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A Combined Optical Coherence Tomography and Intravascular Ultrasound Study on Plaque Rupture, Plaque Erosion, and Calcified Nodule in Patients With ST-Segment Elevation Myocardial Infarction

Incidence, Morphologic Characteristics, and Outcomes After Percutaneous Coronary Intervention

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CME Objective for This Article: At the completion of this article, the learner should be able to: 1) discuss the incidence of plaque rupture, plaque erosion, and calcified nodules, as detected on intravascular imaging, in patients with ST-segment elevation myocardial infarction; and 2) compare the post-procedure outcomes between plaque rupture and calcified nodules in patients with ST-segment elevation myocardial infarction.

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ABSTRACT

OBJECTIVES This study sought to evaluate the incidence of plaque rupture (PR), plaque erosion (PE), and calcified nodule (CN) using optical coherence tomography (OCT) in patients with ST-segment elevation myocardial infarction (STEMI); to compare detailed morphologic plaque characteristics of PR, PE, and CN with optical coherence tomography and intravascular ultrasound; and to compare the post-procedure outcomes among PR, PE, and CN.

BACKGROUND The incidence and detailed morphologic characteristics of PR, PE, and CN in STEMI patients and their outcome after percutaneous coronary intervention (PCI) are unknown.

METHODS A total of 112 STEMI patients who underwent PCI within 12 h from symptom onset were included. Both optical coherence tomography and intravascular ultrasound were performed following aspiration thrombectomy.

RESULTS The incidence of PR, PE, and CN was 64.3%, 26.8%, and 8.0%, respectively. PE and CN, compared with PR, had more fibrous plaque ($p < 0.001$ and $p < 0.001$) and less thin-cap fibroatheroma ($p < 0.001$ and $p < 0.001$) as well as smaller plaque burden ($p = 0.003$ and $p = 0.001$) and remodeling index ($p = 0.003$ and $p < 0.001$). PE had greater plaque eccentricity index than PR and CN ($p < 0.001$ and $p < 0.001$). CN had greater calcified arc and shallower calcium than PR ($p < 0.001$ and $p < 0.001$) or PE ($p < 0.001$ and $p < 0.001$). More than one-half of CN had negative remodeling. PE had a lower incidence of no-reflow phenomenon after PCI than PR ($p = 0.011$).

CONCLUSIONS PE was the underlying mechanism in one-fourth of STEMI. PE was characterized by eccentric fibrous plaque. CN was characterized by superficial large calcium and negative remodeling. PE was associated with less microvascular damage after PCI. (J Am Coll Cardiol Intv 2015;8:1166–76) © 2015 by the American College of Cardiology Foundation.

The majority of acute coronary thromboses are attributable to 3 underlying mechanisms: plaque rupture (PR); plaque erosion (PE); and calcified nodule (CN). PR has been well characterized by both ex vivo and in vivo studies (1–3). Our group recently reported in vivo diagnosis of PE and CN using optical coherence tomography (OCT) in patients with acute coronary syndromes (ACS) (4). In that study, patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS were both included, and intravascular OCT was performed at variable time points after symptom onset. Therefore, the true incidence of PE and CN in patients with acute STEMI has not previously been reported. In addition, information on plaque burden and coronary remodeling in this population has not been studied because only OCT was used.

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The aims of this study were the following: 1) to evaluate the incidence of PR, PE, and CN detected by OCT in patients with STEMI during the acute phase; 2) to study the detailed morphologic characteristics of the culprit plaques using the combination of OCT and intravascular ultrasound (IVUS); and 3) to compare the post-procedure outcomes among these 3 groups.

METHODS

STUDY POPULATION AND PCI PROCEDURES. Of the 145 patients who were admitted to Hirosaki

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CK = creatine kinase

CN = calcified nodule

CSA = cross-sectional area

EEM = external elastic membrane

IVUS = intravascular ultrasound

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

PE = plaque erosion

P+M = plaque plus media

PR = plaque rupture

STEMI = ST-segment elevation myocardial infarction

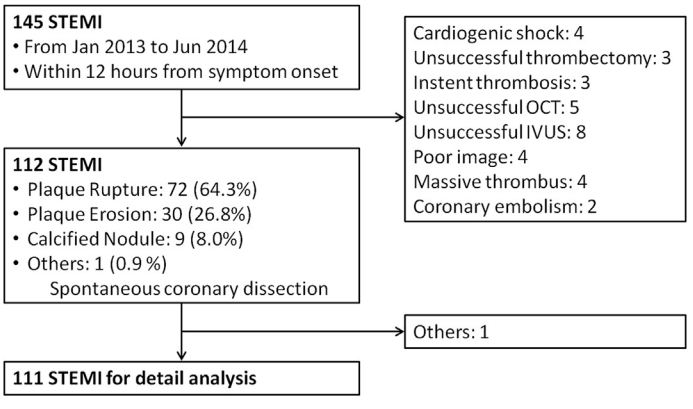
TIMI = Thrombolysis In Myocardial Infarction

