Plaque Composition and No-Reflow Phenomenon During Percutaneous Coronary Intervention of Low-Echoic Structures in Grayscale Intravascular Ultrasound

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SUMMARY

It has been reported that coronary vasa vasorum is associated with plaque vulnerability, and low-echoic structures in grayscale intravascular ultrasound (IVUS) are consistent pathologically with vasa vasorum. However, the association of low-echoic structures with plaque composition and no-reflow phenomenon during percutaneous coronary intervention (PCI) is unclear. We investigated plaque composition in virtual histology IVUS (VH-IVUS) and no-reflow phenomenon during PCI of low-echoic structures.

A total of 106 lesions being treated by VH-IVUS before PCI were included in this study. Low-echoic structure was defined as a small tubular structure exterior to media without a connection to the vessel lumen in ≥ 3 consecutive cross-sectional IVUS images. Lesions with low-echoic structures were found in 42% (45/106).

Lesions with low-echoic structures were more prevalent in acute coronary syndrome (ACS) patients (53% [24/45] versus 20% [12/61], $P < 0.001$), had more positive remodeling (49% [22/45] versus 21% [13/61], $P = 0.003$), a larger number of VH-IVUS derived thin-cap fibroatheromas (VH-TCFAs) (0.64 ± 0.53 versus 0.05 ± 0.22 , $P < 0.001$), more VH-TCFAs with a baseline plaque burden of 70% or more and minimal luminal area of 4.0 mm^2 or less (29% [13/45] versus 2% [1/61], $P < 0.001$), and more frequent no-reflow phenomenon after stent implantation and more final TIMI flow grade 0/1/2 (38% [17/45] versus 5% [3/61], $P < 0.001$; 9% [4/45] versus 0% [0/61], $P = 0.03$) than lesions without low-echo structures.

Lesions with low-echoic structures in grayscale IVUS had high plaque vulnerability and were more prevalent in ACS patients, positive remodeling, and VH-TCFAs, and they had more frequent no-reflow phenomenon during PCI than lesions without low-echoic structures. (Int Heart J 2016; 57: 285-291)

Key words: Vasa vasorum, Virtual histology intravascular ultrasound, Plaque vulnerability

Coronary vasa vasorum is a network of microvessels in the walls of coronary arteries. It has been reported vasa vasorum is more frequently observed in patients with acute myocardial infarction (AMI), lesions with thin-cap fibroatheroma (TCFA), or plaque rupture.¹⁻³⁾ Therefore, vasa vasorum has been identified as a morphological indicator of plaque vulnerability. Vasa vasorum is observed on computed tomography (CT) and optical coherence tomography (OCT) as networks of microvessels.^{4,5)} However, CT is associated with the problem of radiation and difficulties in detecting plaque characteristics. OCT has a limitation with respect to penetration depth so detecting all vasa vasorum could be difficult in large-diameter vessels. As intravascular ultrasound (IVUS) has a penetration depth of 8 to 10 mm, it is believed to be suitable for identifying vasa vasorum in deep areas. In addition, it has been reported that low-echoic structures exterior to media in grayscale IVUS are consistent pathologically with vasa vaso-

rum.⁶⁾ However, there are few reports on the association between the low-echoic structures detected by IVUS and plaque vulnerability. Virtual histology-IVUS (VH-IVUS) analyzes radiofrequency signals acquired by IVUS and displays this by classifying plaque into 4 components. The predictive accuracy of plaque composition by VH-IVUS to corresponding pathological tissue is good at about 90 percent.⁷⁾ It has been reported that the plaque composition of VH-IVUS is associated with coronary events.⁸⁾ Using VH-IVUS, we investigated the association between low-echoic structures and plaque characteristics. In addition, it has been reported no-reflow phenomenon during percutaneous coronary intervention (PCI) is one of the risk factors for cardiac events.⁹⁾ There are also few reports on the association between low-echoic structures and no-reflow phenomenon during PCI. We investigated the association between low-echoic structures and no-reflow phenomenon during PCI.

