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OCT–Defined Morphological Characteristics of Coronary Artery Spasm Sites in Vasospastic Angina

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ABSTRACT

OBJECTIVES The aim of this study was to define the morphological features of coronary artery spasm sites using optical coherence tomography (OCT) in patients with vasospastic angina (VSA).

BACKGROUND Plaque characteristics at coronary artery spasm sites have not been investigated systematically.

METHODS Sixty-nine consecutive patients (80 spasm sites) presenting with VSA who underwent OCT imaging were included in this study. Fibrous cap disruption was identified by the discontinuation of fibrous cap with or without intraplaque cavity formation. OCT-defined erosion was established by the presence of thrombus with or without lumen irregularity overlying an intact fibrous cap on multiple adjacent OCT frames. Other morphological features such as the absence of thrombus with or without lumen irregularity and those not in the previously mentioned criteria were also documented.

RESULTS Plaque was seen on OCT in 79 of the 80 spasm sites. Fibrous cap disruption was detected at 3 sites (4%). OCT-defined erosion was observed at 21 spasm sites (26%). Thrombus with lumen irregularity was observed in 20 sites, whereas 1 site had thrombus without lumen irregularity. Lumen irregularity without thrombus was observed at 49 spasm sites (61%). Spontaneous spasm was seen more frequently in patients with acute myocardial infarction and out-of-hospital cardiac arrest than in patients without these conditions (50.0% vs. 19.3%, $p = 0.025$).

CONCLUSIONS Our results show that OCT-defined erosion at spasm sites occurred in more than one-fourth of patients in this study. Luminal irregularity was observed in nearly two-thirds of the patients without overlying thrombus. These findings suggest the potential role of antiplatelet therapy in VSA. (J Am Coll Cardiol Img 2015;8:1059–67) © 2015 by the American College of Cardiology Foundation.

Coronary artery spasm plays an important role in the pathogenesis of not only variant angina, but also unstable angina, acute myocardial infarction (AMI), ventricular arrhythmia, and sudden cardiac death (1–3). Although spasm sites can be observed as normal or only minimally narrowed by angiography, atherosclerosis is almost always present at focal spasm sites on intravascular ultrasound (4,5). Thrombosis complicated by fibrous cap disruption, considered to be the most important mechanism for the development of acute coronary syndrome (ACS) (6), might be precipitated by vasospastic angina (VSA) facilitating thrombus formation (7,8). Post-mortem examination has also revealed fresh thrombi at the spasm site in the absence of plaque disruption, which suggests that

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AMI = acute myocardial infarction

ECG = electrocardiogram

OCT = optical coherence tomography

OHCA = out-of-hospital cardiac arrest

TCFA = thin-cap fibroatheroma

VSA = vasospastic angina

blood stagnation caused by vasospasm could contribute to intimal injury and thrombosis (9). Although unable to visualize microscopic detail of defects, angioscopic findings have revealed evidence of intimal injury (hemorrhage, flap, thrombus, or ulceration) at the site of coronary artery spasm in patients with VSA (10). Atherosclerotic plaques at the spasm sites, however, have not been studied extensively. Optical coherence tomography (OCT) is a validated high-resolution imaging modality that has the ability to assess the fibrous cap, thrombus, and lumen irregularity associated with atherosclerotic plaque (11,12). The aim of this study was to evaluate the in vivo morphological characteristics of coronary artery spasm sites using OCT in patients with VSA.

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METHODS

STUDY POPULATION. This study was conducted at 2 teaching hospitals (Ulsan University Hospital, Ulsan, South Korea, and Keimyung University Dongsan Medical Center, Daegu, South Korea). Patients were enrolled between October 2011 and July 2012. Consecutive patients diagnosed with VSA were included in this study. To diagnose VSA, the following 2 criteria were used (13): 1) spontaneous or ergonovine-induced coronary artery spasm (producing >90% narrowing of coronary lumen diameter by angiography) associated with chest pain and ischemic ST-segment changes (transient ST-segment elevation or depression ≥0.1 mV, recorded on at least 2 contiguous leads on the 12-lead electrocardiogram [ECG]); and 2) normal or insignificant coronary artery disease (diameter stenosis <50%) after intracoronary nitroglycerin injection.