TCFA = thin-cap fibroatheroma

University Hospital (Hirosaki, Japan) with STEMI between January 2013 and June 2014 and who provided written informed consent for the primary percutaneous coronary intervention (PCI) procedure, 112 patients who had undergone both OCT and IVUS as part of their routine care were retrospectively included in this study (Figure 1). This study cohort was different from our previous study (4). We did not include previous data in this study. STEMI was defined as elevation of creatine kinase-myocardial isoform and/or cardiac troponin T value greater than the upper reference limit with typical chest pain lasting >20 min, and ECG showing new ST-segment elevation of ≥2 mm in at least 2 contiguous precordial electrocardiogram leads, ≥1 mm in at least 2 contiguous limb electrocardiogram leads, or newly appeared left bundle branch block. All patients underwent the interventional procedure within 12 h of symptom onset. Exclusion criteria were cardiogenic shock, unsuccessful reperfusion to achieve antegrade flow after aspiration thrombectomy, in-stent thrombosis, inability to advance an intravascular imaging catheter to the culprit lesion, poor image quality, massive thrombus, and coronary embolism.

All images were deidentified, digitally stored, and sent to Massachusetts General Hospital (Boston). All image analysis was performed at Massachusetts General Hospital. Using the previously established criteria (4), the patients were classified into 4 groups: PR; PE; CN; and others. Angiographic, OCT, IVUS, and patient characteristics were compared among the PR, PE, and CN groups. This collaboration study was approved by the institutional review boards at Massachusetts General Hospital and Hirosaki University Hospital.

FIGURE 1 Study Flow Chart



Of the 145 patients with acute onset STEMI, 112 patients were identified with the underlying mechanism of STEMI using OCT and IVUS. Finally, 111 STEMI patients were enrolled for detail analysis. IVUS = intravascular ultrasound; OCT = optical coherence tomography; STEMI = ST-segment elevation myocardial infarction.

ACQUISITION OF OCT AND IVUS IMAGE. Aspirin 200 mg, clopidogrel 300 mg, and heparin 100 IU/kg were administrated prior to the procedure. None of the patients were pretreated with a thrombolytic agent and a glycoprotein IIb/IIIa inhibitor because the latter agent was not available in Japan. Both OCT and IVUS were performed to the culprit lesion after manual thrombectomy, which was repeated until antegrade coronary flow was restored and analyzable image quality was achieved. A frequency-domain OCT system (ILUMIEN OCT Intravascular Imaging Systems, St. Jude Medical, St. Paul, Minnesota) was used in this study. The technique of intracoronary OCT imaging has been previously described (5).

For IVUS imaging, a 20-MHz, 3.2-F catheter (Eagle Eye Gold Catheter, Volcano Therapeutics, San Diego, California) was used. After positioning the IVUS catheter distal to the target lesion, the catheter was pulled back to the coronary ostium using a motorized pull-back device at 0.5 mm/s.

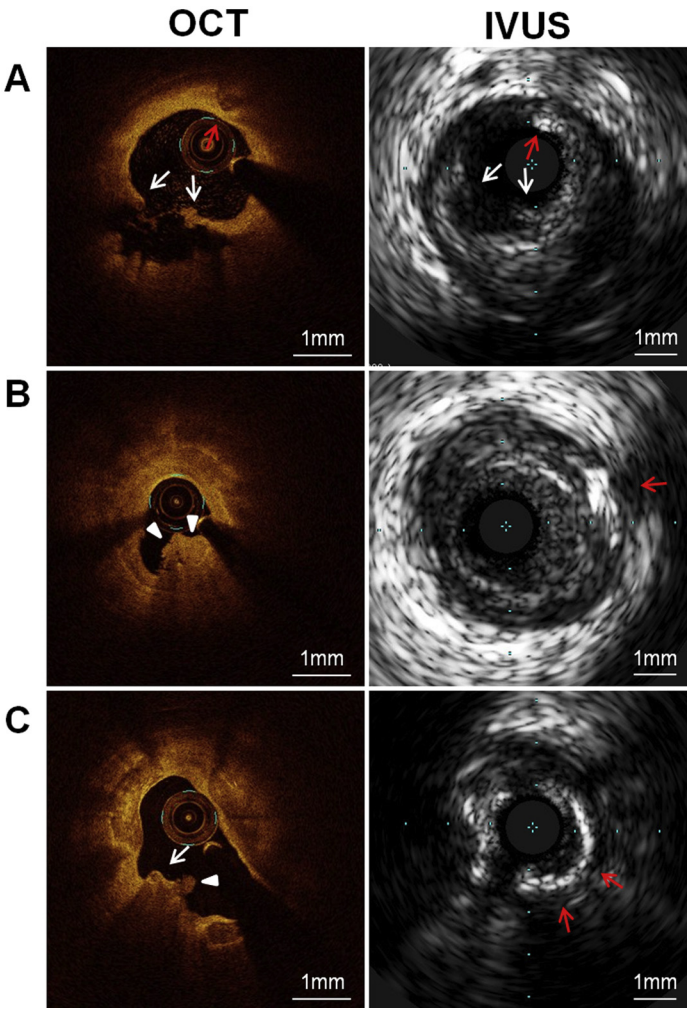
OCT ANALYSIS. OCT images from the entire length of the lesion plus 5 mm proximal and distal reference segments were included in the analysis. The reference was the frame showing the largest lumen area within 10 mm proximal and distal from the target lesions. Plaques were categorized using the previously established criteria (4). PR was defined by the presence of fibrous cap discontinuity with a communication between lumen and inner core of a plaque or with a cavity formation within the plaque (Figure 2A) (3,6). PE was identified by the presence of attached thrombus overlying an intact and visualized plaque, luminal surface irregularity at the culprit lesion in the absence of thrombus, or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus (Figure 2B) (4). CN was defined by fibrous cap disruption detected over a calcified plaque characterized by protruding calcification, superficial calcium, or the presence of substantive calcium proximal and/or distal to the lesion (Figure 2C). Culprit lesions that did not satisfy these criteria were classified as others and included tight stenosis, spontaneous coronary artery dissection, and coronary spasm.

