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Association between High Pericoronary Adipose Tissue Computed Tomography Attenuation and Impaired Flow-Mediated Dilation of the Brachial Artery

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Aims: Pericoronary adipose tissue (PCAT) attenuation on coronary computed tomography angiography (CTA) is a noninvasive biomarker for pericoronary inflammation and is associated with cardiac mortality. We aimed to investigate the association between PCAT attenuation and endothelial dysfunction assessed using flow-mediated dilation (FMD).

Methods: A total of 119 outpatients who underwent both coronary CTA and FMD measurements were examined. PCAT attenuation values were assessed at the proximal 40-mm segments of all three major coronary arteries on coronary CTA. Endothelial function was assessed using FMD. Patients were then classified into two groups: those with endothelial dysfunction (FMD $<4\%$, $n=44$) and those without endothelial dysfunction (FMD $\geq 4\%$, $n=75$).

Results: In all three coronary arteries, PCAT attenuation was significantly higher in patients with endothelial dysfunction than in those without endothelial dysfunction. Multivariate logistic regression analysis revealed that PCAT attenuation in the right coronary artery (odds ratio [OR]=1.543; 95% confidence interval [CI]=1.004–2.369, $p=0.048$) and left anterior descending artery (OR=1.525, 95% CI=1.004–2.369, $p=0.049$) was an independent predictor of endothelial dysfunction. Subgroup analysis of patients with adverse CTA findings (significant stenosis and/or high-risk plaque) and those with coronary artery calcium score >100 showed that high PCAT attenuation in all three coronary arteries was a significant predictor of endothelial dysfunction.

Conclusion: High PCAT attenuation was significantly associated with FMD-assessed endothelial dysfunction in patients with suspected coronary artery disease. Our results suggest that endothelial dysfunction is one of the pathophysiological mechanisms linking pericoronary inflammation to cardiac mortality.

Key words: Coronary computed tomography angiography, Perivascular coronary inflammation, Endothelial dysfunction, Flow-mediated dilation

Introduction

Coronary computed tomography angiography (CTA) is now recommended as a first-line test in patients with stable chest pain[1, 2]. This is due to its effectiveness in the diagnosis of coronary artery disease and due to its risk stratification. Recently, change in pericoronary adipose tissue (PCAT) attenuation, assessed on coronary CTA, was introduced as a novel indicator of localized coronary inflammation[3]. PCAT represents the epicardial adipose tissue, which directly surrounds the coronary arteries. Compared with

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pericardial fat, PCAT plays a more local and direct role in coronary atherosclerosis due to its anatomical proximity to the coronary arterial wall. In the presence of vascular inflammation, inflammatory molecules from the inflamed coronary wall diffuse into the PCAT, leading to smaller adipocytes with a lower lipid content and higher aqueous content[4]. These inflammatory changes of the adipose tissue cause an increase in computed tomography (CT) attenuation of PCAT, which can be identified by coronary CTA examination. The Cardiovascular RISk Prediction using Computed Tomography (CRISP-CT) study showed that high PCAT attenuation indicates a significant risk factor for increased cardiovascular events. It also offered an incremental prognostic value over coronary CTA alone[5]. Despite this encouraging evidence, the mechanisms by which high PCAT attenuation suggests an increased risk of cardiovascular events remain unclear. Recent studies have indicated that one of these mechanisms could have a strong association with coronary endothelial dysfunction[6, 7]. However, there is no report on the relationship between PCAT attenuation and coronary endothelial function.

Endothelial dysfunction plays an important role in the development of atherogenesis and destabilization of established plaques[8]. This dysfunction has been detected in coronary arteries and the resistance arteries[9]. Measurement of the flow-mediated dilation (FMD) of the brachial artery is a useful and noninvasive method for assessing endothelial function. Endothelial dysfunction, measured by FMD of the brachial artery, is established as an independent predictor of future cardiovascular events not only in primary prevention settings but also in patients with advanced atherosclerosis[10-12]. Furthermore, previous studies have demonstrated a significant correlation between endothelial function assessed by FMD of the brachial artery and coronary endothelial function[13, 14].

Aim

Herein, we hypothesized that high PCAT attenuation on coronary CTA was associated with endothelial dysfunction, assessed by FMD of the brachial artery. We tested this hypothesis in a cohort of patients with suspected coronary artery disease who underwent both FMD measurements and coronary CTAs, with the aim of clarifying the mechanisms by which pericoronary inflammation increases the risk of cardiovascular events.