Calcium-channel blockers and nitrates were stopped for at least 48 h before the ergonovine provocation test in elective patients. All patients were prescribed a loading dose of aspirin 200 mg and clopidogrel 300 mg. Unfractionated heparin 100 U/kg was injected intravenously to maintain an activated clotting time ≥250 s during the procedure. After baseline angiography of the left and right coronary arteries, the operator proceeded with the ergonovine provocation test if there was no significant angiographic stenosis seen on multiple angiographic projections (defined as <50% diameter stenosis by visual estimation). Intracoronary ergonovine was used in the left and right coronary arteries, respectively, at incremental doses of 20, 40, and 60 μg with 2-min intervals between doses (13). If angiographic findings showed focal luminal narrowing of more than 90% with chest pain and ECG changes (ST-segment elevation or depression ≥0.1 mV on at least 2 contiguous leads), 200 μg of intracoronary nitroglycerin was used to confirm spontaneous coronary vasospasm (13).

We excluded patients who had fixed stenosis (≥50% of the lumen diameter) in the spasm site; comorbidities such as congestive heart failure, cardiomyopathy, or chronic kidney disease; or past history of fatal arrhythmias, prior myocardial infarction, or cardiogenic shock. This study was approved by the institutional review board ethics committees at participating centers, and written informed consent was obtained from all participants.

OCT IMAGE ACQUISITION. OCT was performed at the spasm site after administration of 200 μg of intracoronary nitroglycerin, and images were acquired with a commercially available frequency-domain OCT system and optic catheter (C7XR and Dragon Fly catheter, LightLab Imaging/St. Jude Medical, Westford, Massachusetts). A 2.7-F OCT imaging catheter was advanced carefully distal to the spasm site along a 0.014-inch guidewire. Automated pullback was performed at 20 mm/s while blood was displaced by a short injection of contrast media through the guiding catheter. Images were digitally stored for off-line analysis.

OCT IMAGE ANALYSIS. All OCT images of culprit vessels were analyzed at 0.5-mm intervals, including spasm segments, by 2 independent investigators (S.H.A. and A.-Y.H.) who were blinded to the clinical presentations. When there was discordance between the observers, a consensus reading was obtained from a third investigator (E.-S.S.).

DEFINITION AND CLASSIFICATION OF SPASM SITES BY OCT. OCT images were analyzed at spasm sites that extended 5 mm proximally and distally from the maximal spasm segments. This was confirmed by an independent, blinded investigator (Eok Rae Cho) with the corresponding coronary angiography using side branches as markers. The OCT-defined morphological characteristics of spasm sites are shown in Figure 1. The presence of plaque at the spasm site is defined in this study as intimal thickening ≥500 μm observed with OCT. Fibrous cap disruption was identified by discontinuation of the fibrous cap with or without intraplaque cavity formation (14). OCT-defined erosion was identified by the presence of thrombus with or without lumen irregularity overlying an intact fibrous cap on multiple adjacent OCT frames. Other morphological features such as the absence of thrombus with or without lumen

irregularity and those not mentioned in the previously mentioned criteria were also documented. Thrombus was defined as a floating or protruding mass into the lumen of a dimension >200 μm and was categorized as either erythrocyte-rich (red) thrombus, defined by high backscattering and high attenuation, or platelet-rich (white) thrombus, defined by homogeneous backscattering with low attenuation (15). The largest thrombus visualized was measured for area size and maximal and minimal diameter.

Tissue characteristics of underlying plaque were defined by use of previously established criteria (12). Plaques were classified as: 1) fibrous (homogeneous, high-backscattering region); or 2) lipid (low-signal region with diffuse border). The presence of ≥1 quadrant of a region with low backscattering and poor delineation was defined as lipid-laden plaque, and those with a thin cap (<65 μm) were defined as thin-cap fibroatheroma (TCFA).

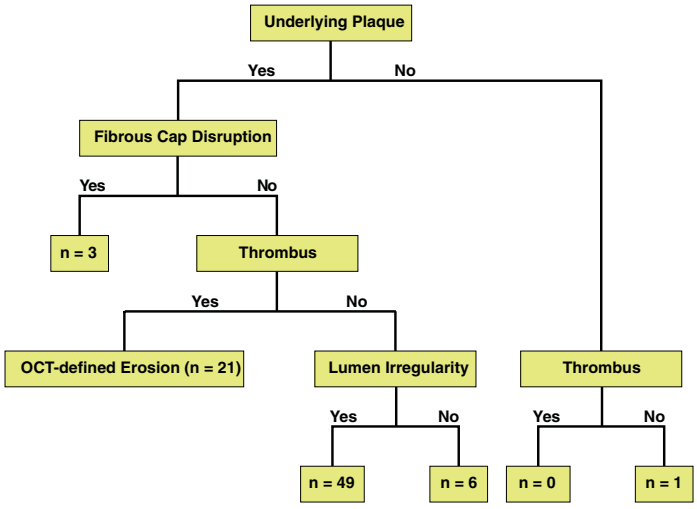
Interobserver variability was assessed by the evaluation of 31% of the random images by 2 independent observers. Intraobserver variability was assessed at 2-week intervals by the evaluation of one-third of the random images by an independent investigator. The interobserver kappa coefficients for plaque disruption, lumen irregularity, thrombus, and plaque classification were 1.000, 0.834, 0.918, and 0.913, respectively. The intraobserver kappa coefficients for plaque disruption, lumen irregularity, thrombus, and plaque classification were 1.000, 1.000, 0.918, and 0.940, respectively.