Tissue characterization of underlying plaque was performed using previously established criteria (7,8). Plaques were classified as primarily fibrous (homogeneous, high backscattering region) or lipid (low-signal region with diffuse border). Lipid plaque was defined as a plaque with lipid arc >90°. For each lipid plaque, the thinnest fibrous cap thickness and the maximal arc of lipid were measured. We evaluated the presence of lipid on every cross section. Additionally, lipid length was measured using the consecutive length of cross section with lipid on longitudinal view. Thin-cap fibroatheroma (TCFA) was defined as a plaque with lipid arc >90° with thinnest fibrous cap thickness <65 μm. Calcification was defined as a signal-poor or heterogeneous region with sharply delineated borders. For each calcification, the maximal calcium arc and the minimal depth from luminal surface to the leading edge of calcification were measured. A microchannel was defined as a sharply delineated signal-poor hole visible on multiple contiguous frames (5,9). Thrombus was semi-quantitatively calculated by summing the number of involved quadrants in each 1-mm interval cross section (10). All OCT images were analyzed by 2 experienced investigators who were blinded to the angiographic data and clinical presentations. When there was discordance between the observers, a consensus reading was obtained from another investigator. Interobserver and intraobserver variability were assessed by the evaluation of all images by 2 independent observers and by the same observer at 2 separate time points.

IVUS ANALYSIS. Quantitative IVUS measurements included the external elastic membrane (EEM) cross-sectional area (CSA), lumen CSA, and the plaque plus media (P+M) CSA at the lesion site (cross section with the minimal lumen CSA) and reference sites. Plaque burden was calculated as the lesion P+M CSA divided by the lesion EEM CSA multiplied by 100 (11). Reference site was identified as the image frame showing the least diseased site within 10 mm proximal and distal to the culprit lesion. Plaque eccentricity index was calculated as (maximal P+M thickness minus minimal P+M thickness) divided by maximal P+M thickness (11), and eccentric plaque was defined by plaque eccentricity index >0.65. This threshold value was determined using receiver-operating characteristic to predict PE. The remodeling index was calculated as the EEM CSA at the lesion site divided by the average of the proximal and distal reference EEM CSA (11). Positive remodeling was defined as plaque with remodeling index >1.05, and negative remodeling was defined as plaque with remodeling index <0.95. IVUS-detected PR was defined as plaque ulceration with a tear detected in the fibrous cap (**Figure 2A**) (11). All IVUS images were analyzed by 2 experienced investigators who were blinded to the angiographic data and clinical presentations. When there was discordance between the observers, a consensus reading was obtained from another investigator.

ANGIOGRAPHIC ANALYSIS. Coronary angiograms performed before intervention, after thrombectomy,

FIGURE 2 Representative Images of Underlying Plaque Morphologies in STEMI



(A) Plaque rupture: disrupted fibrous cap **(white arrows),** large lipid core (1 to 10 o'clock), and spotty calcification **(red arrow)** were observed on both OCT and IVUS. **(B)** Plaque erosion: OCT demonstrated white thrombus **(arrowheads)** on the luminal surface. There was no evidence of fibrous cap disruption. IVUS revealed deep spotty calcification **(red arrow). (C)** Calcified nodule: OCT revealed concave calcification **(white arrow)** with white thrombus **(arrowhead)**. IVUS showed a large calcium sheet near the luminal surface **(red arrows)**. Abbreviations as in **Figure 1**.

and at the end of the procedure were analyzed. We evaluated baseline, post-thrombectomy, and final antegrade coronary flow according to the TIMI (Thrombolysis In Myocardial Infarction) criteria (12) and final myocardial blush grade (13). No-reflow was defined as TIMI flow grade ≤2 or TIMI flow grade 3 with myocardial blush grade ≤1 at the final angiogram (14). Reference diameter, minimal lumen diameter, percentage of diameter stenosis, and lesion length were also measured. Coronary angiograms were analyzed using an off-line quantitative coronary angiography program (CAAS version 5.10.1, Pie Medical Imaging BV, Maastricht, the Netherlands).

STATISTICAL ANALYSIS. Categorical outcomes were presented as counts and percentages, and Fisher exact test or chi-square test was used as appropriate. The distributions of continuous variables were tested for normality with the Kolgormonov-Smirnov test. The mean ± SD was reported when data were normally distributed, and the median (25th, 75th percentiles) were reported when data were not normally distributed. For between-group comparisons, 1-way analysis of variance or Kruskal-Wallis test for continuous outcomes and chi-square or Fisher exact test for categorical outcomes was applied for testing overall differences, and then post-hoc tests for controlling type 1 error by using Bonferroni correction were performed if the overall test was significant. A p value of <0.05 was considered statistically significant for an overall comparison. If the p value of the overall test was <0.05, then 2-group post-hoc comparison was performed using Mann-Whitney *U* test or the independent samples Student *t* test for continuous outcomes, and chi-square or Fisher exact test for categorical outcomes, and the test result was considered significant if the p value was <0.017 (i.e., 0.05 of 3). Receiver-operating characteristic analysis was performed to determine the best cutoff value of plaque eccentricity index for PE. Intra- and interobserver reliability was assessed by kappa statistics. All statistical analyses were performed with SPSS (version 17.0, SPSS Inc., Chicago, Illinois).