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METHODS

Patient population: This study was a retrospective and single center study conducted on consecutive 93 patients having 106 lesions treated by PCI for de novo coronary stenosis at our institution between March 2012 and September 2013, and for which good images were obtained through IVUS studies conducted before the PCI procedure. The exclusion criteria were as follows: 1) vessels 2.0 mm or less in size; 2) stent restenosis; 3) vein graft lesions; 4) lesions in which the IVUS catheter was not able to cross due to calcification or other reasons; 5) lesions with large amounts of thrombus making it difficult to discriminate from plaque; and 6) poor images. This study was performed in accordance with the Code of Federal Regulations and the Declaration of Helsinki. The protocol was approved by the Toho University Omori Medical Center Ethics Committee. Informed consent was obtained from all patients before the procedure. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or medication use. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of an anti-hypertensive drug. Patients with diabetes mellitus had a confirmed diagnosis¹⁰⁾ or were under antidiabetic treatment.

PCI procedure: All patients received aspirin (100 mg/day) and clopidogrel (75 mg/day) before PCI. No patient received a glycoprotein IIb/IIIa inhibitor because this type of drug is not available in Japan. Intravenous heparin (100 U/kg) was administered at the beginning of catheterization. Pre-intervention angiography was performed after the intracoronary administration of 0.1–0.2 mg nitroglycerin. When there were large amounts of thrombus present, IVUS was conducted after thrombus aspiration was performed. This was closely followed by dilatation by an appropriately sized balloon and stent deployment. Thrombus was defined as a discrete intraluminal filling defect.¹¹⁾ Thrombolysis In Myocardial Infarction (TIMI) flow grade was assessed as described previously.¹²⁾ The angiographic no-reflow phenomenon was defined as a decrease of at least 1 grade in TIMI flow immediately after stent implantation compared with before stent implantation or final TIMI flow grade 0 and 1 or 2, with no evidence of thrombus, spasm, or dissection.

IVUS procedure: After the intracoronary administration of 0.1–0.2 mg nitroglycerin, a 20-MHz 3.2-F phased-array IVUS catheter (Eagle Eye, Volcano Therapeutics, Rancho Cordova, CA, USA) was pulled back at the speed of 0.5 mm/s from the distal site of the culprit lesion to the aorto-ostial junction. The culprit vessel was identified on the basis of clinical, electrocardiographic, and angiographic data. In stable angina pectoris (SAP) patients, the culprit vessel was considered to be the ischemia-related vessel identified by exercise or pharmacologic stress test.

IVUS data analysis: The grayscale IVUS and captured radiofrequency data were written onto a DVD-R, and off-line analyses were performed by an independent operator who was blinded to the patient clinical data. Quantitative measurements were conducted according to criteria from the American College of Cardiology (ACC) consensus statement on IVUS.¹³⁾ Using Volcano In-Vision Gold imaging system software (Version 3.0; Volcano Corporation, Rancho Cordova, CA, USA), lumen, external elastic membrane (EEM), and plaque and me-

dia (defined as EEM minus lumen) cross sectional areas (CSA) were measured in all slices. This imaging software automatically calculates plaque and media CSA, and categorizes the plaque into 4 components. These are color-coded with fibrous as green, fibro-fatty as greenish yellow, necrotic core as red, and calcium as white, and are displayed as percent of plaque area. The averaged percent and area over the entire culprit lesion that were automatically calculated by the software were used. The remodeling index was calculated as the lesion external elastic membrane cross-sectional area divided by the proximal reference cross-sectional area. Positive remodeling was defined as a remodeling index > 1.05 . Spotty calcification was defined as the largest arc of calcium deposits under 90° in > 1 cross-sectional image of the lesion. Low-echoic structure was defined as the presence of a small (maximum diameter of 0.5 mm or less) tubular structure exterior to media without a connection to the vessel lumen in ≥ 3 consecutive cross-sectional IVUS images (Figure 1). The measuring range of low-echoic structures was from the distal to the proximal site of the culprit lesion. The number of low-echoic structures was also counted at the maximum site of the culprit lesion. We defined VH-IVUS derived thin-cap fibroatheroma (VH-TCFA) as a lesion meeting the following two criteria in at least 3 consecutive frames: 1) focal necrotic core rich lesions (%necrotic core $> 10\%$) without evident overlying fibrous tissue and 2) %plaque volume $> 40\%$.¹⁴⁾