QUANTITATIVE CORONARY ANGIOGRAPHY. Coronary angiography results were analyzed with the Cardiovascular Angiography Analysis System (CAAS 5.10, Pie Medical Imaging B.V., Maastricht, the Netherlands) by another independent investigator (Jeong Hoon Jang) who was blinded to the OCT analysis. The reference diameter, minimum lumen diameter, diameter stenosis, and spasm site length were measured.

CLINICAL MANIFESTATIONS. Clinical presentations were recorded as out-of-hospital cardiac arrest (OHCA) and AMI according to the American Heart Association guidelines (16). AMI was diagnosed as the typical rise and fall of cardiac injury markers (serum troponin elevation above the 99th percentile of normal), sudden onset of resting chest pain lasting >20 min, or new ischemic changes on ECG. Venous blood samples for creatinine kinase myocardial band and troponin T were obtained from all patients before coronary angiography and at 8-h intervals post-angiography for 24 h.

STATISTICAL ANALYSIS. All statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, Illinois). Categorical variables were described as counts and proportions, and the comparisons were performed with the chi-square test or Fisher exact test. Continuous variables were presented as mean ± SD or medians with interquartile ranges. The differences in means of continuous measurements were examined with the Student *t* test and nonparametric Mann-Whitney *U* test for 2-group comparisons. There were no adjustments made for multiple variables within individuals. All p values were 2-sided analyses with a statistical significance level of <0.05.

FIGURE 1 OCT-Defined Morphological Characteristics of Spasm Sites in Vasospastic Angina



Observation of optical coherence tomography (OCT) images followed the sequence shown: identification of plaque at spasm sites, fibrous cap disruption, presence of thrombus, and lumen irregularity.

RESULTS

CLINICAL CHARACTERISTICS. Sixty-nine patients were included during the study period; their clinical characteristics are summarized in **Table 1** (Online Figure 1). The mean age was 54.4 ± 8.0 years, and 73.9% were men. Six patients had multivessel spasm, and 2 patients had multifocal spasm in the left anterior descending artery and the right coronary artery. Clinical manifestation of AMI/OHCA at admission was observed in 17.4% (n = 12). There were 52 patients diagnosed with VSA by ergonovine provocation test; no cases of fatal arrhythmia were documented during the test. Spontaneous spasm was observed in 17 patients, which was more frequent in the AMI/OHCA than the non-AMI/OHCA group (50% vs. 19.3%;

