follow-up calcified plaque volume, mm ³	1.7 ± 3.3 (0.0–9.2)	29.5 ± 18.2 (9.7–67.5)	175.0 ± 112.8 (67.8–543.0)
Calcified plaque volume change, mm ³ /y	-1.3 ± 4.6 (-18.7 to 1.7)	7.1 ± 3.4 (2.0–12.6)	39.5 ± 35.3 (12.9–167.5)
Baseline EFVi, cm ³	44.4 ± 5.7 (34.2–53.1)	62.0 ± 6.9 (53.4–72.5)	90.6 ± 15.9 (73.1–134.5)
Follow-up EFVi, cm ³	45.2 ± 6.1 (43.3–54.1)	61.9 ± 5.0 (54.5–70.5)	90.9 ± 17.1 (70.8–135.1)
EFVi change, cm ³ /y	-4.1 ± 3.1 (-14.9 to -1.0)	0.2 ± 0.7 (-0.8 to 1.4)	5.4 ± 3.7 (1.5–14.2)

Values are mean ± standard deviation (range). EFVi = indexed epicardial fat volume.

Table 5

OR for prediction of rapid plaque increases (univariate analysis).

	Lipid-rich plaque		Fibrous plaque		Calcified plaque	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	1.025 (0.969–1.085)	0.389	1.033 (0.976–1.093)	0.262	1.046 (0.988–1.108)	0.120
Hypertension	2.510 (0.721–8.743)	0.153	1.523 (0.432–5.370)	0.517	1.094 (0.315–3.799)	0.888
Smoking	3.148 (1.248–7.939)	0.014*	3.947 (1.543–10.096)	0.003*	2.036 (0.821–5.045)	0.124
DM	1.269 (0.490–3.288)	0.625	1.604 (0.623–4.130)	0.329	3.231 (1.244–8.393)	0.015*
Hypercholesterolemia	3.388 (1.240–9.258)	0.017*	5.833 (2.056–16.551)	<0.001*	0.503 (0.164–1.536)	0.212
Low HDL	0.459 (0.137–1.535)	0.186	0.459 (0.137–1.535)	0.186	0.655 (0.210–2.039)	0.456
10-y CHD risk	1.198 (1.076–1.335)	<0.001*	1.397 (1.198–1.628)	<0.001*	1.055 (0.975–1.142)	0.177
Obesity	2.678 (1.069–6.710)	0.033*	2.678 (1.069–6.710)	0.033*	0.933 (0.381–2.284)	0.879
Statin treatment	0.855 (0.329–2.222)	0.747	1.080 (0.421–2.771)	0.872	1.358 (0.534–3.455)	0.522
Baseline EFVi	1.032 (1.009–1.055)	0.004*	1.023 (0.001–1.045)	0.032*	1.014 (0.994–1.035)	0.181

CHD = coronary heart disease, CI = confidence interval, DM = diabetes mellitus, EFVi = indexed epicardial fat volume, HDL = high-density lipoprotein, OR = odds ratio.

* Statistically significant ($P < 0.05$).

females with higher CAC scores. However, in our study, EFV was not significantly related to CAC score or calcified plaque volume. Nakanishi et al^[27] reported that an increase in EFV was associated with a greater progression of CAC. At follow-up, EFV, EFVi, and the degree of change in EFVi (%) were higher in the high progression group than in the low progression group. However, our result does not accord with this previous report.^[27] In our study, the increase in calcified plaque volume was not accompanied by an increase in EFVi in serial studies (Fig. 3). Yerramasu et al^[34] reported that the median EFV was significantly higher in patients who progressed compared with in those who did not progress (93.1 vs 68.8 cm³, respectively, $P < 0.001$). However, our results showed that baseline EFVi did not predict a rapid increase in calcified plaque volume. Our data agree with the results of Otaki et al^[30] who reported that neither baseline EFV nor the change in EFV over time was associated with accumulation of CAC after a median follow-up of 4 years in low-risk patients.