Statistical analysis: Statistical analysis was performed using Stat View version 5.0 (SAS Institute Inc., Cary, NC, USA). Continuous data are expressed as the mean $\pm$ SD. Categorical data are presented as the number (percentage). Continuous variables were compared using the unpaired Student's *t* test. Categorical variables were compared with the chi-square test or Fisher exact test.

Independent predictors of no reflow after stent implantation were identified by multivariable logistic regression and expressed as the odds ratios and their 95% confidence intervals (CI). We selected the variables with a *P* value < 0.05 in univariate models and included them in multivariable models. A *P* value < 0.05 was considered statistically significant.

RESULTS

There were no significant differences in patient characteristics with respect to age, gender, hypertension, dyslipidemia, or lipid profiles (Table I) between the patients with low-echoic structures and patients without low-echoic structures. Patients with low-echoic structures had significantly less diabetes mellitus (24% [11/45] versus 46% [28/61], *P* = 0.03), had more current smokers (56% [25/45] versus 28% [17/61], *P* = 0.005), more family history of coronary artery disease (22% [10/45] versus 7% [4/61], *P* = 0.02), and more acute coronary syndrome (ACS) (53% [24/45] versus 20% [12/61], *P* < 0.001) than the patients without low-echoic structures. Reference vessel diameter was significantly larger in the lesions with low-echoic structures than in the lesions without low-echoic structures (3.18 ± 0.50 mm versus 2.94 ± 0.54 mm, *P* = 0.02). Baseline creatine kinase (CK) was significantly higher in the lesions with low-echoic structures than in the lesions without low-echoic structures (177 ± 228 IU/L versus 108 ± 79 IU/L, *P* = 0.03). Reference vessel diameter was significantly larger

Figure. Representative intravascular ultrasound (IVUS) images of coronary plaques with low-echoic structures and virtual histology thin-cap fibroatheroma (VH-TCFA). Three consecutive cross-sectional IVUS images in the proximal left anterior descending coronary artery (**A, B**). **A:** Grayscale and VH-IVUS images of the culprit lesion: The culprit lesion had a VH-TCFA that contained a large necrotic core and small dense calcium deposits. **B:** Grayscale IVUS images of distal site adjacent to the culprit lesion: Two low-echoic structures (red arrow) were located at the 3 and 9 o'clock positions.

Table I. Baseline Clinical Characteristics

	Lesions with low-echoic structures (n = 45)	Lesions without low-echoic structures (n = 61)	P
Age (years)	65 ± 10	66 ± 11	0.86
Gender (male/female)	38 / 7	55 / 6	0.39
Hypertension	30 (67%)	46 (75%)	0.39
Diabetes mellitus	11 (24%)	28 (46%)	0.03
Dyslipidemia	29 (64%)	44 (72%)	0.40
Current smokers	25 (56%)	17 (28%)	0.005
Prior myocardial infarction	7 (16%)	9 (15%)	> 0.99
Prior coronary bypass	0 (0%)	0 (0%)	> 0.99
Family history of CAD	10 (22%)	4 (7%)	0.02
Clinical presentation			< 0.001
Acute coronary syndrome (ACS)	24 (53%)	12 (20%)	
Stable angina pectoris	21 (47%)	49 (80%)	
Ejection fraction (%)	59.2 ± 11.2	63.0 ± 11.4	0.09
Total cholesterol (mg/dL)	191 ± 52	176 ± 34	0.07
LDL-C (mg/dL)	114 ± 48	102 ± 29	0.10
HDL-C (mg/dL)	49 ± 13	52 ± 12	0.27
Triglycerides (mg/dL)	138 ± 66	125 ± 55	0.25
Baseline CK (IU/L)	177 ± 228	108 ± 79	0.03
Target vessel			0.04
LAD	18 (40%)	36 (59%)	
LCx	8 (18%)	13 (21%)	
RCA	19 (42%)	12 (20%)	

Data are expressed as the mean ± SD or number (percentage). CAD indicates coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CK, creatine kinase; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery.