TABLE 1 Patient Characteristics

	Total Population (N = 69)	AMI/OHCA (n = 12)	Non-AMI/OHCA (n = 57)	p Value
Male	51 (73.9)	9 (75.0)	42 (73.7)	1.000
Age, yrs	54 (49–59)	54 (50–58)	54 (47–59)	0.962
BMI, kg/m^2	24.3 (22.9–26.2)	26.0 (20.3–27.6)	24.3 (22.9–25.9)	0.716
Risk factors				
Diabetes	6 (8.7)	2 (16.7)	4 (7.0)	0.278
Hypercholesterolemia	23 (33.3)	1 (8.3)	22 (38.6)	0.050
Smoking				0.243
Ex-smoker	12 (17.4)	1 (8.3)	11 (19.3)	
Current smoker	31 (44.9)	8 (66.7)	23 (40.4)	
Hypertension	25 (36.2)	5 (41.7)	20 (35.1)	0.667
Family history of CAD	2 (2.9)	1 (8.3)	1 (1.8)	0.320
Previous MI	1 (1.4)	0 (0)	1 (1.8)	1.000
Previous stroke	1 (1.4)	0 (0)	1 (1.8)	1.000
Clinical manifestation				
Spontaneous spasm	17 (24.6)	6 (50.0)	11 (19.3)	0.025
OHCA	4 (5.8)	4 (33.3)	0 (0)	
AMI	11 (15.9)	11 (91.7)	0 (0)	
UA	58 (84.1)	–		
Braunwald class IB	7 (12.1)	–	7 (12.3)	
Braunwald class IIB	25 (43.1)	–	25 (43.9)	
Braunwald class IIIB	26 (44.8)	–	25 (43.9)	
ECG at admission				<0.001
ST-segment elevation	12 (17.4)	8 (66.7)	4 (7.0)	
ST-segment depression	1 (1.4)	0 (0)	1 (1.8)	
T inversion	2 (2.9)	0 (0)	2 (3.5)	
Laboratory findings				
Creatinine, mg/dl	1.1 (0.9–1.2)	1.1 (0.9–1.4)	1.0 (0.9–1.2)	0.021
Total cholesterol, mg/dl	182 (154–207)	161 (136–162)	182 (157–205)	0.383
LDL, mg/dl	93 (77–117)	89 (51–58)	93 (77–124)	0.514
hs-CRP, m/dl	0.06 (0.03–0.16)	0.31 (0.09–0.75)	0.06 (0.03–0.13)	0.021
Peak CK-MB, ng/ml	1.1 (0.7–2.3)	10.6 (4.6–76.7)	0.9 (0.6–1.3)	<0.001
Peak troponin T, ng/ml	0.01 (0.01–0.05)	1.03 (0.26–3.37)	0.01 (0.01–0.03)	<0.001
Echocardiography				
Ejection fraction, %	66 (62–69)	63 (51–68)	66 (62–69)	<0.001
Spasm site (n = 80)				0.919
LAD	35 (43.8)	7 (43.8)	28 (43.8)	
LCx	7 (8.8)	1 (6.3)	6 (9.4)	
RCA	38 (47.5)	8 (50.0)	30 (46.9)	

Values are n (%) or median (interquartile range).

AMI = acute myocardial infarction; BMI = body mass index; CAD = coronary artery disease; CK-MB = creatinine kinase, myocardial band; ECG = electrocardiogram; hs-CRP = high-sensitivity C-reactive protein; LAD = left anterior descending coronary artery; LCx = left circumflex artery; LDL = low-density lipoprotein; MI = myocardial infarction; OHCA = out-of-hospital cardiac arrest; RCA = right coronary artery; UA = unstable angina.

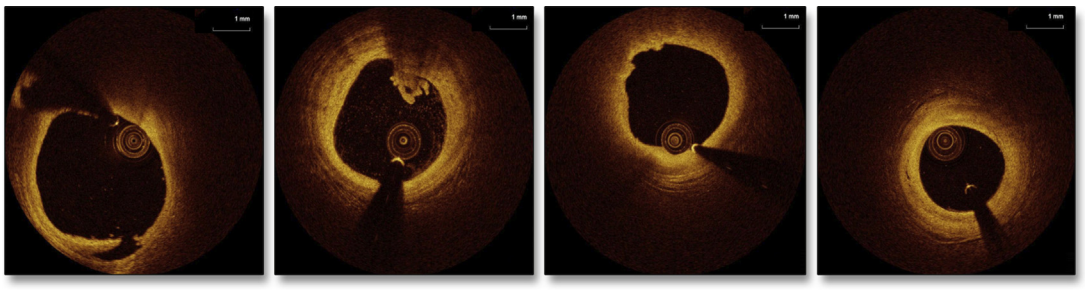
p = 0.025). Admission ECG showing ST-segment elevation was present in 8 patients (66.7%) in the AMI/OHCA group and 4 (7.0%) in the non-AMI/OHCA group (p < 0.01) (Table 1).

Coronary spasm was detected most frequently in the right coronary artery (47.5%), followed by the left anterior descending coronary artery (43.8%). The minimal lumen diameter after intracoronary nitrate injection was comparable between the 2 groups (AMI/OHCA vs. non-AMI/OHCA, 2.34 ± 0.66 mm vs. 2.35 ± 0.74 mm; p = 0.945). Forty spasm sites (50.0%) showed slow coronary flow (TIMI [Thrombolysis In Myocardial Infarction] flow grade 0 to 2) during coronary artery spasm. There was no statistically significant difference in the proportion of patients with slow coronary flow between the AMI/OHCA and non-AMI/OHCA groups (31.3% vs. 54.7%; p = 0.094). Five patients (7.2%) had to have stents implanted because of low fractional flow reserve values (<0.75) after nitroglycerin injection.

