Original article

Cardio-ankle vascular index is associated with coronary plaque composition assessed with iMAP-intravascular ultrasound in patients with coronary artery disease

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A B S T R A C T

Background: The cardio-ankle vascular index (CAVI) is an indicator of arterial stiffness and has been reported to be associated with the severity of coronary artery disease and cardiovascular events. However, whether CAVI can predict the composition of coronary plaques remains unclear.

Methods: We enrolled 208 patients who underwent percutaneous coronary intervention (PCI) for culprit lesions evaluated with iMAP-intravascular ultrasound (IVUS), a radiofrequency imaging system for characterizing tissues. iMAP-IVUS classified the culprit plaque composition as fibrotic, lipidic, necrotic, or calcified, and the respective absolute volumes [fibrotic volume (FV), lipidic volume (LV), necrotic volume NV, and calcified volume] and their ratios (%) within the total plaque volume were calculated. A plaque with a median %NV of $\geq$ 33.2% was defined as a larger NV (LNV) plaque. We measured CAVI and divided the patients into two groups according to CAVI ≥ 8 (high CAVI, $n = 164$) or <8 (low CAVI, $n = 44$).

Results: Culprit plaques had significantly greater absolute NV ($p = 0.016$), %NV ($p = 0.01$), and smaller %FV ($p = 0.02$) in patients with high CAVI than in those with low CAVI. Patients with high CAVI had a higher prevalence of LNV plaques in culprit lesions than those with low CAVI (54% vs. 34%, $p = 0.026$). CAVI correlated significantly and positively with absolute NV, LV, and negatively with %FV. In logistic regression analysis after adjustment for the classic coronary risk factors and possible variables associated with vulnerable plaques, high CAVI had an independent and significant association with the presence of LNV plaques (OR, 3.37; 95% CI, 1.45–7.79; $p = 0.0032$).

Conclusions: A high CAVI is associated with the composition of coronary culprit plaques, particularly increased amount of necrotic tissue, in patients with coronary artery disease undergoing PCI .

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Introduction

Acute coronary syndrome (ACS) mostly occurs owing to the rupture of vulnerable or high-risk plaques, which are characterized by the presence of a large necrotic core and a thin fibrous cap [1]. Although predicting patients with vulnerable plaques may be relevant to prognosis and optimal treatment choice, no simple, reliable, and noninvasive method has been established.

Arterial stiffness is an established parameter reflecting the progression of atherosclerosis and cardiovascular disease [2]. Brachial-ankle pulse wave velocity (ba-PWV) has been widely used as a reliable indicator of arterial stiffness [3]. However, ba-PWV is affected by blood pressure at the time of examination [4]. Therefore, the clinical use of ba-PWV for the assessment of arterial stiffness may be inappropriate in patients with coronary artery disease (CAD) who take multiple antihypertensive medications that affect blood pressure. Conversely, the cardio-ankle vascular index (CAVI) is a new indicator of arterial stiffness developed in Japan, which essentially reflects the stiffness of the aorta, femoral artery, and tibial artery [5]. CAVI is easy to measure, highly reproducible, and essentially independent of blood pressure because of the adjustment of blood pressure based on the stiffness parameter β [6]. Previous clinical studies have reported that CAVI can reflect the severity of CAD and cardiovascular events [7–9]. However, the association between CAVI and coronary plaque characteristics, especially vulnerable features including large necrotic cores, has not been fully

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investigated. Thus, the aim of the present study was to determine whether CAVI could reflect the composition of coronary culprit plaques in patients with CAD undergoing percutaneous coronary intervention (PCI).