Despite extensive research, the mechanistic understanding of atherosclerotic calcification in humans remains limited.^[35] In the progression of atherosclerotic lesions, recurrent plaque rupture and hemorrhage with subsequent healing might lead to calcified plaque.^[36] In addition, CAC growth under treatment with statins represents plaque repair rather than continuing plaque expansion.^[37] Therefore, calcified plaque seems to arise from preexisting plaque. Lipid-rich plaque, however, occurs relatively early in the process of atherosclerosis, which might be more affected by EFV compared with calcified plaque. In a report by Greif et al,^[38] EFV was elevated in patients with exclusively noncalcified plaque, compared to in those with mixed and

calcified plaque. It is therefore likely that EFV is associated with plaque formation per se, rather than plaque calcification.^[34]

Rajani et al^[17] reported that EFV is greater in patients with coronary plaque. However, they compared patient groups with and without coronary plaque. In contrast, our study population included only patients with coronary plaque. Moreover, they evaluated it according to coronary plaque type. However, plaque can also mix with various components, the volume of which we measured in our study. Therefore, the predictive ability of EFVi in our study is relevant to the plaque composition, but not the type of plaque.

In previous reports,^[39–42] the association between epicardial fat and CAD has been evaluated using echocardiography. However, assessment of epicardial fat by echocardiography is not optimal, because the method is highly acoustic and time-window-dependent, is associated with difficulties in differentiating between epicardial and pericardial fat,^[43] and has low reproducibility.^[44] MDCT is a more accurate and highly reproducible method of quantifying EFV due to its higher spatial resolution.^[45,46] However, volumetric quantification of epicardial fat using CT is time-consuming, requires an advanced cardiac imaging workstation, and should be performed only by an experienced observer.^[47] Manual tracing of the pericardium is also somewhat difficult at the bifurcation level of the pulmonary artery, and there may be a partial volume averaging effect near the diaphragm. Nevertheless, in our study, the ICC for interobserver agreement was very high (0.975 for baseline EFV and 0.970 for follow-up EFV).

This study had several limitations that should be considered. First, the study was a retrospective observational trial with a limited number of heterogeneous patients. Therefore, potential biases cannot be ruled out despite use of multivariate regression analysis, especially because the model has not been evaluated. Second, the study population was derived from a single center, and was composed exclusively of ethnic Koreans who were referred for CCTA. Therefore, the results cannot be generalized to a wider population. Third, information regarding lifestyle (e.g., dietary changes and exercise) and treatment that may have affected EFV was not available. However, the EFVi was indexed by body surface area to correct for weight fluctuations between CT examinations. Fourth, it is somewhat doubtful that the accuracy of CCTA is sufficient for detecting small noncalcified atherosclerotic plaques. In addition, the CT density of the plaque can be affected by the contrast media used within the coronary artery,^[48] and serial MDCT for obtaining EFV is subject to

Table 6

OR for prediction of rapid plaque increases (multivariate analysis).

	Lipid-rich plaque		Fibrous plaque	
	OR (95% CI)	P	OR (95% CI)	P
10-y CHD risk	1.184 (1.062–1.320)	0.002*	1.413 (1.201–1.663)	<0.001*
Obesity	Not included in the model		3.757 (1.141–12.370)	0.030*
Baseline EFVi	1.029 (1.005–1.053)	0.016*	Not included in the model	

CHD = coronary heart disease, CI = confidence interval, EFVi = indexed epicardial fat volume, OR = odds ratio.

* Statistically significant ($P < 0.05$).

interscan variability. Regarding this limitation, we found that the intracoronary lumen density was not significantly different ($P=0.811$) between baseline and follow-up CT examinations. Finally, we did not evaluate stenosis severity or plaque instability.

In conclusion, in addition to the 10-year CHD risk based on the Framingham Risk Score, EFVi was shown to be an independent predictor of a rapid increase in lipid-rich plaque volume. However, changes in EFVi were not associated with parallel changes in coronary plaque volume.