OCT FINDINGS. OCT findings are presented in Figure 2 and Table 2. A representative case of OCT-defined erosion is demonstrated in Figure 3. Thrombus was identified in 23 of 80 spasm sites (28.8%). According to the OCT-defined characteristics in Figure 1, 3 spasm sites (4%) were classified as fibrous cap disruption, and 21 spasm sites (26%) with intact fibrous cap and thrombus were classified as OCT-defined erosion. Of the remaining spasm sites, there were 49 (61%) with luminal irregularity in the absence of thrombus (Online Figure 2), 6 (7.5%) without thrombus or luminal irregularity, and 1 (1.25%) without plaque or thrombus. Among the 3 fibrous cap disruption cases, 2 were the culprits of AMI. Three of 4 patients who presented with OHCA had AMI with spasm sites that demonstrated OCT-defined erosion; the remaining OHCA patient had a spasm site that demonstrated luminal irregularity in the absence of thrombus. Among the OCT-defined erosion spasm sites, there was 1 spasm site that showed thrombus without lumen irregularity. One patient who presented as having an AMI had multiple spasm sites on the left anterior descending coronary artery and right coronary artery. Table 2 shows the OCT findings in fibrous cap disruption and OCT-defined erosion groups. White thrombus was predominantly detected, being observed at 82.6% of spasm sites, compared with red thrombus, which was seen at 17.4% of sites. Thrombus was mainly located at the spasm sites rather than proximal to the spasm sites. Both fibrous and lipid plaques were detected at spasm sites (Table 2). TCFA was rarely seen (2 spasm sites [2.5%]) and was only observed at OCT-defined erosion sites. The mean cap thickness of lipid plaques was 146 ± 67 μm.

CLINICAL MANIFESTATIONS IN PATIENTS WITH THROMBUS. The characteristics of spasm sites with thrombus (fibrous cap disruption and OCT-defined erosion) in 24 patients are listed in Table 3. These thrombotic lesions were detected in 50.0% of the AMI/OHCA group (6 of 12 patients) and 31.6% of the non-AMI/OHCA group (18 of 57 patients; p = 0.22);

FIGURE 2 Characteristics of Spasm Sites as Assessed by OCT in Patients With Vasospastic Angina



Fibrous Cap Disruption: Fibrous cap discontinuity with or without a cavity formed inside the plaque

OCT-defined Erosion: Underlying visualized plaque with intact fibrous cap, lumen irregularity and thrombus

Luminal irregularity

No luminal irregularity or thrombus

Each **panel** depicts the specific optical coherence tomography (OCT)–defined characteristics and findings.

patients with severe clinical presentation (AMI/OHCA group) showed a trend toward more thrombotic spasm sites, but this did not attain statistical significance. VSA was diagnosed spontaneously (without provocation) in 41.7% and provocatively in 25.0% of these thrombotic lesions ($p = 0.136$). There was no significant difference in thrombus size between the AMI/OCHA and non-AMI/OHCA groups (0.19 ± 0.25 mm^2 vs. 0.32 ± 0.62 mm^2; $p = 0.49$).

DISCUSSION

The major findings of this OCT study evaluating morphological characteristics of coronary artery spasm sites in VSA patients include the following: 1) thrombus was frequently detected in patients with VSA (28.8% of total spasm sites); 2) OCT-defined erosion, identified as the concurrence of thrombus and intact fibrous cap, was common in patients with VSA (26%); and 3) spontaneous spasm was observed more frequently in the AMI/OHCA group than in the non-AMI/OHCA group.

In pathological studies, plaque erosion is defined as a loss of endothelial lining with lacerations of the superficial intimal layers in the absence of fibrous cap disruption (17). OCT imaging does not adequately provide the resolution required to identify and assess the endothelial lining. Taking the limitations of OCT into account with regard to pathological findings, we have suggested applicable diagnostic criteria that can be used to analyze OCT findings of spasm sites in VSA. These descriptions may be helpful for future OCT studies and to investigate the underlying pathophysiology of VSA.