Table II. Angiographic and Procedure Characteristics

	Lesions with low-echoic structures (<i>n</i> = 45)	Lesions without low-echoic structures (<i>n</i> = 61)	<i>P</i>
Quantitative coronary angiography			
Reference vessel diameter (mm)	3.18 ± 0.50	2.94 ± 0.54	0.02
Pre-minimal luminal diameter (mm)	0.77 ± 0.42	0.96 ± 0.37	0.02
Pre-diameter stenosis (%)	75 ± 14	66 ± 14	0.002
Post-minimal luminal diameter (mm)	2.98 ± 0.44	2.83 ± 0.49	0.09
Post-diameter stenosis (%)	6 ± 10	3 ± 10	0.20
Thrombus before PCI	13 (29%)	2 (3%)	< 0.001
Procedure			
Thrombectomy	9 (20%)	0 (0%)	< 0.001
Before dilatation	45 (100%)	61 (100%)	> 0.99
Stent			
Stent diameter (mm)	3.19 ± 0.35	2.95 ± 0.43	0.003
Stent length (mm)	21.6 ± 7.4	23.2 ± 7.5	0.28
Maximal pressure (atm)	13 ± 3	13 ± 2	0.98
Maximum balloon diameter (mm)	3.52 ± 0.53	3.24 ± 0.58	0.02
Maximum balloon pressure (atm)	18 ± 4	18 ± 3	0.82
Initial TIMI flow grade 0/1/2	15 (33%)	4 (7%)	< 0.001
Final TIMI flow grade 0/1/2	4 (9%)	0 (0%)	0.03
Before stenting			
TIMI flow grade 0/1/2	7 (16%)	0 (0%)	0.002
After stenting			
TIMI flow grade 0/1/2	18 (40%)	3 (5%)	< 0.001
Incidence of no-reflow after stent implantation	17 (38%)	3 (5%)	< 0.001

PCI indicates percutaneous coronary intervention; and TIMI, Thrombolysis In Myocardial Infarction.

Table III. Gray-Scale and Virtual Histology Intravascular Ultrasound Findings

	Lesions with low-echoic structures (<i>n</i> = 45)	Lesions without low-echoic structures (<i>n</i> = 61)	<i>P</i>
Grayscale IVUS characteristics			
Lesion length (mm)	18.2 ± 6.5	19.9 ± 6.7	0.19
Lumen CSA (mm ²)	5.6 ± 1.9	4.8 ± 1.6	0.02
EEM CSA (mm ²)	16.6 ± 5.5	13.9 ± 4.5	0.006
Plaque and Media CSA (mm ²)	10.9 ± 4.4	9.0 ± 3.4	0.01
Positive remodeling	22 (49%)	13 (21%)	0.003
Spotty calcification	35 (78%)	24 (39%)	< 0.001
VH-IVUS characteristics			
Fibrous (%)	59.0 ± 8.2	54.9 ± 11.5	0.04
Fibro-fatty (%)	14.1 ± 6.9	11.5 ± 5.1	0.03
Necrotic core (%)	21.1 ± 7.8	22.1 ± 6.6	0.47
Dense calcium (%)	5.7 ± 4.0	11.5 ± 8.1	< 0.001
Fibrous area (mm ²)	4.8 ± 2.4	3.5 ± 1.5	< 0.001
Fibro-fatty area (mm ²)	1.6 ± 1.1	1.1 ± 0.7	0.003
Necrotic core area (mm ²)	1.7 ± 1.0	1.5 ± 0.8	0.18
Dense calcium area (mm ²)	0.4 ± 0.3	0.8 ± 0.7	0.003
VH-TCFAs	28 (62%)	3 (5%)	< 0.001
Number of VH-TCFAs	0.64 ± 0.53	0.05 ± 0.22	< 0.001
Plaque burden ≥ 70%, MLA ≤ 4 mm ² , and VH-TCFAs (+)	13 (29%)	1 (2%)	< 0.001