Methods

Patients

A total 930 consecutive patients with CAD who underwent PCI for de novo culprit lesions with intracoronary imaging at Nagasaki University Hospital between April 2010 and March 2017 were screened retrospectively. Among them, 234 patients who underwent both CAVI measurement and intravascular ultrasound (IVUS) were included in the analysis. CAVI was measured routinely for all patients, but IVUS use was at the discretion of the treating physician. Patients were excluded if they had a significant left main disease or ostial lesions, in which it is difficult to determine appropriate reference site and measure accurate plaque volume by IVUS [10]. Patients with severely calcified lesions (arc of calcium >180°) were excluded, because acoustic shadows behind dense calcium are frequently classified as necrotic tissue on iMAP-IVUS [11]. In addition, patients were excluded if they had chronic total occlusion or poor-quality IVUS images. To obtain correct CAVI measurements, patients with ankle-brachial index <0.9 measured in both legs and those with atrial fibrillation were also excluded. Thus, 208 patients with stable angina pectoris ($n = 145$) and ACS ($n = 63$) were included in the final analysis. We defined stable angina pectoris as no change in the frequency, duration, or intensity of angina symptoms within 6 weeks before admission. ACS included acute myocardial infarction ($n = 36$) and unstable angina pectoris ($n = 27$). We defined acute myocardial infarction as acute myocardial injury with clinical evidence of acute myocardial ischemia, detection of an increase and/or a decrease in cardiac troponin level of at least one unit above the 99th percentile upper reference limit, and at least one of the following: symptoms of myocardial ischemia, new ischemic electrocardiogram changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, and identification of a coronary thrombus on angiography [12]. We defined unstable angina pectoris as angina at rest, accelerated angina, or new-onset angina without elevated cardiac markers. This study was approved by the institutional ethics committee and conducted in compliance with the committee's guidelines (Reference number 17071008). The present study also complied with the Declaration of Helsinki for investigations involving humans. To obtain informed consent, we applied opt-out method on our institution's website (http://www.mh.nagasaki-u.ac.jp/research/rinsho/patients/open_junkanki.html).

CAVI measurement

CAVI was measured using a VaSera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) following a previously described method [13]. The patients rested on a bed in a supine position for 10 min before the measurements. The CAVI value was based on the stiffness parameter calculated using the following formula: $\ln(Ps/Pd) \times 2\rho/\Delta P \times PWV2$ (where ρ = blood density, Ps = systolic blood pressure, Pd = diastolic blood pressure, $\Delta P = Ps - Pd$, and PWV = pulse wave velocity between the aortic and ankle values). The CAVI value was calculated as the average of the right and left CAVI measurements. The previously proposed normal (reference) value of CAVI is <8.0 [14]. On the basis of this value, the patients were divided into two groups: 44 patients with a CAVI of <8 (low CAVI) and 164 patients with a CAVI of ≥8 (high CAVI).

Angiographic analysis

The angiographic lesion morphology was classified according to the American College of Cardiology/American Heart Association classification [15], and the culprit vessels (left anterior descending coronary artery, left circumflex artery, or right coronary artery) and lesion locations (proximal, mid, or distal) were assessed. Minimal lumen diameter, reference vessel diameter, diameter stenosis, and lesion length were measured on quantitative coronary angiograms using the CASS II system (Pie Medical Imaging, Maastricht, Netherlands). Culprit lesions were identified on the basis of the associations among left ventricular wall motion abnormalities, electrocardiographic findings, scintigraphic defects, and angiographic lesion morphology.

IVUS procedure

After the administration of intracoronary isosorbide dinitrate (1 mg), IVUS imaging of target lesions was performed. An IVUS system (iLAB; Boston Scientific Corporation, Marlborough, MA, USA) and a 40-MHz IVUS imaging catheter (OptiCross, Boston Scientific) with automated pullback at 0.5 mm/s were used to capture IVUS images. The acquired images were digitally stored for subsequent offline analysis.

IVUS analysis

IVUS analysis was performed every 1.0 mm independently of the cardiac cycle, using a validated software (QIvus 2.1; Medis Medical Imaging Systems, Leiden, Netherlands). Grayscale IVUS analysis was performed according to criteria from a clinical expert consensus document on standards for measurements and assessment of IVUS from the Japanese Association of Cardiovascular Intervention and Therapeutics [10]. The lumen and external elastic membrane (EEM) cross-sectional area (CSA) were measured. Plaque plus media (P+M) CSA was calculated as EEM minus lumen CSA, and plaque burden was calculated as P+M CSA divided by EEM CSA. The length of the culprit lesion was calculated as the distance between the proximal and distal reference sites. Vessel, lumen, and plaque volumes were calculated as Σ EEM CSA, Σ lumen CSA, and Σ P+M CSA, respectively.