RESULTS

PREVALENCE OF PLAQUE RUPTURE, PLAQUE EROSION, AND CALCIFIED NODULE. In the 112 cases of STEMI, the prevalence of PR, PE, and CN was 72 (64.3%), 30 (26.8%), and 9 (8.0%), respectively. Another cause of STEMI included 1 case (0.9%) of spontaneous coronary dissection. Finally, 111 patients in which STEMI was caused by PR, PE, or CN were included for morphologic characterization and analysis. Intraobserver and interobserver kappa coefficients for plaque classification were 0.85 and 0.87, respectively.

BASELINE CHARACTERISTICS. The baseline clinical and angiographic characteristics are shown in Tables 1 and 2. Patients with PE were younger than those with CN ($p = 0.004$) and less frequently obese than those with PR ($p = 0.012$). There were no significant differences in the other clinical variables among the 3 groups.

The location of the culprit lesion and angiographic parameters were similar among the 3 groups. Severe calcification was more frequently seen in CN than in PR ($p < 0.001$) or PE ($p = 0.002$). Although PR required a slightly greater number of stents than PE did ($p = 0.010$), stent diameter, total stent length, and maximal balloon pressure were similar among the 3 groups.

OCT FINDINGS. Both PE and CN, when compared with PR, had a higher prevalence of fibrous plaque ($p < 0.001$ and $p < 0.001$), and a lower prevalence of lipid plaque ($p < 0.001$ and $p < 0.001$) and TCFA ($p < 0.001$ and $p < 0.001$) (Table 3, Figure 3A and 3B). Among lipid plaques, PE and CN had smaller lipid burden than PR did (Table 3).

PE had a lower prevalence of microchannels than PR did ($p < 0.001$) (Figure 3C). Although the prevalence of calcification and calcium arc were similar between PE and PR, the location of calcification in PE was deeper in the vessel wall than it was in PR ($p < 0.001$) (Table 3).

CN had larger calcium arc and more superficial calcium in the vessel wall than PR ($p < 0.001$ and $p < 0.001$) or PE ($p < 0.001$ and $p < 0.001$) (Table 3). There were no differences in other OCT characteristics between PE and CN. Post-thrombectomy thrombus score was similar among the 3 groups.

IVUS FINDINGS. Among the 72 OCT-detected PR, IVUS could detect only 17 PR (23.6%). Compared with PR, PE had larger lumen CSA ($p = 0.005$), smaller plaque burden ($p = 0.003$), and greater plaque eccentricity index ($p < 0.001$) at the lesion site (Table 4). Receiver-operating characteristic curve analysis showed that a plaque eccentricity index of 0.65 was the best cutoff to predict PE (area under the curve: 0.744, sensitivity: 73.3%, specificity: 70.4%, positive predictive value: 47.8%, and negative predictive value: 87.7%). We therefore used this cutoff value to define eccentric plaque, which was more frequent in PE than in PR ($p < 0.001$) or CN ($p = 0.001$) (Figure 4A). The majority of culprit

TABLE 1 Baseline Clinical Characteristics

	PR (n = 72)	PE (n = 30)	CN (n = 9)	p Value	p Value* PR vs. PE	PE vs. CN	PR vs. CN
Age, yrs	71.0 (60.0, 76.8)	65.0 (59.8, 70.0)	74.0 (71.0, 77.0)	0.037	0.096	0.004	0.209
Male	54 (75.0)	26 (86.7)	9 (100.0)	0.120			
Risk factors							
Smoking	35 (48.6)	14 (46.7)	2 (22.2)	0.324			
Diabetes mellitus	32 (44.4)	8 (26.7)	6 (66.7)	0.070			
Dyslipidemia	47 (65.3)	22 (73.3)	6 (66.7)	0.730			
Hypertension	51 (70.8)	17 (56.7)	8 (88.9)	0.145			
Obesity (BMI >25.0 kg/m^2)	32 (44.4)	5 (16.7)	2 (22.2)	0.019	0.012	0.653	0.291
Previous history							
Previous MI	3 (4.2)	2 (6.7)	2 (22.2)	0.110			
Previous PCI	1 (1.4)	2 (6.7)	1 (11.1)	0.193			
Medications							
Aspirin	5 (6.9)	1 (3.3)	0 (0)	0.577			
ACEI/ARB	21 (29.2)	6 (20.0)	2 (22.2)	0.607			
Beta-blocker	6 (8.3)	1 (3.3)	0 (0)	0.460			
Calcium channel blocker	28 (38.9)	9 (30.0)	5 (55.6)	0.365			
Statin	13 (18.1)	6 (20.0)	2 (22.2)	0.941			
Insulin	3 (4.2)	1 (3.3)	0 (0)	0.815			
Laboratory findings							
Troponin T, ng/ml	0.21 (0.07, 0.73)	0.08 (0.03, 0.37)	0.81 (0.06, 2.19)	0.130			
CK, IU/l	238 (125, 550)	150 (94, 343)	465 (104, 845)	0.146			
CK-MB, IU/l	23 (8, 54)	11 (6, 45)	48 (6, 147)	0.250			
Onset to reperfusion time, min	397 ± 301	342 ± 240	465 ± 99	0.496			