Methods

Population Study

This was a single-center retrospective study. We recruited 131 outpatients with suspected stable coronary artery disease from Okayama University Hospital, who underwent clinically indicated FMD measurement and coronary CTA between August 2011 and September 2015. Our exclusion criteria were as follows: (1) patients with ages <30 years, (2) serum creatine levels ≥ 1.5 mg/dL, (3) patients with a history of percutaneous coronary intervention or coronary bypass surgery graft, and (4) the duration between FMD measurement and coronary CTA was >60 days. **Supplemental Fig. 1** shows the flow diagram of the study design. Finally, 119 patients were analyzed in this study. Of these, 76 patients (64%) had chest pain [cardiac ($n=20$), possibly cardiac or noncardiac ($n=56$)], and 43 (36%) had no symptoms but was suspected to have coronary artery disease due to abnormalities found in other tests, such as the electrocardiogram or stress electrocardiogram. Of 20 patients with cardiac chest pain, the distribution of Canadian Cardiovascular Society classes I, II, III, and IV was 45% ($n=9$), 45% ($n=9$), 10% ($n=2$), and 0% ($n=0$), respectively. The median duration between FMD measurement and coronary CTA examination was 7 days (interquartile range, 2–16 days).

This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committees of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. The requirement for informed consent was waived due to the low-risk nature of the study and the inability to obtain consent directly from all participants. Instead, we described the protocol extensively at Okayama University Hospital and on the hospital website (http://okayama-u-cvm.jp/) and provided patients with the opportunity to withdraw from the study.

Measurement of FMD of the Brachial Artery

We measured FMD of the brachial artery using a 10-MHz linear-array transducer probe (Unex Company Ltd., Nagoya, Japan) in all patients, as previously described[15]. We recorded longitudinal images of the brachial artery at baseline with a stereotactic arm. Artery diameter was measured after supine rest for ≥ 5 min, from clear anterior (media adventitia) and posterior (intima media) interfaces, which were determined manually. We performed suprasystolic compression (50 mmHg higher than systolic blood pressure) on the right forearm for 5 min and measured the artery diameter continuously from

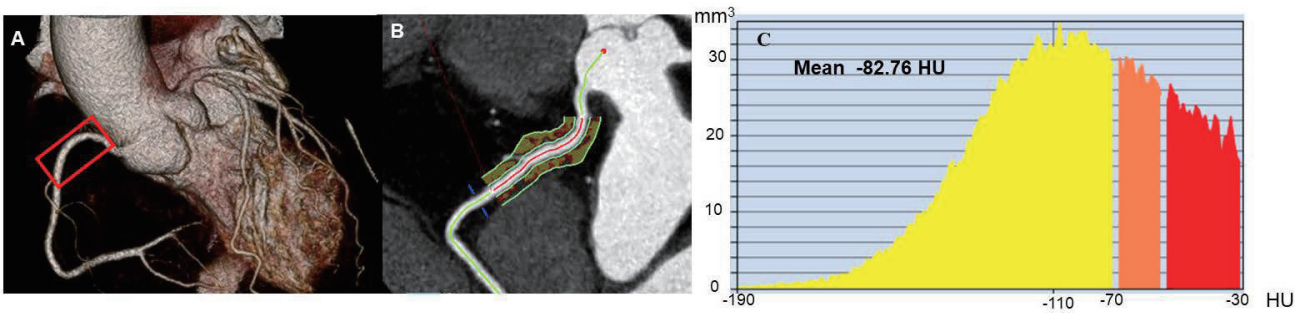

Fig. 1. Representative case of pericoronary adipose tissue attenuation measured by coronary computed tomography angiography

Three-dimensional reconstruction of the heart. (A) Pericoronary adipose tissue attenuation between −190 HU and −30 HU in the longitudinal view. (B) Pericoronary adipose tissue attenuation around the proximal 10–50 mm of the right coronary artery. (C) Histogram of CT attenuation within the traced area.

30 s before to ≥ 2 min after cuff release. A single technician (Y.O.), blinded to the clinical and CT data, performed all measurements of FMD. Based on previous studies, an FMD of 4% was described to be an optimal cutoff value for endothelial dysfunction[16]. Patients were divided into two groups: those with endothelial dysfunction (FMD <4%) and those without endothelial dysfunction (FMD ≥ 4%). The median interval between the two tests (coronary CTA and FMD measurements) was 7 days.

Acquisition and Analyses of Coronary CTA

All patients arrived at the hospital 1 h before the scheduled CT time and mandatorily received a dose of oral short-acting nitroglycerine. If their heart rate was >70 beats/min, we administered an oral or intravenous β-blocker to further reduce the rate. CT was performed using a 128-slice CT scanner (SOMATOM Definition Flash; Siemens Medical Solutions, Erlangen, Germany), as previously described[17]. On coronary CTA analysis, we evaluated coronary artery segments with a diameter >2 mm and defined plaque characteristics in accordance with the Society of Cardiovascular Computed Tomography[18]. Two experienced cardiovascular imaging researchers (K.O. and T.M.) interpreted the coronary CTA findings. Plaque characteristics were defined according to the coronary artery disease reporting and data system[18]. High-risk plaque features were defined as positive remodeling, low-attenuation plaques, spotty calcification, and napkin-ring sign. We defined positive remodeling as having an index of >1.1 [19, 20]. Plaques with a CT attenuation number <30 Hounsfield units (HU) were defined as low-attenuation plaques[21]. Spotty calcification was defined as a calcium burden length <1.5 times the vessel diameter and a width less than two-thirds of the vessel diameter[22, 23]. The napkin-ring sign was defined as a lesion with a ring-like attenuation pattern with peripheral high-attenuation tissue surrounding a central lower-attenuation portion[24]. Stenosis was significant if there was luminal narrowing of >50% in major epicardial vessels[25]. We defined adverse CTA findings as the presence of high-risk plaque features and/or significant stenosis based on previous studies[20, 25].