IVUS indicates intravascular ultrasound; CSA, cross-sectional area; EEM, external elastic membrane; VH-IVUS, virtual histology IVUS; TCFA, thin-cap fibroatheroma; and MLA, minimal luminal area.

in the lesions with low-echoic structures than in the lesions without low-echoic structures (3.18 ± 0.50 mm versus 2.94 ± 0.54 mm, *P* = 0.02) (Table II). The lesions with low-echoic structures had significantly more thrombus before PCI than the lesions without low-echoic structures (29% [13/45] versus 3% [2/61], *P* < 0.001). Stent diameter was significantly larger in the lesions with low-echoic structures than in the lesions with-

out low-echoic structures (3.19 ± 0.35 mm versus 2.95 ± 0.43 mm, *P* < 0.003). Maximum balloon diameter was significantly larger in the lesions with low-echoic structures than in the lesions without low-echoic structures (3.52 ± 0.53 mm versus 3.24 ± 0.58 mm, *P* = 0.02). The frequency of final TIMI flow grade 0/1/2 was significantly higher in the lesions with low-echoic structures than in the lesions without low-echoic struc-

Table IV. Comparison of Number of Low-Echoic Structures Between Acute Coronary Syndrome and Stable Angina Pectoris

	ACS (<i>n</i> = 36)	SAP (<i>n</i> = 70)	<i>P</i>
Number of low-echoic structures	1.2 ± 1.1	0.5 ± 0.9	0.002

ACS indicates acute coronary syndrome; SAP, stable angina pectoris.

Table V. Comparison of Number of Low-Echoic Structures Between Lesions With VH-TCFAs and Lesions Without VH-TCFAs

	Lesions with VH-TCFAs (<i>n</i> = 31)	Lesions without VH-TCFAs (<i>n</i> = 75)	<i>P</i>
Number of low-echoic structures	1.7 ± 1.0	0.4 ± 0.8	< 0.001

VH-TCFA indicates virtual histology intravascular ultrasound derived thin-cap fibroatheroma.

Table VI. Independent Predictors of No-Reflow After Stent Implantation by Multivariable Logistic Regression

	Odds ratio	95% CI	<i>P</i>
Thrombus before PCI	4.63	1.19 – 18.01	0.03
Reference vessel diameter	1.97	0.70 – 5.57	0.20
Low-echoic structures	4.93	1.04 – 23.35	0.04
VH-TCFAs	2.13	0.55 – 8.31	0.28

CI indicates confidence interval.

tures (9% [4/45] versus 0% [0/61], $P = 0.03$). The incidence of no-reflow phenomenon after stent implantation in lesions with low-echoic structures was significantly higher than in lesions without low-echoic structures (38% [17/45] versus 5% [3/61], $P < 0.001$). EEM CSA and plaque and media CSA were significantly larger in the lesions with low-echoic structures than in the lesions without low-echoic structures ($16.6 \pm 5.5 \text{ mm}^2$ versus $13.9 \pm 4.5 \text{ mm}^2$, $P = 0.006$; $10.9 \pm 4.4 \text{ mm}^2$ versus $9.0 \pm 3.4 \text{ mm}^2$, $P = 0.01$) (Table III). The frequency of positive remodeling and spotty calcification was significantly higher in the lesions with low-echoic structures than in the lesions without low-echoic structures (49% [22/45] versus 21% [13/61], $P = 0.003$; 78% [35/45] versus 39% [24/61], $P < 0.001$). In VH-IVUS analysis, dense calcium in the lesions with low-echoic structures was significantly lower than in the lesions without low-echoic structures ($5.7 \pm 4.0\%$ versus $11.5 \pm 8.1\%$, $P < 0.001$; $0.4 \pm 0.3 \text{ mm}^2$ versus $0.8 \pm 0.7 \text{ mm}^2$; $P = 0.003$). The frequency of VH-TCFAs in the lesions with low-echoic structures was significantly higher than in the lesions without low-echoic structures (62% [28/45] versus 5% [3/61], $P < 0.001$). The number of VH-TCFAs in the lesions with low-echoic structures was significantly higher than the lesions without low-echoic structures (0.64 ± 0.53 versus 0.05 ± 0.22 , $P < 0.001$). The frequency of VH-TCFAs with a baseline plaque burden of 70% or more and minimal luminal area (MLA) of 4.0 mm^2 or less in the lesions with low-echoic structures was significantly higher than in the lesions without low-echoic structures (29% [13/45] versus 2% [1/61], $P < 0.001$). For subgroup analysis of ACS and VH-TCFAs, the number of low-echoic structures in the ACS patients was significantly higher than in the SAP patients (1.2 ± 1.1 versus 0.5 ± 0.9 , $P = 0.002$). The number of low-echoic structures in the lesions with VH-TCFAs was significantly higher than in the lesions without VH-TCFAs (1.7 ± 1.0 versus 0.4 ± 0.8 , $P < 0.001$) (Table IV,