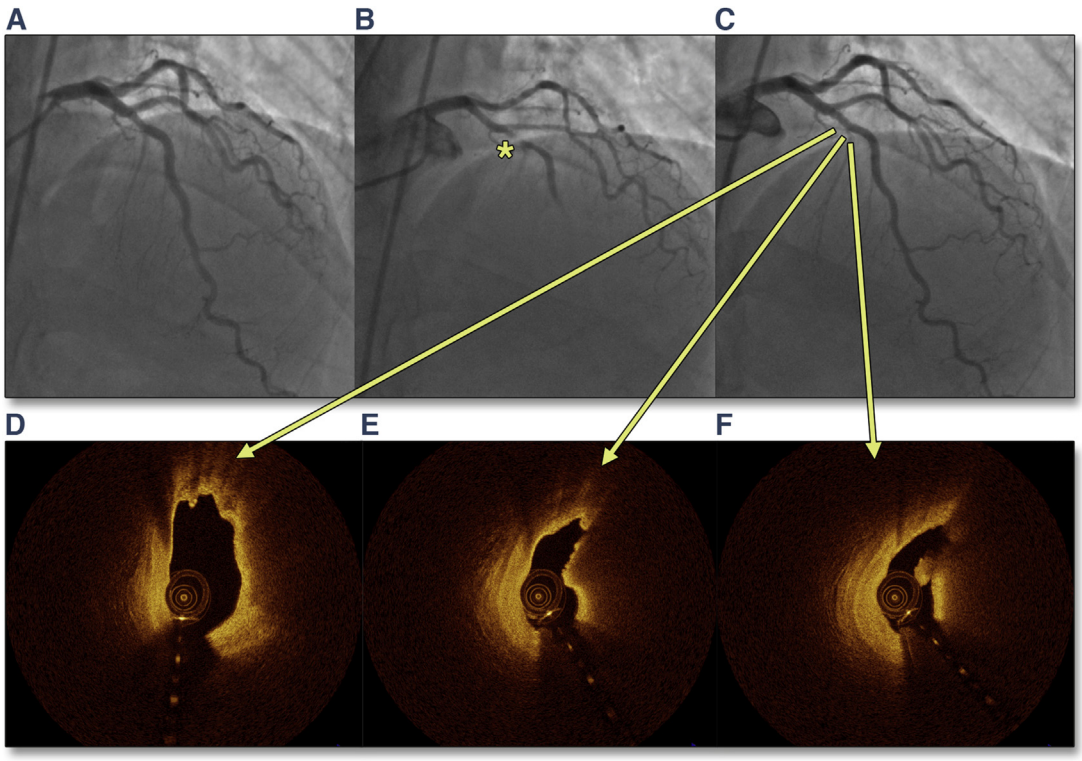
In ACS patients, plaque erosion had a lower frequency of lipid plaque (43.6% vs. 100%; $p < 0.001$) and thicker fibrous cap (169.3 ± 99.1 μm vs. 60.4 ± 16.6 μm; $p < 0.001$) than plaque rupture (18). In the present study, lipid plaque was detected at 56.3% of all spasm sites and at 55.0% of OCT-defined erosion sites. Fibrous plaque was seen at 45.0% of OCT-defined erosion sites, and mean cap thickness was 146 ± 95 μm. The patient population and definition

TABLE 2 OCT Findings at Spasm Sites

	Total Spasm Sites (n = 80)	Fibrous Cap Disruption (n = 3)	OCT-Defined Erosion (n = 21)
Thrombus	23 (28.8)		
Characteristics			
Red thrombus	4 (17.4)	0 (0)	4 (19.0)
White thrombus	19 (82.6)	2 (100.0)	17 (81.0)
Location			
Proximal to spasm site	4 (17.4)	0 (0)	4 (19.0)
At spasm site	19 (82.6)	2 (100.0)	17 (81.0)
Size			
Area of thrombus, mm^2	0.29 ± 0.56	0.08 ± 0.09	0.31 ± 0.58
Maximal diameter, mm	0.64 ± 0.55	0.28 ± 0.18	0.68 ± 0.56
Plaque			
Fibrous plaque	35 (43.8)	1 (33.3)	10 (47.6)
Lipid plaque	45 (56.3)	2 (66.7)	11 (52.4)
TCFA, <65 μm	2 (4.4)	0 (0)	2 (18.2)
Cap thickness, μm	146.4 ± 67.2	130.0 ± 42.4	146.4 ± 95.4

Values are n (%) or mean ± SD.
OCT = optical coherence tomography; TCFA = thin-cap fibroatheroma.