We assessed the plaque composition in the entire culprit lesion using the software of iMAP (Boston Scientific), a radiofrequency imaging system for characterizing tissues. This imaging system uses a pattern-recognition algorithm to decipher the spectra obtained from the fast Fourier transformation of a human autopsy database of coronary atheromas [16]. The iMAP system uses color coding, and depicts fibrotic tissues as light green, lipidic tissues as yellow, necrotic tissues as pink, and calcified tissues as light blue areas. The amounts of each component were reported in absolute volume (FV, fibrotic volume; LV, lipidic volume; NV, necrotic volume; and CV, calcified volume). The percentage of each component volume within the total plaque volume was also calculated (%FV, %LV, %NV, and %CV). We defined a plaque with a median %NV of ≥ 33.1% as a larger NV (LNV) plaque, which was used as a surrogate marker of vulnerable plaques. Guidewire artifacts were masked from all images.

Laboratory analysis

Blood samples were collected before PCI. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using routine laboratory methods. The estimated glomerular filtration rate (mL/min/1.73 m²) was calculated using the Modification of Diet in Renal Disease equation for Japanese patients [17]. Chronic kidney

disease (CKD) was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2.

In-hospital outcome

Incidence of slow/no flow during PCI and in-hospital adverse cardiovascular events after PCI, including cardiac death, stroke, stent thrombosis, target lesion revascularization, and unplanned revascularization, were investigated.

Statistical analysis

Statistical analysis was performed using JMP® 14 (SAS Institute Inc., Cary, NC, USA). Continuous values are expressed as mean $\pm$ standard deviation for normally distributed variables or median (interquartile range) for skewed variables, and analyzed using Wilcoxon's rank sum test. Categorical data are presented as numbers (%), and analyzed using the chi-square or Fisher exact test. Relations between CAVI and iMAP-IVUS parameters were evaluated by univariate Pearson correlation coefficients. Logistic regression analysis was performed to determine the odds ratio and 95% confidence interval for an LNV plaque stratified according to high CAVI. Adjustments were made for variables including age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, ACS, CKD, and statin use. A value of $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Table 1 summarizes the patients' clinical characteristics. Patients with high CAVI were significantly older ($p < 0.0001$); had a significantly higher prevalence of CKD ($p = 0.02$), history of stroke ($p = 0.03$), and carotid artery disease ($p = 0.04$); and had a significantly lower body mass index ($p = 0.02$) than those with low CAVI.

Angiographic lesion characteristics

Table 2 lists the angiographic lesion characteristics. Patients with high CAVI had a higher prevalence of proximal lesions ($p = 0.04$) and more complex lesions with American College of Cardiology/American Heart Association classification type B2 to C than those with low CAVI ($p = 0.03$).

Grayscale and iMAP-IVUS Findings

Table 3 summarizes the grayscale and iMAP-IVUS findings in culprit lesions. There were no significant differences in grayscale IVUS parameters between patients with low and high CAVI. Culprit plaques in patients with high CAVI had significantly greater absolute NV, %NV, and smaller %FV than those in patients with low CAVI. The prevalence of LNV plaques was significantly higher in patients with high CAVI compared to those with low CAVI. In patients with ACS, patients with high CAVI had significantly greater plaque volume, absolute NV, %NV, and higher prevalence of LNV plaque than those with low CAVI. Similar differences were not demonstrated in patients with SAP. Representative images of iMAP-IVUS analysis are shown in Fig. 1.

Correlations between CAVI and grayscale and iMAP-IVUS parameters

Table 4 lists the correlations between CAVI and grayscale and iMAP-IVUS parameters. CAVI correlated significantly and positively with plaque volume, percent PV, absolute NV, LV, and negatively

Table 1
Patients' characteristics.