V). Multivariable analysis showed that low-echoic structures and thrombus were independent predictors of no-reflow after stent implantation (odds ratio 4.93, 95% CI 1.04–23.35, $P = 0.04$; odds ratio 4.63, 95% CI 1.19–18.01, $P = 0.03$, respectively) (Table VI).

DISCUSSION

This paper is the first to report an investigation on the association of IVUS-detected low-echoic structures with plaque vulnerability and no-reflow phenomenon during PCI. The major findings of the present study were that: 1) Lesions with low-echoic structures were more prevalent in ACS patients, and were associated with thrombus, positive remodeling, spotty calcification, and VH-TCFAs; 2) Lesions with TCFAs or ACS had a larger number of low-echoic structures than lesions without TCFAs or ACS; 3) No-reflow phenomenon during PCI was frequently observed in lesions with low-echoic structures. **Relationship between low-echoic structures and clinical characteristics:** In this study, lesions with low-echoic structures were more frequent in ACS patients and had more thrombus. It has been reported that vasa vasorum is frequently observed in AMI patients and lesions with ruptured plaques, therefore, neovascularization is concomitant with unstable plaque.¹⁻³⁾ These reports are consistent with the results of this study in which many IVUS-detected low-echoic structures were present in ACS patients and thrombotic lesions. The relation between vasa vasorum and coronary risk factors such as hypertension and hyperlipidemia has also been reported in animal models,^{15,16)} and in this study patients with low-echoic structures had a greater number of current smokers and a family history of coronary artery disease, and less diabetes mellitus than patients without low-echoic structures. With respect to current

smokers and a family history of coronary artery disease, the cause of the differences may be that the lesions with low-echoic structures were more frequent in ACS patients and less frequent in SAP patients. About diabetes mellitus, it was difficult to explain the cause of difference from clinical presentation. Patients with low-echoic structures included a high ratio of current smokers and had slightly higher total cholesterol levels. Therefore, smoking and poorly controlled dyslipidemia may have greater effects on the development of low-echoic structures than diabetes mellitus in this study.

Relationship between low-echoic structures and TCFAs: Pathological studies have reported that lesions with TCFAs have a high degree of neovascularization, and OCT studies have reported that lesions with microchannel structures have a large number of TCFAs.^{1,5)} These reports are consistent with the results of our study in which lesions with low-echoic structures had a large number of TCFAs. In addition, based on the fact that ACS patients or lesions with TCFAs had a large number of low-echoic structures, it is conceivable that low-echoic structures also show the plaque vulnerability of lesions with ACS and TCFA. Previous OCT studies have reported that lesions with microchannels have a thinner fibrous cap, therefore, microchannels indicate TCFA activity.⁵⁾ This result is consistent with our findings that low-echoic structures showed the plaque vulnerability of lesions with ACS and TCFA. A previous study has reported that a baseline plaque burden of 70% or more, MLA of 4.0 mm² or less, and the presence of VH-TCFA are independent determinants of future cardiac events.¹⁷⁾ In our study, the lesions with low-echoic structures had more TCFAs with a plaque burden of 70% or more, and MLA of 4.0 mm² or less. This is also why we believed that the lesions with low-echoic structures were clinically vulnerable plaque to rupture.