References

- Bertaso AG, Bertol D, Duncan BB, et al. Epicardial fat: definition, measurements and systematic review of main outcomes. *Arq Bras Cardiol* 2013;101:e18–28.
- Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003;108:2460–6.
- Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685–95.
- Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007;153:907–17.
- Alexopoulos N, Katritsis D, Raggi P. Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis. *Atherosclerosis* 2014;233:104–12.
- Gorter PM, de Vos AM, van der Graaf Y, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. *Am J Cardiol* 2008;102:380–5.
- Ahmadi N, Nabavi V, Yang E, et al. Increased epicardial, pericardial, and subcutaneous adipose tissue is associated with the presence and severity of coronary artery calcium. *Acad Radiol* 2010;17:1518–24.
- Dey D, Wong ND, Tamarappoo B, et al. Computer-aided non-contrast CT-based quantification of pericardial and thoracic fat and their associations with coronary calcium and metabolic syndrome. *Atherosclerosis* 2010;209:136–41.
- Bettencourt N, Toschke AM, Leite D, et al. Epicardial adipose tissue is an independent predictor of coronary atherosclerotic burden. *Int J Cardiol* 2012;158:26–32.
- Djaberi R, Schuijff JD, van Werkhoven JM, et al. Relation of epicardial adipose tissue to coronary atherosclerosis. *Am J Cardiol* 2008;102:1602–7.
- Sarin S, Wenger C, Marwaha A, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am J Cardiol* 2008;102:767–71.
- Iwasaki K, Matsumoto T, Aono H, et al. Relationship between epicardial fat measured by 64-multidetector computed tomography and coronary artery disease. *Clin Cardiol* 2011;34:166–71.
- Alexopoulos N, McLean DS, Janik M, et al. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis* 2010;210:150–4.
- Okada K, Ohshima S, Isobe S, et al. Epicardial fat volume correlates with severity of coronary artery disease in nonobese patients. *J Cardiovasc Med (Hagerstown)* 2014;15:384–90.
- Oka T, Yamamoto H, Ohashi N, et al. Association between epicardial adipose tissue volume and characteristics of noncalcified plaques assessed by coronary computed tomographic angiography. *Int J Cardiol* 2012;161:45–9.
- Ito T, Suzuki Y, Ehara M, et al. Impact of epicardial fat volume on coronary artery disease in symptomatic patients with a zero calcium score. *Int J Cardiol* 2013;167:2852–8.
- Rajani R, Shmilovich H, Nakazato R, et al. Relationship of epicardial fat volume to coronary plaque, severe coronary stenosis, and high-risk coronary plaque features assessed by coronary CT angiography. *J Cardiovasc Comput Tomogr* 2013;7:125–32.
- Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 2003;41:159–68.
- Min JK, Lin FY, Gidseg DS, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the warranty period for remaining normal? *J Am Coll Cardiol* 2010;55:1110–7.
- Cho JY, Sun JS, Sur YK, et al. Relationship between left ventricular mass and coronary artery disease in young adults: a single-center study using cardiac computed tomography. *Int J Cardiovasc Imaging* 2015;31:187–96.
- Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51:5–40.
- Hamdan A, Asbach P, Wellnhofer E, et al. A prospective study for comparison of MR and CT imaging for detection of coronary artery stenosis. *JACC Cardiovasc Imaging* 2011;4:50–61.
- Bauer RW, Thilo C, Chiaramida SA, et al. Noncalcified atherosclerotic plaque burden at coronary CT angiography: a better predictor of ischemia at stress myocardial perfusion imaging than calcium score and stenosis severity. *AJR Am J Roentgenol* 2009;193:410–8.
- Blackmon KN, Streck J, Thilo C, et al. Reproducibility of automated noncalcified coronary artery plaque burden assessment at coronary CT angiography. *J Thorac Imaging* 2009;24:96–102.
- Oberoi S, Meinel FG, Schoepf UJ, et al. Reproducibility of noncalcified coronary artery plaque burden quantification from coronary CT angiography across different image analysis platforms. *AJR Am J Roentgenol* 2014;202:W43–9.
- Apfaltrer P, Schindler A, Schoepf UJ, et al. Comparison of epicardial fat volume by computed tomography in black versus white patients with acute chest pain. *Am J Cardiol* 2014;113:422–8.
- Nakanishi R, Rajani R, Cheng VY, et al. Increase in epicardial fat volume is associated with greater coronary artery calcification progression in subjects at intermediate risk by coronary calcium score: a serial study using non-contrast cardiac CT. *Atherosclerosis* 2011;218:363–8.
- Park MJ, Jung JI, Oh YS, et al. Assessment of epicardial fat volume with threshold-based 3-dimensional segmentation in CT: comparison with the 2-dimensional short axis-based method. *Korean Circ J* 2010;40:328–33.
- Bastarrrika G, Broncano J, Schoepf UJ, et al. Relationship between coronary artery disease and epicardial adipose tissue quantification at cardiac CT: comparison between automatic volumetric measurement and manual bidimensional estimation. *Acad Radiol* 2010;17:727–34.
- Otaki Y, Rajani R, Cheng VY, et al. The relationship between epicardial fat volume and incident coronary artery calcium. *J Cardiovasc Comput Tomogr* 2011;5:310–6.
- Alexopoulos N, Melek BH, Arepalli CD, et al. Effect of intensive versus moderate lipid-lowering therapy on epicardial adipose tissue in hyperlipidemic post-menopausal women: a substudy of the BELLES trial (Beyond Endorsed Lipid Lowering with EBT Scanning). *J Am Coll Cardiol* 2013;61:1956–61.
- Nakazato R, Rajani R, Cheng VY, et al. Weight change modulates epicardial fat burden: a 4-year serial study with noncontrast computed tomography. *Atherosclerosis* 2012;220:139–44.
- Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;291:210–5.
- Yerramasu A, Dey D, Venuraju S, et al. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. *Atherosclerosis* 2012;220:223–30.
- Otsuka F, Sakakura K, Yahagi K, et al. Has our understanding of calcification in human coronary atherosclerosis progressed? *Arterioscler Thromb Vasc Biol* 2014;34:724–36.
- Stary HC. Natural history and histological classification of atherosclerotic lesions: an update. *Arterioscler Thromb Vasc Biol* 2000;20:1177–8.
- Henein M, Granåsen G, Wiklund U, et al. High dose and long-term statin therapy accelerate coronary artery calcification. *Int J Cardiol* 2015;184:581–6.
- Greif M, Becker A, von Ziegler F, et al. Pericardial adipose tissue determined by dual source CT is a risk factor for coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2009;29:781–6.
- Chaowalit N, Somers VK, Pellikka PA, et al. Subepicardial adipose tissue and the presence and severity of coronary artery disease. *Atherosclerosis* 2006;186:354–9.
- Ahn SG, Lim HS, Joe DY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. *Heart* 2008;94:e7.
- Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. *J Am Soc Echocardiogr* 2009;22:1311–9.
- Park JS, Choi SY, Zheng M, et al. Epicardial adipose tissue thickness is a predictor for plaque vulnerability in patients with significant coronary artery disease. *Atherosclerosis* 2013;226:134–9.