	Low CAVI ($n = 44$)	High CAVI ($n = 164$)	p-value
Age (years)	60.4 ± 13.1	69.7 ± 8.8	< 0.0001
Male sex	32 (73%)	139 (85%)	0.07
Body mass index (kg/m^2)	25.4 ± 4.4	23.7 ± 2.3	0.02
Hypertension	34 (77%)	122 (74%)	0.84
Hypercholesterolemia	26 (59%)	100 (61%)	0.86
Diabetes mellitus	15 (34%)	63 (38%)	0.72
Chronic kidney disease	14 (32%)	85 (52%)	0.02
Hemodialysis	2 (5%)	9 (5%)	1.00
Current smoking	16 (36%)	42 (26%)	0.18
Clinical presentation			0.71
Acute coronary syndrome	12 (27%)	51 (31%)	
Stable angina pectoris	32 (73%)	113 (69%)	
Prior myocardial infarction	2 (5%)	25 (15%)	0.07
Prior PCI	14 (32%)	51 (31%)	1.00
Prior CABG	2 (5%)	3 (2%)	0.28
Prior stroke	2 (5%)	29 (18%)	0.03
Carotid artery disease	0 (0%)	14 (9%)	0.04
Medications			
ARB/ACEI use	19 (43%)	73 (44%)	1.00
Ca blocker use	19 (43%)	63 (38%)	0.6
Beta blocker use	7 (16%)	44 (27%)	0.16
Diuretic use	5 (11%)	17 (10%)	0.78
Statin use	22 (50%)	76 (46%)	0.73
Insulin use	1 (2%)	15 (9%)	0.20
Laboratory data			
Total cholesterol (mg/dL)	184 ± 68	166 ± 41	0.17
Triglyceride (mg/dL)	111 (83–173)	102 (83–135)	0.17
LDL cholesterol (mg/dL)	109 ± 61	101 ± 34	0.82
HDL cholesterol (mg/dL)	43.6 ± 12.8	42.5 ± 11.3	0.63
hsCRP (mg/dL)	1.30 (0.49–3.80)	1.18 (0.42–4.67)	0.81

Data are expressed as mean $\pm$ standard deviation, median (interquartile range), or number (percentage).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; Ca blocker, calcium channel blocker; CAVI, cardio-ankle vascular index; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention.

Table 2
Angiographic lesion characteristics.

	Low CAVI ($n = 44$)	High CAVI ($n = 164$)	p-value
Target vessel			
LAD/LCX/RCA	19/10/12 (46%/24%/29%)	79/27/52 (50%/17%/33%)	0.56
Target lesion location			
Proximal/mid/distal	14/23/7 (32%/52%/16%)	77/52/35 (47%/31%/21%)	0.04
ACC/AHA classification			
A–B1	17 (40%)	36 (22%)	0.03
B2–C	26 (60%)	126 (78%)	
Quantitative coronary angiography findings			
Minimum lumen diameter (mm)	0.74 ± 0.38	0.70 ± 0.32	0.75
Reference diameter (mm)	2.90 ± 0.58	2.91 ± 0.61	0.97
%Diameter stenosis	74 ± 14	76 ± 11	0.66
Lesion length (mm)	18.7 ± 10.8	19.0 ± 8.6	0.46

Data are expressed as mean $\pm$ standard deviation or number (percentage).
AHA, American Heart Association; ACC, American College of Cardiology; CAVI, cardio-ankle vascular index; LAD, left anterior descending artery; LCX, circumflex branch of left coronary artery; RCA, right coronary artery.

with %FV. CAVI also correlated positively with %NV, %LV, and absolute CV, but those relations were not significant.

Predictors of LNV plaques

Table 5 shows the results of the logistic regression analysis of high CAVI for the presence of LNV plaques. Univariate logistic regression analysis showed that high CAVI was a significant factor associated with LNV plaques. After adjustment for age, sex, hy-

Table 3
Grayscale and iMAP-IVUS findings.