Values are median (25th, 75th percentiles), mean ± SD, or n (%). *A p value of <0.017 was considered significant.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CK = creatine kinase; CK-MB = creatine kinase myocardial band; CN = calcified nodule; MI = myocardial infarction; PCI = percutaneous coronary intervention; PE = plaque erosion; PR = plaque rupture.

TABLE 2 Baseline Angiographic Characteristics

	PR (n = 72)	PE (n = 30)	CN (n = 9)	p Value	p Value* PR vs. PE	PE vs. CN	PR vs. CN
Lesion location				0.308			
LAD	33 (45.8)	18 (60.0)	6 (66.7)				
LCX	7 (9.7)	2 (6.7)	0 (0)				
RCA	32 (44.4)	10 (33.3)	3 (33.3)				
QCA							
Reference LD, mm	2.96 ± 0.62	2.96 ± 0.49	2.83 ± 0.46	0.820			
MLD, mm	0.27 ± 0.57	0.24 ± 0.44	0.22 ± 0.28	0.953			
Percentage of diameter stenosis	91.5 ± 15.9	92.3 ± 13.6	93.0 ± 9.3	0.949			
Lesion length, mm	13.4 ± 7.3	13.5 ± 5.4	15.4 ± 7.8	0.716			
Type B2/C lesion	55 (76.4)	25 (83.3)	6 (66.7)	0.538			
Multivessel disease	31 (43.1)	10 (33.3)	5 (55.6)	0.443			
TIMI flow grade 0	49 (68.1)	17 (56.7)	4 (44.4)	0.264			
TIMI flow grade ≤ 1	54 (75.0)	22 (73.3)	6 (66.7)	0.863			
Bifurcation	11 (15.3)	6 (20.0)	0 (0.0)	0.344			
Severe calcification	1 (1.4)	0 (0.0)	4 (44.4)	<0.001	1.000	0.002	<0.001
Thrombectomy	72 (100)	30 (100)	9 (100)	1.000			
Stent implantation	72 (100)	28 (93.3)	9 (100)	0.064			
Number of stent(s)	1.2 ± 0.5	0.9 ± 0.2	1.1 ± 0.3	0.036	0.010	0.272	0.664
Stent diameter, mm	3.10 ± 0.47	3.27 ± 0.46	3.11 ± 0.49	0.258			
Total stent length, mm	25.9 ± 13.5	20.2 ± 5.0	22.8 ± 7.3	0.085			
Maximal balloon pressure, atm	16.6 ± 3.5	17.3 ± 3.4	19.6 ± 4.4	0.072			

Values are n (%) or mean ± SD. *p < 0.017 was considered significant.

LAD = left anterior descending artery; LCX = left circumflex artery; LD = lumen diameter; MLD = minimal lumen diameter; QCA = quantitative coronary angiography; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

TABLE 3 Quantitative OCT Findings After Thrombectomy

	PR (n = 72)	PE (n = 30)	CN (n = 9)	p Value	p Value* PR vs. PE	PE vs. CN	PR vs. CN
Fibrous plaque	0 (0)	17 (56.7)	4 (44.4)	<0.001	<0.001	0.706	<0.001
Lipid plaque	72 (100)	13 (43.3)	5 (55.6)	<0.001	<0.001	0.706	<0.001
Minimum FCT, μm	50 (40, 59)	130 (95, 190)	170 (64, 320)	<0.001	<0.001	0.961	0.001
Maximum arc, degrees	360 (298, 360)	211 (168, 285)	154 (102, 312)	<0.001	<0.001	0.459	0.005
Length, mm	13.1 (9.1, 17.6)	8.1 (6.8, 9.8)	5.8 (5.0, 12.0)	0.002	<0.001	0.657	0.027
Calcification	50 (69.4)	15 (50.0)	9 (100)	0.014	0.074	0.007	0.105
Minimum depth,† μm	80 (50, 173)	160 (60, 270)	20 (10, 40)	<0.001	0.117	<0.001	<0.001
Maximum arc, degrees	56 (38, 93)	55 (42, 91)	251 (157, 360)	<0.001	0.889	<0.001	<0.001
Thrombus score	6.5 (3.0, 13.3)	9.0 (4.0, 15.0)	23.0 (5.5, 32.0)	0.117			

Values are n (%) or median (25th, 75th percentiles). *p < 0.017 was considered significant. †Minimum depth is measured from the luminal surface to calcification.
FCT = fibrous cap thickness; OCT = optical coherence tomography; other abbreviations as in Table 1.

PR had positive remodeling, whereas more than one-half of culprit CN had negative remodeling (Figures 4B and 4C).