Measurement of Coronary Artery Calcium Score

We recorded the coronary artery calcium (CAC) score based on the following parameters: 120 kVp, 150 mAs, and 3-mm thickness. All data were evaluated using a dedicated workstation (AZE Virtual Place; Canon Medical Systems Corporation, Otawara, Japan). The CAC score was calculated using the Agatston method, which multiplies the area of each calcified plaque by a density factor determined by the peak pixel intensity within the plaque[26]. The plaque-specific scores for all the slices were added. The density factors were 1, 2, 3, and 4 for plaques with peak intensities of 130–199, 200–299, 300–399, and ≥ 400 HU, respectively. Patients with a high CAC score were defined as those having a CAC score >100 based on the previous cohort studies[27].

Analysis of PCAT Attenuation

We measured the amount of PCAT attenuation for all patients in all three coronary arteries using a dedicated workstation (Aquarius iNtuition Edition version 4.4.13; TeraRecon Inc., Foster City, CA, USA). We used an automated method to trace proximal 40-mm segments of the left anterior descending artery (LAD) and left circumflex artery (LCX) and proximal 10–50-mm segments of the right coronary artery (RCA) while making manual adjustments to the automatic delineation of the coronary vessel wall **(Fig. 1)**[28]. We were unable to extract the segmentations of one LAD and three LCX

due to technical difficulties. PCAT was defined as the adipose tissue located within a radial distance from the outer vessel wall equal to the diameter of the coronary vessel, and adipose tissue was defined as all voxels with an attenuation between –190 HU and –30 HU. Based on the above, PCAT attenuation was automatically calculated as the mean CT attenuation value. Two investigators (M.N. and T.N.), who were blinded to the clinical and CT data, performed the PCAT attenuation analysis.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range. Dichotomous variables were expressed as numbers and percentages. Differences in continuous variables between the two groups were analyzed using Student's *t*-test and the Mann–Whitney *U* test. Categorical data were compared using χ^2 and Fisher's tests. In subsequent analyses, triglyceride data were log-transformed because they did not show a normal distribution. We used Pearson's correlation coefficient to assess the association among the three coronary arteries. We performed univariate and multivariate logistic regression analyses to ascertain the association between PCAT attenuation and endothelial dysfunction, and the results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). We conducted a multivariate logistic regression analysis to ascertain the independent predictors of endothelial dysfunction. We further performed subgroup analysis in patients classified as high-risk based on coronary CT results. Variables with *p*-values <0.05 in the univariate test were entered into the multivariate model. All reported *p*-values were two-sided, and statistical significance was set at $p<0.05$. Statistical analyses were performed using SPSS statistical software (Version 28; IBM Corp., Armonk, NY, USA) and the R statistical package (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Patient Characteristics and PCAT Attenuation Values

The mean age of the 119 patients was 64 years, and 72 (61%) were men. The mean FMD was 5.3% ± 2.6%. Coronary CTA revealed a median CAC score of 48, and significant stenosis and high-risk plaque features were detected in 52 (44%) and 73 (61%) patients, respectively. The mean PCAT attenuation values were –66.9 ± 7.7 HU in the RCA ($n=119$), –68.4 ± 6.9 HU in the LAD ($n=118$), and –64.3 ± 6.9 HU in the LCX ($n=116$), respectively. The RCA, LAD, and LCX PCAT attenuation values were normally distributed. There were significant mutual correlations among PCAT attenuation of the RCA, LAD, and LCX **(Supplemental Fig. 2)**.

Comparison of Baseline Patient Characteristics

Patients with FMD <4% ($n=44$) were assigned to the endothelial dysfunction group. A comparison of the baseline characteristics between patients with and without endothelial dysfunction is shown in **Table 1**. Patients with endothelial dysfunction were older ($p=0.001$), had a higher prevalence of calcium channel blocker use ($p=0.024$), and had lower levels of estimated glomerular filtration rate (eGFR) [$p=0.034$]. There were no differences in the two groups in smoking status and prevalence of hypertension, dyslipidemia, or diabetes mellitus. In addition, coronary CTA findings showed no differences in the CAC score ($p=0.072$), the prevalence of significant stenosis ($p=0.288$), and high-risk plaque features ($p=0.434$) between the two groups. As shown in **Fig. 2**, RCA, LAD, and LCX PCAT attenuations were significantly higher in patients with endothelial dysfunction than in those without endothelial dysfunction.