	All (n = 208)			ACS (n=63)			SAP (n=145)		
	Low CAVI (n = 44)	High CAVI (n = 164)	p-value	Low CAVI (n = 12)	High CAVI (n = 51)	p-value	Low CAVI (n = 32)	High CAVI (n = 113)	p-value
Grayscale IVUS analysis									
Vessel volume (mm³)	191 [135–191]	206 [140–302]	0.16	209 [139–272]	262 [194–384]	0.08	169 [103–268]	185 [122–252]	0.54
Lumen volume (mm³)	65 [41–94]	69 [49–97]	0.41	78 [56–94]	87 [58–112]	0.46	62 [34–98]	61 [44–84]	0.52
Plaque volume (mm³)	121 [77–164]	140 [86–202]	0.11	136 [84–173]	192 [134–279]	0.038	115 [62–164]	121 [74–174]	0.58
Percent PV (%)	65 ± 8	63 ± 7	0.12	64 ± 5	69 ± 9	0.06	64 ± 8	65 ±8	0.56
iMAP-IVUS analysis									
Absolute volume									
Fibrotic (mm³)	59 [38–76]	61[41–96]	0.38	60 [53–83]	83 [55–110]	0.31	57 [33–74]	54 [38–83]	0.71
Lipidic (mm³)	12 [6–19]	15 [8–23]	0.08	14 [8–22]	21 [13–26]	0.1	11 [5–20]	13 [7–20]	0.35
Necrotic (mm³)	27 [16–59]	46 [23–76]	0.016	27 [18–70]	65 [41–104]	0.016	30 [12–59]	37 [17–70]	0.19
Calcified (mm³)	1.2 [0.7–3.1]	2.0 [1.0–3.3]	0.12	1.1 [0.5–2.8]	2.6 [1.1–4.5]	0.06	1.2 [0.7–3.1]	1.7 [0.9–2.9]	0.67
Relative volume									
Fibrotic (%)	54 ± 16	48 ± 13	0.02	54 ± 16	46 ± 11	0.15	54 ± 15	49 ± 14	0.08
Lipidic (%)	10 ± 3	11 ± 2	0.16	11 ± 3	11 ± 2	0.53	10 ± 2	11 ± 2	0.23
Necrotic (%)	29 ± 12	34 ± 12	0.01	28 ± 12	37 ± 10	0.025	29 ± 12	33 ± 13	0.14
Calcified (%)	1.8 ± 1.5	1.7 ± 1.2	0.78	1.1 ± 1.0	1.6 ± 1.1	0.1	2.0 ± 1.6	1.7 ± 1.3	0.46
Prevalence of LNV plaque (%)	34	54	0.026	33	67	0.049	34	49	0.16