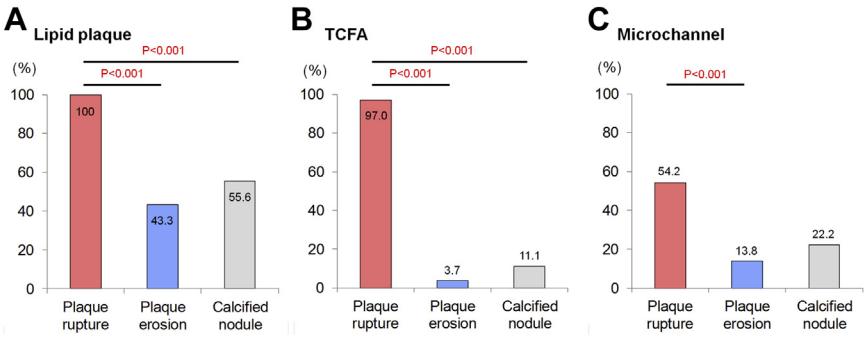
POST-PCI OUTCOME. On angiography, post-procedure minimal lumen diameter and percentage of diameter stenosis were similar among the 3 groups (Table 5). Although the incidence of TIMI flow grade ≤2 after thrombectomy and after PCI was also similar among the 3 groups, PE had a lower incidence of myocardial blush grade ≤1 and no reflow compared with PR (p = 0.010 and p = 0.011) (Figure 5). Peak creatine kinase (CK) was higher in PR, but this difference did not reach statistical significance.

DISCUSSION

Comprehensive in vivo evaluation of culprit plaque morphology in patients with acute STEMI was performed using both OCT and IVUS. The main findings were: 1) the incidence of PR, PE, and CN in STEMI was 64.3%, 26.8%, and 8.0%, respectively; 2) PE was associated with less frequent lipid plaque, smaller plaque burden, more eccentric plaque, and less frequent positive remodeling when compared with PR; 3) CN frequently showed negative remodeling and superficial large calcium.

INCIDENCE OF UNDERLYING PLAQUE MORPHOLOGIES IN STEMI. The in vivo diagnosis of PE and CN has recently been demonstrated using OCT, a high-resolution imaging modality. PR, PE, and CN have now been shown in both ex vivo and in vivo studies to be the primary mechanisms underlying acute coronary thrombosis (1,4). In our previous study, the incidence of culprit PR, PE, and CN was 44%, 31%, and 8%, respectively, in patients presenting with ACS (4). Our current study showed a higher incidence of PR (64.3%), a discrepancy that may be explained by

FIGURE 3 OCT Characteristics of 3 Underlying Mechanisms of STEMI



The prevalence of lipid plaque **(A)** and thin-cap fibroatheroma (TCFA) **(B)** was higher in plaque rupture than in the other 2 groups. Plaque rupture had a higher prevalence of microchannel **(C)** than plaque erosion. There were no significant differences in the frequency of these OCT characteristics between plaque erosion and calcified nodule. A p value of <0.017 was considered significant. Abbreviations as in Figure 1.

TABLE 4 Quantitative IVUS Findings After Thrombectomy

	PR (n = 72)	PE (n = 30)	CN (n = 9)	p Value	p Value* PR vs. PE	PE vs. CN	PR vs. CN
Lesion segment							
Lumen CSA, mm^2	2.9 ± 0.5	3.8 ± 2.6	3.3 ± 1.0	0.015	0.005	0.631	0.017
EEM CSA, mm^2	20.5 ± 7.4	19.5 ± 6.1	16.2 ± 4.2	0.112			
P+M CSA, mm^2	17.7 ± 7.3	15.7 ± 5.6	12.9 ± 4.3	0.196			
Plaque burden, %	84.7 ± 4.8	80.2 ± 9.9	78.2 ± 9.0	0.002	0.003	0.580	0.001
Plaque eccentricity index	0.54 ± 0.21	0.71 ± 0.16	0.51 ± 0.09	<0.001	<0.001	<0.001	0.677
Remodeling index	1.21 ± 0.20	1.06 ± 0.29	0.85 ± 0.18	<0.001	0.003	0.056	<0.001
Reference segment							
Lumen CSA, mm^2	8.0 ± 3.0	8.3 ± 2.7	8.4 ± 3.8	0.851			
EEM CSA, mm^2	17.2 ± 5.8	18.7 ± 5.2	19.1 ± 3.7	0.343			

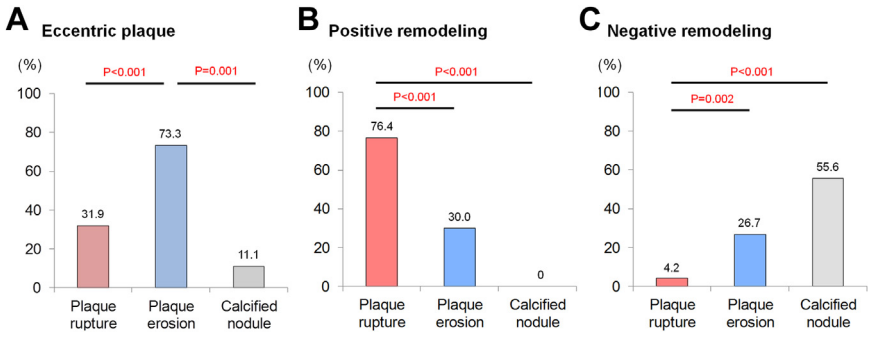
Values are mean ± SD. *p < 0.017 was considered significant.
CSA = cross-sectional area; EEM CSA = external elastic membrane; IVUS = intravascular ultrasound; P+M = plaque plus media; other abbreviations as in Table 1.