Association between Endothelial Dysfunction and PCAT Attenuation

As shown in **Table 2**, univariate regression analysis revealed that age, use of calcium channel blockers, eGFR, and PCAT attenuation of all three coronary arteries were significantly associated with endothelial dysfunction. Multivariate logistic regression analysis using RCA PCAT attenuation showed that age (OR, 1.050; 95% CI, 1.004–1.098; $p=0.032$) and RCA PCAT attenuation (OR, 1.543; 95% CI, 1.004–2.369; $p=0.048$) were independent predictors of endothelial dysfunction. In similar analyses that included LAD PCAT attenuation, age (OR, 1.054; 95% CI, 1.007–1.104; $p=0.023$) and LAD PCAT attenuation (OR, 1.505; 95% CI, 1.002–2.321; $p=0.049$) were also independently associated with endothelial dysfunction. However, LCX PCAT attenuation was not statistically significant in the multivariate logistic regression model (OR, 1.505; 95% CI, 0.987–2.296; $p=0.058$).

Association between Endothelial Dysfunction and PCAT Attenuation in Patients with Adverse Coronary CTA Findings and High CAC Score

We further performed subgroup analysis to evaluate the association between endothelial dysfunction and PCAT attenuation in patients at

Table 1. Comparison of baseline characteristics between patients with (FMD <4%) and without endothelial dysfunction (FMD ≥ 4%)

Variables	Total	Flow-mediated dilation		*p* value
		<4%	≥ 4%	
N	119	44 (37)	75 (63)	
Age (years)	64 ± 12	68 ± 10	61 ± 12	0.001
Male	72 (61)	30 (68)	42 (56)	0.189
Body mass index (kg/m^2)	24 ± 4	24 ± 4	25 ± 4	0.380
Current smoker	32 (27)	14 (32)	18 (24)	0.353
Hypertension	77 (65)	32 (73)	45 (60)	0.161
Dyslipidaemia	67 (56)	24 (55)	43 (57)	0.767
Diabetes mellitus	95 (80)	34 (77)	61 (81)	0.594
Systolic blood pressure (mmHg)	126 ± 17	128 ± 17	124 ± 17	0.212
Diastolic blood pressure (mmHg)	74 ± 10	73 ± 10	75 ± 10	0.575
Beta blocker	15 (13)	8 (18)	7 (9)	0.160
Ca channel blocker	44 (37)	22 (50)	22 (29)	0.024
ACE-I or ARB	55 (46)	23 (52)	32 (43)	0.310
Statin	56 (47)	21 (48)	35 (47)	0.911
Insulin therapy	33 (28)	9 (21)	24 (32)	0.174
Oral antihyperglycemic drugs	66 (56)	24 (55)	42 (56)	0.878
eGFR (mL/min/1.73 m^2)	73 ± 18	68 ± 19	75 ± 17	0.034
Triglyceride (mg/dL)	105 (81–156)	113 (80–168)	102 (81–145)	0.462
HDL cholesterol (mg/dL)	53 ± 16	53 ± 17	54 ± 15	0.626
LDL cholesterol (mg/dL)	109 ± 30	106 ± 29	113 ± 32	0.265
HbA1c (%)	7.7 ± 1.9	7.4 ± 1.7	7.9 ± 2.0	0.144
CAC score	48 (0–270)	126 (8–400)	13 (0–248)	0.072
CAC score >100	53 (45)	23 (52)	30 (40)	0.193
Significant stenosis (>50%)	52 (44)	22 (50)	30 (40)	0.288
High-risk plaque features	73 (61)	29 (66)	44 (59)	0.434
RCA PCATa (HU)	-66.9 ± 7.7	-64.7 ± 8.0	-68.2 ± 7.3	0.016
LAD PCATa (HU)	-68.4 ± 6.9	-66.5 ± 7.6	-69.6 ± 6.2	0.018
LCX PCATa (HU)	-64.3 ± 6.9	-62.3 ± 6.7	-65.4 ± 6.8	0.035

Data are presented as mean ± standard deviation, median [25th, 75th percentile], or number (%).
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAC score, coronary artery calcium score; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; PCATa, pericoronary adipose tissue attenuation; RCA, right coronary artery.

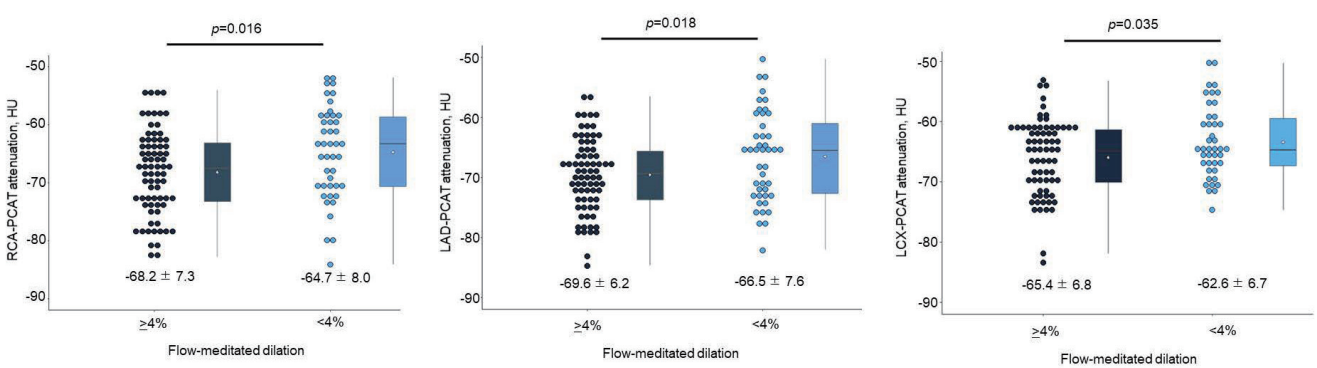

Fig. 2. The comparison of pericoronary adipose tissue attenuation between patients with and without endothelial dysfunction