ACS, acute coronary syndrome; CAVI, cardio-ankle vascular index; IVUS, intravascular ultrasound; LNV, larger nectotic tissue volume; PV, plaque volume; SAP, stable angina pectoris.
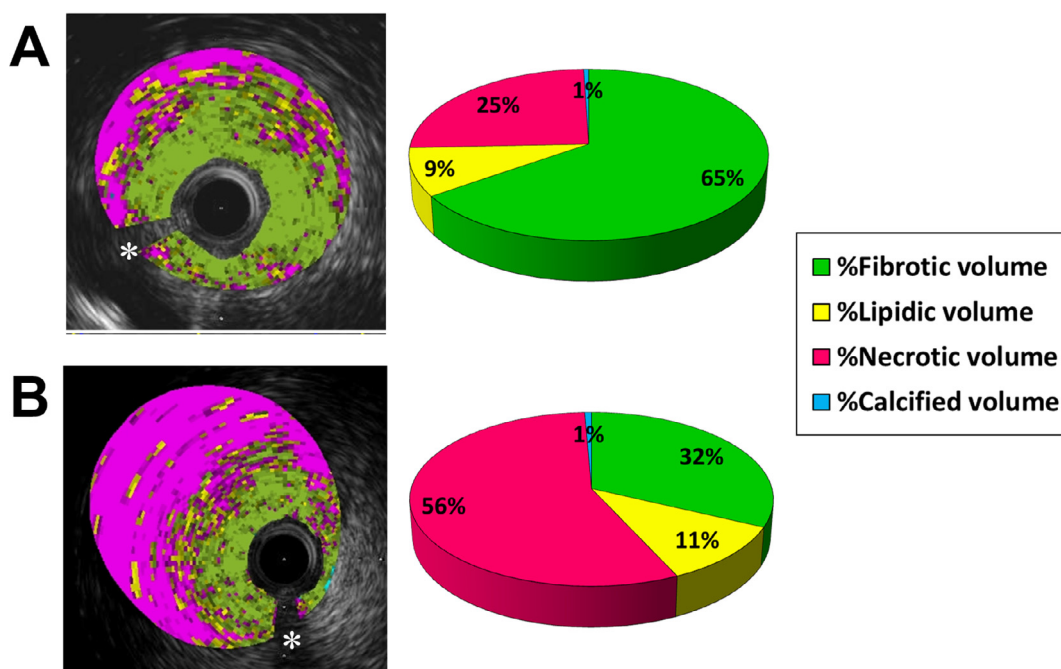
Fig. 1. Representative images of iMAP-intravascular ultrasound. (A) A culprit lesion in 72-year-old man with stable angina pectoris (SAP) whose cardio-ankle vascular index (CAVI) was 7.6. His predominant plaque component was fibrotic tissue. (B) A culprit lesion in a 74-year-old man with SAP whose CAVI was 10.9. His main plaque component was necrotic tissue. This is a typical image of larger necrotic volume plaque. *Guidewire artifacts.

pertension, hypercholesterolemia, diabetes mellitus, smoking, ACS, CKD, and statin use, high CAVI remained significantly associated with the presence of LNV plaques.

In-hospital outcomes

The incidence of slow/no flow during PCI was similar between patients with low and high CAVI (15% vs. 16%, p = 1.00). There were no in-hospital adverse cardiovascular events after PCI including cardiac death, stroke, stent thrombosis, target lesion revascularization, and unplanned revascularization in both groups.

Discussion

The main findings of the present study were as follows. In iMAP-IVUS analysis, culprit plaques in patients with high CAVI had

significantly greater %NV and smaller %FV than those in patients with low CAVI. Patients with high CAVI had a higher prevalence of LNV plaques in culprit lesions than those with low CAVI. In multivariate analysis, high CAVI was an important determinant of LNV plaques. These results suggest a possible relationship between CAVI and the composition of coronary plaques, especially larger necrotic tissue.

Arterial stiffness and atherosclerosis have some common determinants, including older age, sex, and hypertension [18]. As arterial stiffness is the principal cause of increased systolic blood pressure and pulsatility of flow, CAVI may reflect the cumulative damage on the arterial wall. Several studies have investigated the relationship between arterial stiffness assessed using CAVI and coronary atherosclerosis. Nakamura et al. demonstrated that CAVI is strongly associated with the presence and severity of coronary atheroscle-

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Table 4
Correlations between CAVI and iMAP-IVUS parameters.

	CAVI	
	r	*p*-value
Grayscale IVUS analysis		
Vessel volume (mm³)	0.12	0.075
Lumen volume (mm³)	0.04	0.5
Plaque volume (mm³)	0.15	0.029
Percent PV (%)	0.19	0.006
iMAP-IVUS analysis		
Absolute volume		
Fibrotic (mm³)	0.08	0.23
Lipidic (mm³)	0.17	0.017
Necrotic (mm³)	0.17	0.013
Calcified (mm³)	0.13	0.056
Relative volume		
Fibrotic (%)	-0.14	0.047
Lipidic (%)	0.12	0.09
Necrotic (%)	0.13	0.06
Calcified (%)	0.002	0.97

CAVI, cardio-ankle vascular index; IVUS, intravascular ultrasound; PV, plaque volume.