FIGURE 3 Representative Case of OCT-Defined Erosion



(A) Coronary angiography shows nonsignificant stenosis in mid-left anterior descending coronary artery. **(B)** Intracoronary ergonovine injection resulted in complete occlusion. **(C)** This normalized with 200 μg of intracoronary nitroglycerin administration. **(E, F)** Optical coherence tomography (OCT) revealed a red thrombus with high backscattering protrusion mass with signal-free shadowing. **(D to F)** An intact fibrous cap and an irregular luminal surface are visible. **Asterisk** indicates the total occlusion site by ergonovine provocation test and **arrows** indicate the sites of OCT findings after nitroglycerine injection.

of lipid plaque used were different between the present study and the previous study of plaque erosion (18). In the previous study, patients with ACS were selected, and lipid plaque was defined with lipid content in ≥2 quadrants. In the present study, patients with VSA were included, and even though they had clinical manifestations of ACS, the lipid plaque was defined as lipid content in ≥1 quadrant. Therefore, more lipid plaque was documented in the present study using this definition. In the present study, we found fibrous cap disruption in 4% of spasm sites, and it was not related to TCFA or cavity in the lipid plaque. Also, non-thin-cap disruption was the main finding of plaque disruption seen in our VSA patients (2 of 3).

Platelet-rich white thrombus was predominantly observed at plaque erosion sites. There was no difference in the incidence and size of thrombus at provoked compared with spontaneous spasm sites. There was no correlation between thrombus and clinical manifestations in this study. This may be related to the thrombus size, which was relatively small to cause obstruction, and may suggest that the contact of platelets with plaque erosion may not suffice to form large thrombus. It is thought that thrombosis that accompanies vasospasm is a result of grossly reduced blood flow secondary to critical vascular constriction. In an animal study using electron microscopy, a 40% to 60% reduction in luminal diameter of the left anterior descending coronary arteries resulted in endothelial denudation, platelet deposition, and thrombus formation in areas proximal to the point of maximal constriction (19). The endothelial damage from constriction may result in thrombus formation at the spasm site, followed by partial or total arterial occlusion at that site, especially if superimposed on pre-existing arteriosclerosis.

TABLE 3 Clinical Manifestations of Fibrous Cap Disruption and OCT-Defined Erosion

Patient #	OCT Findings	Clinical Manifestation	Age (yrs)/Sex	Ergonovine Provocation	Vessel	ECG on Admission	Braunwald Chest Pain Class	Smoking Status	Peak CK-MB (ng/ml)	Peak Trop-T (ng/ml)	Area of Thrombus (mm^2)	Maximal Diameter of Thrombus (mm)
1	Fibrous cap disruption	AMI	58/M	–	RCA	ST-segment elevation	-	Nonsmoker	32.6	3.15	-	-
2	Fibrous cap disruption	AMI	50/M	+	RCA	ST-segment elevation	-	Current	192.1	3.44	0.14	0.40
3	OCT-defined erosion	AMI, OHCA	54/M	–	LAD	ST-segment elevation	-	Current	78.0	1.53	0.03	0.28
4	OCT-defined erosion	AMI, OHCA	53/M	–	RCA	ST-segment elevation	-	Current	491.6	4.85	0.64	1.38
5	OCT-defined erosion	AMI, OHCA	54/F	+	RCA	ST-segment elevation	-	Current	9.4	0.53	0.07	0.51
6	OCT-defined erosion	AMI	59/M	–	RCA	ST-segment elevation	-	Current	11.8	0.42	0.07	0.62
7	Fibrous cap disruption	UA	46/F	+	LAD	Normal	III	Nonsmoker	1.4	0.04	0.01	0.15
8	OCT-defined erosion	UA	59/M	–	LAD	ST-segment depression	II	Nonsmoker	1.3	0.02	1.15	1.86
9	OCT-defined erosion	UA	45/M	+	LAD	T inversion	III	Current	0.7	0.05	2.49	2.33
10	OCT-defined erosion	UA	76/F	–	RCA	T inversion	II	Current	0.8	0.01	0.03	0.19
11	OCT-defined erosion	UA	57/M	+	LAD	Normal	III	Ex-smoker	1.1	0.01	0.23	0.75
12	OCT-defined erosion	UA	55/M	–	RCA	Normal	II	Ex-smoker	2.0	0.08	0.20	0.73
13	OCT-defined erosion	UA	58/M	–	LAD	Normal	III	Current	0.9	0.01	0.10	0.48
14	OCT-defined erosion	UA	61/M	+	RCA	Normal	I	Current	2.5	0.01	0.01	0.16
15	OCT-defined erosion	UA	43/M	+	RCA	Normal	III	Current	1.2	0.01	0.06	0.35
16	OCT-defined erosion	UA	53/M	+	RCA	Normal	III	Nonsmoker	2.6	0.02	0.08	0.51
17	OCT-defined erosion	UA	53/M	+	LAD	Normal	II	Current	0.5	0.01	0.15	0.66
18	OCT-defined erosion	UA	49/M	–	LCx	Normal	III	Nonsmoker	NA	NA	0.02	0.20
19	OCT-defined erosion	UA	43/M	+	RCA	Normal	II	Nonsmoker	0.6	0.02	0.03	0.24
20	OCT-defined erosion	UA	47/M	+	LAD	Normal	III	Nonsmoker	0.9	0.01	0.04	0.35
21	OCT-defined erosion	UA	51/F	–	LAD	Normal	II	Nonsmoker	0.4	0.01	0.05	0.31
22	OCT-defined erosion	UA	43/M	+	RCA	Normal	II	Nonsmoker	0.7	0.01	0.17	1.01
23	OCT-defined erosion	UA	45/F	+	LAD	Normal	III	Current	0.6	0.02	0.83	0.83
24	OCT-defined erosion	UA	59/M	+	RCA	Normal	I	Current	NA	NA	0.11	0.46