A combined dot plot and boxplot showing the comparison of PCAT attenuation between patients with (<4%) and without endothelial dysfunction (>4%).
PCAT, pericoronary adipose tissue; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery

Table 2. Factors associated with endothelial dysfunction

	Univariate		Multivariate (model 1)		Multivariate (model 2)		Multivariate (model 3)	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age (years)	1.064 (1.022–1.107)	0.002	1.050 (1.004–1.098)	0.032	1.054 (1.007–1.104)	0.023	1.048 (1.002–1.097)	0.041
Male	1.684 (0.771–3.677)	0.191						
Body mass index (kg/m^2)	0.959 (0.873–1.053)	0.378						
Current Smoker	1.478 (0.647–3.377)	0.354						
Hypertension	1.778 (0.792–3.991)	0.163						
Dyslipidaemia	0.893 (0.422–1.889)	0.767						
Diabetes mellitus	0.780 (0.313–1.945)	0.595						
Systolic blood pressure (mmHg)	1.014 (0.992–1.037)	0.215						
Diastolic blood pressure (mmHg)	0.989 (0.954–1.026)	0.572						
Beta blocker	2.159 (0.724–6.433)	0.167						
CCB	2.409 (1.113–5.215)	0.026	1.565 (0.672–3.645)	0.300	1.590 (0.687–3.685)	0.279	1.737 (0.753–4.003)	0.195
ACE-I or ARB	1.472 (0.697–3.109)	0.311						
Statin	1.043 (0.495–2.199)	0.911						
Insulin therapy	0.546 (0.227–1.316)	0.178						
Oral antihyperglycemic drugs	0.943 (0.446–1.993)	0.878						
eGFR (mL/min/1.73 m^2)	0.976 (0.954–0.999)	0.039	0.993 (0.967–1.020	0.606	0.997 (0.971–1.024	0.843	0.995 (0.969–1.022	0.726
Log (Triglyceride) (mg/dL)	1.001 (0.997–1.006)	0.593						
HDL cholesterol (mg/dL)	0.994 (0.971–1.018)	0.623						
LDL cholesterol (mg/dL)	0.993 (0.981–1.005)	0.264						
HBA1c (%)	0.857 (0.697–1.055)	0.146						
CAC score >100	1.643 (0.776–3.480)	0.195						
Significant stenosis (>50%)	1.500 (0.708–3.176)	0.289						
High-risk plaque features	1.362 (0.628–2.955)	0.434						
RCA PCATa (per SD)	1.616 (1.084–2.410)	0.019	1.543 (1.004–2.369)	0.048				
LAD PCATa (per SD)	1.594 (1.072–2.370)	0.021			1.525 (1.002–2.321)	0.049		
LCX PCATa (per SD)	1.520 (1.022–2.260)	0.039					1.505 (0.987–2.296)	0.058

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAC, coronary artery calcium score; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; PCATa, pericoronary adipose tissue attenuation; RCA, right coronary artery.

high-risk of cardiovascular events based on coronary CTA findings. CTA verified high-risk patients were defined as those with adverse coronary CTA findings (significant stenosis and/or high-risk plaque features) (n=75) and those with a CAC score >100 (n=53). In patients with adverse coronary CTA findings, RCA, LAD, and LCX PCAT attenuation were significantly higher in the group with endothelial dysfunction than in the group without endothelial dysfunction **(Table 3)**. **Supplemental Table 1** demonstrates that age, use of calcium channel blockers, and PCAT attenuation of all three coronary arteries were significant predictors of endothelial dysfunction in the univariate logistic regression analysis. Multivariate logistic regression analysis showed that RCA PCAT (OR, 1.970; 95% CI, 1.113–3.485; p=0.020), LAD PCAT (OR, 1.895; 95% CI, 1.102–3.259; p=0.021), and LCX PCAT attenuation (OR, 1.854; 95% CI, 1.064–3.230; p=0.029) were all independent predictors of endothelial dysfunction after adjustment for age and use of calcium channel blockers. In patients with high CAC score, PCAT attenuation in all three coronary arteries was also significantly higher in the endothelial dysfunction group **(Table 4)**. As shown in **Supplemental Table 2**, RCA, LAD, and LCX PCAT attenuation were the only significant predictors of endothelial dysfunction in the univariate logistic regression analysis.