Relationship between low-echoic structures and spotty calcification: In this study, lesions with low-echoic structures had few dense calcium deposits and large amounts of spotty calcium deposits. From reports that found IVUS and CT reveal large amounts of spotty calcium in ACS, and that lesions with spotty calcification accelerate plaque progression, such lesions are believed to be vulnerable.¹⁸⁻²⁰⁾ The large amount of spotty calcium in lesions with low-echoic structures suggested the possibility that low-echoic structures indicated plaque vulnerability. Based on the fact that lesions with low-echoic structures were more frequent in ACS patients, TCFAs, and microcalcification, IVUS might prove that low-echoic structures were closely associated with plaque vulnerability.

Detection of vasa vasorum among various modalities: OCT has high resolution, but the penetration depth is shallow. Therefore, it is difficult to detect vasa vasorum in deep areas of large vessels. Even reports on OCT-detected vasa vasorum exclude vessel diameters over 4 mm.⁵⁾ Vasa vasorum have been detected through CT in an animal model,²¹⁾ but there are few *in vivo* reports and its consistency with vasa vasorum in pathology is unclear. In addition, CT has various problems that include radiation and difficulties in detecting plaque characteristics. IVUS has a penetration depth of approximately 10 mm, and it is believed that it can sufficiently identify findings outside the vessel wall. Detection by IVUS is conducted through contrast echocardiography but this is a complex procedure.²²⁾ Conversely, detection of low-echoic structures by grayscale IVUS is simple and easy. Previous studies have reported that low-echoic structures in grayscale IVUS are consistent pathologically

with vasa vasorum.⁶⁾ In our study, lesions with low-echoic structures had high plaque vulnerability and were present in many ACS patients and with VH-TCFAs and microcalcification *in vivo*. Therefore, we believe that low-echoic structures in grayscale IVUS might be consistent with vasa vasorum *in vivo*. **Relationship between low-echoic structures and no-reflow phenomenon during PCI:** Lesions with low-echoic structures had more no-reflow phenomenon during PCI, and furthermore, low-echoic structures were an independent predictor of no-reflow phenomenon after stent implantation. It has been reported that lesions with IVUS-detected TCFAs frequently have distal embolization,²³⁾ and pathological studies have reported that the fibrous cap of TCFAs are ruptured and thrombus is formed, and finally ACS is induced.²⁴⁾ In our study, lesions with low-echoic structures had a large number of VH-TCFAs, and there is the possibility that iatrogenic rupture of TCFA through stent expansion induced distal embolization. Neovascularization is considered to be the source of intraplate hemorrhage,²⁵⁾ and it is possible that distal embolization was induced through the iatrogenic creation of intraplate hemorrhage through balloon dilatation. The lesions with low-echoic structures had high CK and low ejection fraction before PCI. It is believed the myocardial damage before PCI had some impact on no-reflow phenomenon during PCI.

Limitations: Detection of vasa vasorum might be affected by surrounding structures such as small branches, veins, and small coronary fistulas. In this study, the definition of low-echoic structures excluded a connection with the vessel lumen and large structures (more than 0.5 mm). Therefore, the influence of surrounding structures on the detection of vasa vasorum was thought to be small. However, future studies on a larger number of lesions are needed to study the consistency between the IVUS findings and pathology. This was a retrospective and single center study on a limited number of patients who were able to undergo IVUS studies. It is necessary to conduct further large-scale studies.

Conclusions: Lesions with low-echoic structures in grayscale IVUS had high plaque vulnerability and were more prevalent in ACS patients and were associated with positive remodeling, spotty calcification, and VH-TCFAs with large plaque burden and small luminal area, and they had more frequent no-reflow phenomenon during PCI than lesions without low-echoic structures.

DISCLOSURE

The authors do not have any potential conflicts of interest associated with this paper.

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