Table 5
Logistic regression analysis of high CAVI for an LNV plaque.

	Odds ratio (95% CI)	*p*-value
Unadjusted	2.29 (1.14–4.59)	0.019
Model 1	3.24 (1.46–7.19)	0.003
Model 2	3.65 (1.61–8.30)	0.0013
Model 3	3.49 (1.52–8.03)	0.0022
Model 4	3.37 (1.45–7.79)	0.0032

The presented odds ratios were for high CAVI. Model 1: adjusted for age and sex. Model 2: adjusted for all factors in model 1 plus hypertension, hypercholesterolemia, diabetes mellitus, and smoking. Model 3: adjusted for all factors in model 2 plus acute coronary syndrome and chronic kidney disease. Model 4: adjusted for all factors in model 3 plus statin use.
CAVI, cardio-ankle vascular index; CI, confidence interval; LNV, larger necrotic volume.

rosis on coronary angiography [7]. Horinaka et al. showed that CAVI is associated with the plaque burden in angiographically normal left main coronary artery, as evaluated using grayscale IVUS [19]. However, the relationship between arterial stiffness and coronary plaque composition, especially vulnerable plaque features, has not been well investigated.

In the present study, we clarified the association between CAVI and the composition of coronary culprit plaques by using iMAP-IVUS for the first time.

The most interesting finding of the present study was that high CAVI, as a marker of increased arterial stiffness, was an independent predictor of the presence of LNV plaques after adjustment for various coronary risk factors. This is important because plaques containing greater necrotic tissue are considered a risk indicator for plaque instability. Several mechanisms might explain the association between arterial stiffness and vulnerable plaques. Arterial stiffening may lead to early pulse wave reflection, causing an increase in central systolic blood pressure, a decrease in diastolic blood pressure, and a subsequent increase in pulse pressure [2]. Selwaness et al. previously demonstrated that pulse pressure is the strongest determinant of intraplaque hemorrhage, a high-risk component of vulnerable plaques, in carotid atherosclerosis [20]. The presence of atherosclerotic changes may impair the elastic properties of the wall, whereas reduced large artery compliance enhances the wave reflection and augmentation of the pulsatile component of blood pressure, leading to the progression of atherosclerotic changes [21]. Therefore, pulse pressure can be considered both a cause and a consequence of arterial stiffness [22]. On the other hand, the alteration of coronary flow reserve needs to be considered. Coronary flow reserve reflects the coronary circulation

capacity to dilate and increase flow encompassing both the epicardial and microvascular coronary circulations [23]. The diminished elasticity of the stiff aorta, combined with the absence of diastolic augmentation from the reflected pressure wave, has the potential to reduce coronary perfusion pressure and coronary blood flow. Previous experimental and clinical studies have shown that coronary flow reserve varies with aortic stiffness [24,25]. Coronary flow reserve is also affected by epicardial stenosis as well as microvascular dysfunction induced by traditional atherosclerotic risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, and smoking [26]. Of note, decreased coronary flow reserve in these pathological conditions is thought to be associated with endothelial dysfunction [27]. Endothelial dysfunction is related to vasoconstriction, pro-inflammatory, proliferative, and procoagulatory milieu, contributing to all stages of plaque formation and pathogenesis of plaque vulnerability. Segmental endothelial dysfunction of the coronary artery is associated with greater necrotic tissue in coronary plaques, as assessed using iMAP-IVUS [28]. Taken together with our results, aortic stiffness is a possible factor associated with vulnerable coronary plaque through decreased coronary flow reserve and endothelial dysfunction.