Discussion

To the best of our knowledge, this is the first study to demonstrate that increased PCAT attenuation is significantly associated with endothelial dysfunction, assessed by FMD of the brachial artery. In addition, this association was significant in patients

Table 3. Comparison of PCAT attenuation between patients with (FMD <4%) and without endothelial dysfunction (FMD ≥ 4%) in patients with adverse coronary CTA findings

	Flow-mediated dilation		*p* value
	<4%	≥ 4%	
N	31 (41)	44 (59)	
RCA PCATa, HU	-64.2 ± 7.7	-68.8 ± 6.8	0.009
LAD PCATa, HU	-66.2 ± 7.5	-70.2 ± 6.0	0.012
LCX PCATa, HU	-62.0 ± 7.0	-65.5 ± 6.6	0.033

Data are presented as mean ± standard deviations or numbers (%).
CTA, computed tomography angiography; HU, Hounsfield units; LAD, left anterior descending artery; LCX, left circumflex artery; PCATa, pericoronary adipose tissue attenuation; RCA, right coronary artery.

Table 4. Comparison of PCAT attenuation between patients with (FMD <4%) and without endothelial dysfunction (FMD ≥ 4%) in patients with high CAC score

	Flow-mediated dilation		*p* value
	<4%	≥ 4%	
N	23 (43)	30 (57)	
RCA PCATa, HU	-63.8 ± 7.9	-69.1 ± 6.9	0.013
LAD PCATa, HU	-64.3 ± 7.3	-69.7 ± 6.0	0.004
LCX PCATa, HU	-61.7 ± 6.9	-66.1 ± 5.8	0.016

Data are presented as mean ± standard deviations or numbers (%).
CAC score, coronary artery calcium score; HU, Hounsfield units; LAD, left anterior descending artery; LCX, left circumflex artery; PCATa, pericoronary adipose tissue attenuation; RCA, right coronary artery.

with adverse coronary CTA findings and in those with high CAC scores. Our results may help to understand the mechanism by which increased PCAT attenuation is associated with cardiovascular events.

In a previous CRISP-CT study, increased PCAT attenuation was related to the risk of cardiovascular events[5]. In this study, PCAT attenuation is only weakly correlated with high-risk plaques. This suggests that it captures different biological information than that of coronary CTA findings. Thus, the mechanisms by which higher PCAT attenuation increases the risk of cardiovascular events remain unclear. Previous studies have suggested that the significant association between increased PCAT attenuation and plaque progression or functional myocardial ischemia could lead to increased cardiovascular events[29, 30]. Recently, several clinical studies have demonstrated that PCAT attenuation was significantly higher in patients with vasospastic angina and those with coronary microvascular dysfunction[6, 7], suggesting a strong association with coronary endothelial dysfunction. Here we demonstrate a significant association between increased PCAT attenuation and peripheral endothelial dysfunction, as assessed by FMD of the brachial artery. Although FMD of the brachial artery does not allow direct assessment of coronary artery endothelial function, previous studies have revealed a significant correlation between FMD-assessed peripheral endothelial function and coronary artery endothelial function[13, 14]. Therefore, our results suggest that coronary endothelial dysfunction can partly explain the mechanism underlying the association between increased PCAT attenuation and cardiovascular events.

Vascular inflammation plays a critical role in the early stages of atherosclerosis. Oikonomou *et al.* showed that increased PCAT attenuation also provides better prognostic information in patients with adverse coronary CTA findings or high CAC scores. Their results indicated that pericoronary inflammation plays an important role in the stage of advanced atherosclerosis[5]. It has been shown that impaired FMD of the brachial artery is an independent predictor of cardiovascular events in patients with established coronary artery disease[10, 31]. We demonstrate a significant correlation between high PCAT attenuation and impaired FMD of the brachial artery in patients with adverse CTA findings and those with high CAC scores. Our results indicate that high PCAT attenuation potentially contributes to disease progression, even in patients with advanced atherosclerosis.

The strong association between PCAT attenuation and endothelial dysfunction of the brachial artery can be explained in terms of systemic inflammation. PCAT attenuation represents the change in intracellular lipid accumulation caused by early and chronic inflammation[28]. Furthermore, it indicates its role as a surrogate measure of coronary focal inflammation. However, a recent study has demonstrated a positive correlation between serum levels of systemic proinflammatory mediators and inflammatory disease activity[32, 33]. Moreover, Elnabawi *et al.* reported in a recent prospective cohort study that biologic therapy was associated with a decrease in PCAT attenuation in patients with psoriasis[34]. These results suggest that PCAT attenuation represents not only coronary focal inflammation but also systemic inflammation. It has also been reported that endothelial dysfunction, assessed by FMD of the brachial artery, is associated with increased levels of proinflammatory cytokines[35]. Therefore, increased PCAT attenuation and endothelial dysfunction are common pathologies of systemic inflammation activation.