- [43] Abbara S, Desai JC, Cury RC, et al. Mapping epicardial fat with multidetector computed tomography to facilitate percutaneous transepticardial arrhythmia ablation. *Eur J Radiol* 2006;57:417–22.
- [44] Saura D, Oliva MJ, Rodríguez D, et al. Reproducibility of echocardiographic measurements of epicardial fat thickness. *Int J Cardiol* 2010;141:311–3.
- [45] Rossner S, Bo WJ, Hiltbrandt E, et al. Adipose tissue determinations in cadavers—a comparison between cross-sectional planimetry and computed tomography. *Int J Obes* 1990;14:893–902.
- [46] Gorter PM, van Lindert AS, de Vos AM, et al. Quantification of epicardial and peri-coronary fat using cardiac computed tomography; reproducibility and relation with obesity and metabolic syndrome in patients suspected of coronary artery disease. *Atherosclerosis* 2008;197:896–903.
- [47] Yorgun H, Canpolat U, Hazırolan T, et al. Epicardial adipose tissue thickness predicts descending thoracic aorta atherosclerosis shown by multidetector computed tomography. *Int J Cardiovasc Imaging* 2012;28:911–9.
- [48] Cademartiri F, Mollet NR, Runza G, et al. Influence of intracoronary attenuation on coronary plaque measurements using multislice computed tomography: observations in an ex vivo model of coronary computed tomography angiography. *Eur Radiol* 2005;15:1426–31.