In the present study, patients with CAVI ≥8.0 were defined as having high CAVI, which was a significant predictor for the presence of LNV plaques. This value was based on the proposed cut-off values of CAVI of 8.0 and 9.0 (<8 for normal, ≥8 and <9 for borderline, and ≥9 for abnormal) [14]. However, the cut-off values of CAVI for identifying advanced coronary atherosclerosis or vulnerable plaques have been controversial. Nakamura et al. revealed that the cut-off value of CAVI for the presence of angiographically determined CAD is 8.81 (sensitivity 83.9%, specificity 70%) [7]. Tanaka et al. proposed that CAVI ≥8.0 might be associated with subclinical/asymptomatic atherosclerosis and CAVI ≥9.0 is associated with an increased cardiovascular risk [14]. However, the utility of CAVI as a predictive factor for cardiovascular outcomes has been shown only in clinical studies that included patients with atherosclerotic risk factors or a history of cardiovascular disease. Thus, caution should be taken when applying these CAVI cut-off values to the general population.

In the present study, we used iMAP-IVUS, the most recently developed radiofrequency-IVUS system, to analyze coronary plaque composition. In an ex vivo validation study, the accuracy of iMAP-IVUS for detecting necrotic, lipidic, fibrotic, and calcified tissue was 97%, 98%, 95%, and 98%, respectively [16]. The iMAP-IVUS system uses a sheath-based mechanical imaging 40 MHz catheter that enables more precise pullback, as well as the measurement of the size and composition of atherosclerotic plaques [29]. Previous iMAP-IVUS studies revealed that culprit plaques in patients with ACS are associated with more necrotic and smaller fibrotic components [30–33]. We have previously reported that coronary lesions with greater necrotic areas in iMAP-IVUS are closely associated with the presence of optical coherence tomography (OCT)-derived thin-cap fibroatheroma [11]. These findings suggest that iMAP-IVUS can provide useful information for identifying vulnerable plaques. However, a definite cut-off value of necrotic tissue volume on iMAP-IVUS for detecting vulnerable plaques has not been determined. In the present study, an LNV plaque with a median %NV of ≥33.1% was used as a surrogate for vulnerable plaques; however, no supporting evidence was presented. Prospective clinical data linking the amount of necrotic tissue on iMAP-IVUS to the presence of vulnerable plaques and the development of adverse cardiac events should be obtained in the future.

Clinical implications

Greater necrotic tissue in coronary lesions is not only a feature of vulnerable plaques but also a predictor of future coronary

events. Therefore, patients with high CAVI should be managed with intensive lipid-lowering therapy with statins for plaque modification and stabilization. The presence of a large necrotic tissue in PCI target lesions is a risk factor for myocardial perfusion injury after PCI [34]. Therefore, it seems likely that estimating the major components of culprit plaques by using CAVI is promising in terms of planning treatment strategies and predicting the complexity of PCI. Prospective and large-scale studies are needed to elucidate these possibilities.

Study limitations

The present study had some limitations. First, this retrospective study was performed at a single center and included a small study population. Second, IVUS use was at the discretion of the treating physician. This selection bias is the main limitation of this study. Third, we excluded patients with ankle-brachial index <0.90 and atrial fibrillation because it is difficult to accurately measure CAVI in such patients [5]. Therefore, our results may not be applicable to these patient groups. Fourth, OCT may be more desirable in tissue characterization than iMAP-IVUS. OCT is a high-resolution intravascular imaging modality that can visualize the detailed structure of the coronary plaque, including thin-cap fibroatheroma, plaque rupture, macrophages, microvessels, or layered plaque [35]. Fifth, the cross-sectional design of the present study precluded addressing whether high CAVI values reflect the progression of coronary arteriosclerosis to cardiovascular events and mortality. In addition, a causal relationship between CAVI and coronary plaque vulnerability was not determined. Finally, we did not examine whether decreasing CAVI through appropriate treatments or interventions can translate into coronary plaque stabilization. From these viewpoints, a multicenter prospective cohort study on CAVI in patients with CAD is needed.

Conclusion

High CAVI is an independent predictor of the composition of coronary culprit plaques, particularly greater necrotic tissue, in patients with CAD undergoing PCI. CAVI is a clinically useful surrogate marker for the prediction of coronary plaque vulnerability.

Acknowledgments

Funding

Disclosures

The authors declare that there is no conflict of interest.

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