From the result of the CRISP-CT study, therapeutic strategies targeted at reducing PCAT attenuation are essential for the prevention of cardiovascular events[5]. Statin therapy is well established for the prevention of cardiovascular events, and this is partly explained by its beneficial effects on endothelial function[36, 37]. Furthermore, recent studies by Dai *et al.* indicated that PCAT attenuation can markedly reduce in response to statin therapy[38]. These results support our results that demonstrated the strong association between PCAT attenuation and endothelial function. Other therapies have been reported to improve endothelial function, which would be promising approaches to reduce PCAT attenuation[9]. Further studies are needed to investigate the effects of these therapies on PCAT attenuation and their clinical outcomes.

It has been reported that PCAT attenuation has incremental prognostic value over coronary CTA findings[5, 28]. Meanwhile, we have demonstrated the association between endothelial dysfunction and increased PCAT attenuation, and its association was significant in the subgroup with adverse coronary CTA findings (significant stenosis and/or high-risk plaque features) and those with CAC score >100. Overall, the measurement of PCAT attenuation may benefit patients with low FMD, adverse coronary CTA findings and those with high CAC score for risk stratification.

However, this study has some limitations that need to be addressed. First, this was a single-center study, and the number of patients was relatively small. In addition, we included only Japanese patients. Thus, our results do not necessarily reflect other ethnic groups. Second, we could not evaluate longitudinal change on FMD and coronary CTA findings since none of the patients in this study underwent these examinations repeatedly. In addition, analysis on the association of these measurements with clinical outcomes was difficult due to the small sample size of this study. Further study will be needed to investigate prognostic significance of changes in these parameters. Third, although we consecutively enrolled patients, our study population had well-controlled blood pressure, low-density lipoprotein-cholesterol levels, and triglyceride levels since almost half of the patients had taken statins or antihypertensive medications at enrollment. Therefore, we cannot deny that selection bias may have affected our findings. Fourth, potential confounders, such as atherosclerosis in brachial artery, may affect the results of FMD. Fifth, information concerning inflammatory markers, such as high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-α, was not available in this study. Future studies are needed to demonstrate the common pathologies of systemic inflammation between endothelial dysfunction and increased PCAT attenuation.

Conclusion

In conclusion, high PCAT attenuation was significantly associated with endothelial dysfunction, assessed by FMD of the brachial artery. We suggest that endothelial dysfunction is one of the mechanisms by which patients with increased PCAT inflammation are at risk of increased cardiovascular events. Further research is needed to investigate the direct association between PCAT attenuation and coronary endothelial function in a larger population to confirm our results.

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Conflict of Interest

All authors declare no conflicts of interest

associated with this manuscript.

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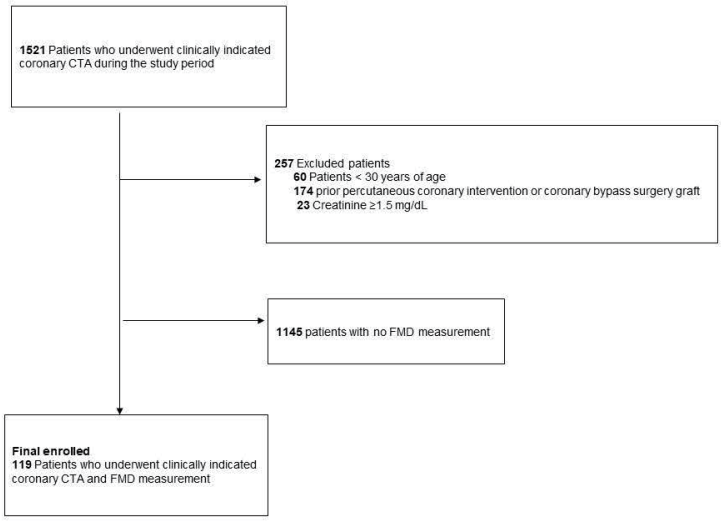
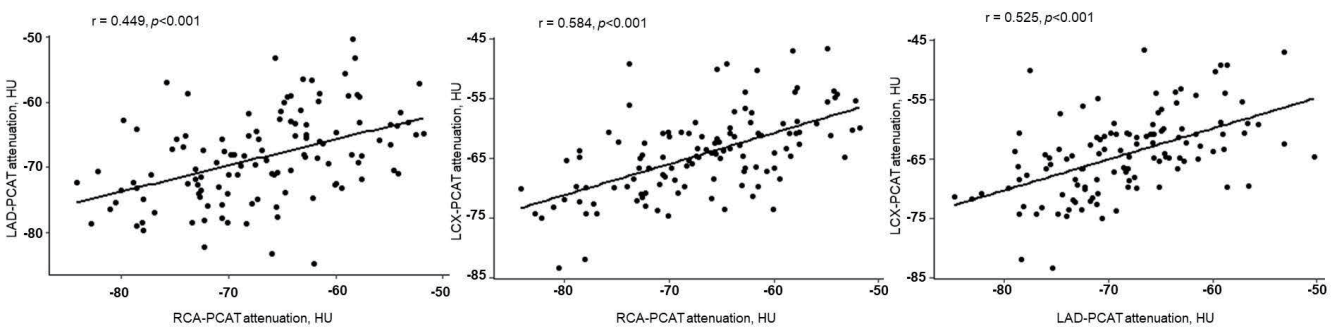