F = female; M = male; NA = not applicable; OCT = optical coherence tomography; Trop-T = troponin-T; other abbreviations as in Table 1.

In another animal study, provoked spasm sites showed intimal injuries (up to 60.9%) in the form of endothelial cell protrusions, denudation, and macrophage extravasation (20). It was suggested that vasospasm contributed to both superficial plaque injury and actual plaque disruption (20). The interaction of platelets with the damaged vessel wall and the ensuing reaction might further potentiate the coronary spasm (9).

Previous OCT findings in ACS patients have shown that 40% of thrombotic coronary occlusions were caused by plaque erosion without significant stenosis (21). In this study, all enrolled VSA patients presented with clinical manifestations of ACS. Because plaque erosion was a common finding in our study, it is possible that the ACS was triggered by spasm-related plaque erosion. ACS with nonobstructive lesions could be amenable to treatment with antiplatelet drugs alone, without invasive angioplasty or coronary stent deployment, with satisfactory clinical outcomes (21).

Although more than one-half of all spasm sites did not have any apparent thrombus (which does not fulfill the pathological definition of plaque erosion), luminal irregularity was observed in the majority of these cases. There is a distinct possibility that lumen irregularity in the absence of thrombus may represent plaque erosion. There is uncertainty about the cause-and-effect relationship between the occurrence of vasospasm and the denudation of the endothelium, followed by thrombus formation. In other words, the denudation of the endothelium with or without thrombus formation may cause vasospasm, or repeated spasm may have caused the current findings. OCT was performed after the spasm provocation test or spontaneous spasm, and therefore, it is theoretically possible that thrombus might have been increased or appeared with the coronary artery spasm.

The clinical benefits of antiplatelet therapy in VSA, especially aspirin, have been debated. Recent studies have proposed the use of cilostazol for its vasodilatory properties in the treatment of VSA (22). In our recently published STELLA (A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Therapeutic Exploratory Study to Evaluate the Efficacy and Safety of Pletal [Cilostazol] in Subjects With Vasospastic Angina) trial, patients with VSA were randomized to receive

cilostazol in addition to amlodipine, with significant improvement in angina frequency and intensity (23). In addition to its vasodilatory properties, cilostazol also has antiplatelet actions that may allow for the prevention of thrombotic complications. Therefore, further research is needed to study this agent's antiplatelet role in VSA patients.

STUDY LIMITATIONS. The findings of the present study are based on a small cohort of patients with angiographic evidence of coronary artery spasm. Also, the proposed definitions using the OCT criteria in this study are for classification of spasm sites in confirmed VSA cases presenting with ACS; therefore, we are unable to broadly generalize this classification as being applicable to all ACS cases. In addition, because OCT was performed only after the spasm provocation test or spontaneous spasm, thrombus might have increased or appeared with the spasm. A further dedicated and larger study to address this possibility is needed.

CONCLUSIONS

Our results show that OCT-defined erosion is a common finding at the site of VSA, with accompanying thrombus present in a substantial proportion of cases. This finding suggests the potential role for antiplatelet therapy in VSA.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coronary artery spasm is 1 of the causes of ACS, including AMI and sudden cardiac death. OCT-defined erosion and thrombus are commonly observed at the site of coronary artery spasm in patients with VSA.

TRANSLATIONAL OUTLOOK: Additional research is needed to reveal the cause-and-effect relationship between the occurrence of vasospasm and the development of erosions and thrombus, and further studies are necessary to examine the potential role of antiplatelet therapy in VSA.

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KEY WORDS acute myocardial infarction, cardiac arrest, intravascular imaging, plaque erosion, plaque rupture, Prinzmetal angina

APPENDIX For supplemental figures, please see the online version of this article.