differences in the study populations. In the previous study, all ACS patients were included, and the patients were imaged at various time points. In the current study, only STEMI patients who presented within 12 h of symptom onset were included. An overview of a post-mortem study including sudden cardiac death and acute myocardial infarction patients concluded that the incidence of coronary thrombosis caused by PR was 73% (range 47% to 100%), which is similar to our current results (15). The incidence of PE in previous autopsy studies ranged from 25% to 44% (1,16–18), which is also consistent with our result (26.8%). CN comprised 8.0% of STEMI presentations in our study; previous autopsy data showed a similar incidence of CN (4%) (1).

MORPHOLOGIC CHARACTERISTICS OF PLAQUE EROSION IN STEMI. Previous pathology studies have reported that PE, compared with PR, had less "vulnerable" plaque features: smaller size of necrotic core; less inflammatory infiltration; fewer number of vasa vasorum; and lower incidence of positive remodeling (1,2,18). Our current in vivo intravascular study similarly demonstrated that culprit PE had fewer "vulnerable" plaque features than culprit PR did, including a lower prevalence of lipid plaque and TCFA, smaller size of lipid core, less frequent microchannels, and lower incidence of positive remodeling. In contrast, negative remodeling was more frequently observed in PE. STEMI caused by PE had larger lumen CSA and smaller plaque burden at the culprit lesion site than PR did.

In addition, culprit PE was more eccentric than culprit PR. Stenotic segments are known to increase vascular wall shear stress (19), and high shear stress or sharp gradients at eccentric plaque can induce platelet adhesion (20). Calcification in PE has not been well reported. Only 1 previous pathology study

FIGURE 4 IVUS Characteristics of 3 Underlying Mechanisms of STEMI



Eccentric plaque was more frequent in plaque erosion than in the other 2 groups **(A)**. The majority of plaque rupture had positive remodeling **(B)**, whereas more than one-half of the calcified nodule group had negative remodeling **(C)**. A p value of <0.017 was considered significant. Abbreviations as in Figure 1.

TABLE 5 Post-Thrombectomy and Final Angiographic Findings

	PR (n = 72)	PE (n = 30)	CN (n = 9)	p Value	p Value* PR vs. PE	PE vs. CN	PR vs. CN
Post-thrombectomy							
MLD, mm	1.06 ± 0.59	0.89 ± 0.58	0.96 ± 0.42	0.430			
Percentage of diameter stenosis	64.4 ± 16.9	70.0 ± 16.0	66.1 ± 13.7	0.307			
TIMI flow grade ≤2	14 (19.4)	5 (16.7)	3 (33.3)	0.541			
Post-procedure							
MLD, mm	2.62 ± 0.46	2.70 ± 0.57	2.40 ± 0.62	0.328			
Percentage of diameter stenosis	13.0 ± 9.5	13.8 ± 11.6	17.0 ± 14.6	0.563			
TIMI flow grade ≤2	15 (20.8)	2 (6.7)	1 (11.1)	0.191			
Myocardial blush grade ≤1	22 (30.6)	2 (6.7)	2 (22.2)	0.034	0.010	0.223	0.719
No reflow	28 (38.9)	4 (13.3)	2 (22.2)	0.033	0.011	0.607	0.473

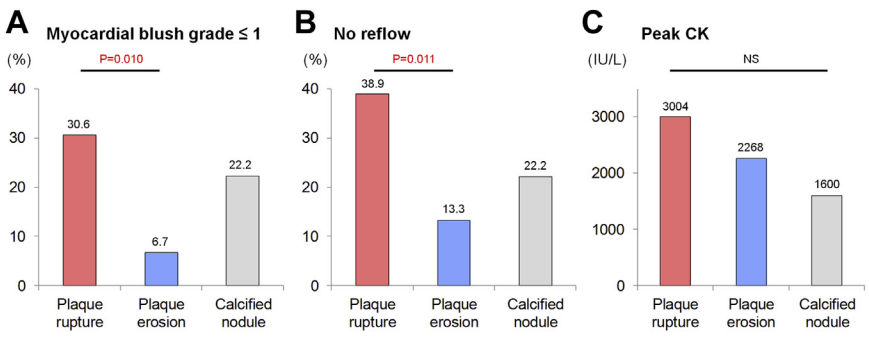
Values are mean ± SD or n (%). *A p value of <0.017 was considered significant.
Abbreviations as in Tables 1 and 2.

showed the incidence of calcification to be around 60% in eroded plaques (21). Our study showed a similar incidence (54.3%). Although no significant difference was seen in the prevalence and size of calcification between PE and PR, the location of calcification was deeper in PE.