Supplemental Fig. 1. Flowchart showing the study design

CTA, computed tomography angiography; FMD, flow-mediated dilation



Supplemental Fig. 2. The correlations of pericoronary adipose tissue attenuation among the three coronary arteries

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery

Supplemental Table 1. Factors associated with endothelial dysfunction (FMD <4%) in patients with adverse coronary CTA findings

	Univariate		Multivariate (model 1)		Multivariate (model 2)		Multivariate (model 3)	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age (years)	1.064 (1.006–1.125)	0.029	1.056 (0.998–1.117)	0.059	1.061 (1.001–1.126)	0.047	1.057 (1.000–1.119)	0.052
Male	1.858 (0.698–4.942)	0.215						
Body mass index (kg/m^2)	0.941 (0.815–1.086)	0.403						
Current smoker	1.619 (0.577–4.542)	0.360						
Hypertension	1.990 (0.729–5.433)	0.179						
Dyslipidaemia	1.052 (0.415–2.667)	0.914						
Diabetes mellitus	0.639 (0.210–1.940)	0.429						
Systolic blood pressure (mmHg)	1.003 (0.978–1.030)	0.806						
Diastolic blood pressure (mmHg)	0.986 (0.940–1.034)	0.556						
Beta blocker	2.400 (0.616–9.353)	0.207						
CCB	2.602 (1.006–6.729)	0.049	2.076 (0.745–5.786)	0.162	2.045 (0.736–5.685)	0.170	2.367 (0.846–6.622)	0.101
ACE-I or ARB	1.541 (0.610-3.889)	0.360						
Statin	0.659 (0.261–1.666)	0.379						
Insulin therapy	0.696 (0.240–2.012)	0.503						
Oral antihyperglycemic drugs	0.519 (0.204–1.317)	0.167						
eGFR (mL/min/1.73 m^2)	0.981 (0.253–1.010)	0.201						
Log (Triglyceride) (mg/dL)	1.491 (0.618–3.594)	0.374						
HDL cholesterol (mg/dL)	1.000 (0.968–1.033)	0.992						
LDL cholesterol (mg/dL)	0.999 (0.983–1.015)	0.885						
HbA1c (%)	0.782 (0.585–1.046)	0.098						
CAC score >100	1.086 (0.409–2.887)	0.868						
RCA-PCATa (per SD)	1.983 (1.162–3.384)	0.012	1.970 (1.113–3.485)	0.020				
LAD-PCATa (per SD)	1.878 (1.123–3.143)	0.016			1.895 (1.102–3.259)	0.021		
LCX-PCATa (per SD)	1.691 (1.028–2.781)	0.039					1.854 (1.064–3.230)	0.029

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAC score, coronary artery calcium score; CCB, calcium channel blocker; CTA, computed tomography angiography; FMD, flow-mediated dilation; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; PCATa, pericoronary adipose tissue attenuation; RCA, right coronary artery.

Supplemental Table 2. Factors associated with endothelial dysfunction (FMD <4%) in patients with high CAC scores

Variables	Univariate	
	Odds ratio (95% CI)	*p* value
Age (years)	1.038 (0.967–1.115)	0.299
Male	1.889 (0.579–6.166)	0.292
Body mass index (kg/m^2)	0.951 (0.804–1.124)	0.556
Current smoker	1.765 (0.463–6.721)	0.405
Hypertension	1.889 (0.579–6.166)	0.292
Dyslipidaemia	1.361 (0.452–4.100)	0.584
Diabetes mellitus	0.980 (0.300–3.196)	0.973
Systolic blood pressure (mmHg)	1.012 (0.985–1.039)	0.388
Diastolic blood pressure (mmHg)	0.994 (0.946–1.044)	0.809
Beta blocker	2.884 (0.717–11.273)	0.137
CCB	2.812 (0.911–8.679)	0.072
ACE-I or ARB	1.778 (0.590–5.355)	0.072
Statin	0.955 (0.322–2.834)	0.933
Insulin therapy	0.750 (0.160–3.524)	0.716
Oral antihyperglycemic drugs	0.531 (0.176–1.602)	0.261
eGFR (mL/min/1.73 m^2)	0.990 (0.958–1.023	0.546
Log (Triglyceride) (mg/dL)	2.158 (0.769–6.055)	0.144
HDL cholesterol (mg/dL)	1.008 (0.973–1.043)	0.665
LDL cholesterol (mg/dL)	0.989 (0.968–1.010)	0.283
HbA1c (%)	0.790 (0.511–1.222)	0.289
Significant stenosis (>50%)	0.696 (0.204–2.372)	0.562
High-risk plaque features	0.230 (0.022–2.372)	0.217
RCA–PCATa (per SD)	2.124 (1.138–3.964)	0.018
LAD–PCATa (per SD)	2.384 (1.248–4.552)	0.008
LCX–PCATa (per SD)	2.218 (1.111–4.428)	0.024

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAC score, coronary artery calcium score; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; PCATa, pericoronary adipose tissue attenuation; RCA, right coronary artery.