MORPHOLOGIC CHARACTERISTICS OF CALCIFIED NODULE IN STEMI. In our series, only 9 cases (8.0%) of STEMI were caused by CN. However, these cases showed characteristic morphologic features. First, most of CN contained superficially located large calcification, which is termed pathologically as a "calcium sheet" (15,22). A previous IVUS study validated by histology similarly showed that superficial calcium was among the key findings of CN, although the depth of calcium in the vessel wall was not assessed (23). Although large calcium in CN might be affected by the definition of CN in this study, the histology study showed that the possible mechanism of CN is a break of calcium sheet into the lumen. Our finding, therefore, is in line with histology (2). Second, negative remodeling was most frequent in CN than in PR and PE. Lumen CSA was similar between CN and PR, but CN was more constrictive. These findings might suggest CN had smaller plaque burden than PR. Third, CN occurred more frequently in elderly patients. Our data are therefore consistent with the findings from a previous IVUS study which reported that negative remodeling and large-size calcification without plaque rupture were frequently seen in older acute myocardial infarction patients (24).

ACUTE OUTCOMES AFTER PRIMARY PCI. In our previous OCT study of patients with ACS, PR was more frequently identified in patients presenting

FIGURE 5 Acute Outcomes After Primary PCI



Plaque erosion was associated with better outcomes than plaque rupture. Plaque erosion had a lower incidence of myocardial blush grade ≤1 and no reflow than plaque rupture did **(A, B)**. There was a trend toward higher peak creatine kinase (CK) elevation in plaque rupture than in the other groups **(C)**. A p value of <0.017 was considered significant. PCI = percutaneous coronary intervention.

with STEMI than in those presenting with non-ST-segment elevation ACS (4). This finding suggests that PR may be associated with a larger infarct size than PE or CN are. A previous IVUS and angioscopy study (25) in AMI patients showed that PR was associated with higher peak CK level after primary PCI than PE, although neither IVUS nor angioscopy are ideal for diagnosing PE (3). In the current study of STEMI patients, PR was associated with worse myocardial perfusion than PE. Ruptured site releases highly thrombogenic substrates such as lipid and tissue factor (26), which may induce recurrent local thrombosis and distal embolization, perturbing the coronary microcirculation. In addition, it was reported that TCFA was associated with microvascular obstruction after PCI (27). Indeed, the increased incidence of no reflow was mainly driven by the increased incidence of myocardial blush grade ≤1. Despite a trend toward a higher peak CK in PR, the difference in peak CK among the 3 groups did not reach statistical significance. The use of aggressive manual thrombectomy to remove a large amount of thrombus may have minimized potential differences in myocardial injury among the 3 groups.

STUDY LIMITATIONS. Although this is the first systematic in vivo study of the culprit lesion in patients with STEMI using both OCT and IVUS, there are several limitations that should be acknowledged. First, this was a single-center study, and the analysis was done retrospectively. Second, thrombectomy was performed to facilitate reperfusion prior to intravascular imaging. Although care was taken to avoid excessive mechanical trauma during thrombectomy, it is possible that this procedure may have altered the morphologic features of the underlying plaque. Third, residual thrombus can limit the accurate evaluation of OCT images. We therefore excluded patients with significant residual thrombus from analysis. Fourth, the OCT definition of PE is in some ways a diagnosis of exclusion, requiring the absence of fibrous cap disruption or superficial calcium underlying thrombus. The absence of an endothelial lining is a key criterion for the pathological diagnosis of PE. Despite the highest resolution among available intravascular imaging modalities, the current OCT system does not have a high enough resolution to visualize endothelial cells. Fifth, IVUS evaluation in the presence of thrombus or heavy calcification is still challenging. Several previous IVUS studies, however, have shown the efficacy of IVUS evaluation in the coronary arteries in patients with STEMI cases (28,29) or heavily calcified lesions (24). Our results are similar to the results of those studies. Sixth, although the reperfusion time was relatively longer in our study than in the previously published study (28), the reperfusion time was not different among the 3 groups (397 ± 301 min in PR, 342 ± 240 min in PE, and 465 ± 99 min in CN; p = 0.496). Finally, the number of CN cases was small. Further studies of larger size are required to investigate this subgroup. Our result, however, is in line with previous pathology studies showing a low incidence of CN.

CONCLUSIONS

This study demonstrates that PR, PE, and CN were the underlying mechanisms in 64.3%, 26.8%, and 8.0% of patients with STEMI, respectively. PE was characterized by eccentric fibrous plaque with fewer features of plaque vulnerability. CN was characterized by superficial calcium sheets and negative remodeling. PE was associated with less microvascular damage after PCI.

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PERSPECTIVES

WHAT IS KNOWN? OCT enables us to diagnose PE and CN in vivo. The incidence and morphologic characteristics of PR, PE, and CN in patients with STEMI as well as the outcomes after primary PCI have been unknown.

WHAT IS NEW? This study reports that the incidence of PR, PE, and CN in STEMI is 64.3%, 26.8%, and 8.0%, respectively. The culprit lesions with PR have higher prevalence of TCFA, microchannel, and positive remodeling. Those with PE have higher prevalence of fibrous eccentric plaque. Those with CN have superficial calcium sheets and negative remodeling. PR results in worse outcome following PCI.

WHAT IS NEXT? The findings of this study will help to expand the understanding of the underlying patho-physiology and to develop optimal therapeutic strategies of STEMI. The role of OCT in optimizing PCI requires further study in large-scale prospective trials.

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KEY WORDS calcified nodule, intravascular ultrasound, optical coherence tomography, plaque erosion, ST-segment elevation myocardial infarction

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