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Optical Coherence Tomography Analysis of Clinical and Subclinical Plaque Rupture

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Abstract

Background: Coronary plaque ruptures occur not only in acute coronary syndrome (ACS) patients but also in non-ACS patients. There is a great interest in the reason why some plaque ruptures lead to ACS but others do not. We used optical coherence tomography (OCT) to identify anatomic features that lead to the development of culprit lesions causing ACS after plaque rupture.

Methods: We assessed 102 plaque ruptures by using OCT and compared lesion morphologies between symptomatic plaque rupture in unstable angina pectoris (UAP; n=67) and silent plaque rupture in stable angina pectoris (SAP; n=35).

Results: In the cross-sectional view, rupture was observed at plaque shoulder in 67% of UAP and 71% of SAP (p=0.660). In the longitudinal view, plaque rupture was located proximally to the minimal lumen area (MLA) site in 49% of UAP and 57% of SAP (p=0.449). Distance between the rupture site and the MLA site was similar in UAP and SAP (2.64 ± 1.45 mm vs. 2.99 ± 1.70 mm, p=0.280). Maximal ruptured cavity area was significantly greater in UAP compared with SAP (1.57 ± 0.54 mm^2 vs.1.30 ± 0.72 mm^2, p=0.032). Lumen area at rupture site (3.00 ± 0.86 mm^2 vs. 3.45 ± 1.18 mm^2, p=0.030) and MLA (2.69 ± 0.80 mm^2 vs. 3.12 ± 1.14 mm^2, p=0.029) was significantly smaller in UAP compared with SAP. The frequency of lipid-rich plaque (84% vs. 63%, p=0.019) and intracoronary thrombus (94% vs. 3%, p<0.001) was significantly higher in UAP compared with SAP.

Conclusions: The present OCT study found 4 risk factors linking ruptured plaques to acute coronary syndromes: greater degree of plaque rupture, smaller lumen, lipid-rich plaque, and evidence of thrombus. It is conceivable that the greater degree of plaque rupture in the lipid-rich plaque provokes more increased thrombus formation and the smaller lumen requires less thrombus to precipitate an acute coronary event.

Keywords: Plaque rupture; Optical coherence tomography; Acute coronary syndrome

Abbreviations: ACS: Acute Coronary Syndromes; IVUS: Intravascular Ultrasound; MLA: Minimal Lumen Area; OCT: Optical Coherence Tomography; SAP: Stable Angina Pectoris; UAP: Unstable Angina Pectoris

Introduction

Plaque rupture and subsequent thrombus formation is the most common cause leading to acute coronary syndromes (ACS). Autopsy studies have reported that plaque ruptures were found in 60–65% of individuals dying suddenly with luminal thrombi [1].

However, several studies using intravascular imaging techniques have shown plaque rupture in patients with stable angina or asymptomatic ischemia [2,3]. Thus, it is not clear why some plaque ruptures lead to clinical manifestations, whereas others remain asymptomatic and heal. Optical coherence tomography (OCT) is a high resolution (10-20 μm) imaging technique that offers microscopic visualization of coronary plaques. Recent studies have shown that OCT is useful for assessing vulnerable plaque features *in vivo* [4,5]. Therefore, we used OCT to compare lesion morphology between symptomatic plaque rupture in unstable angina pectoris (UAP) and silent plaque rupture in stable angina pectoris (SAP).

Materials and Methods

Study population

A total of 102 (UAP = 67, SAP = 35) patients who underwent OCT in Social Insurance Kinan Hospital, Wakayama, Japan and had plaque rupture in de novo culprit lesions were studied retrospectively. UAP was defined as angina at rest within 48 hours (Braunwald clinical classification III) [6]. Patients with secondary UAP and post-infarction angina were not included. SAP was defined as chest pain on exertion, positive stress test and no change in frequency, duration, or intensity of symptoms within 4 weeks before catheter examination. Patient hospital records were reviewed to obtain information on clinical demographic data and medical history. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of anti-hypertensive drugs. Hypercholesterolemia was defined as a present or past history of low-density lipoprotein–cholesterol level >140 mg/dl, or use of statin. Diabetes mellitus was defined as a fasting blood sugar >126 mg/dl and hemoglobin A1c >6.5%, or use of anti-diabetic medications (insulin or oral hypoglycemics). This study was approved by the Ethics Committee of Social Insurance Kinan Hospital, and all patients gave written informed consent before catheter examination.

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Coronary angiography

Coronary angiography was performed by the conventional femoral approach using 6-F sheaths and catheters. All patients received oral aspirin (162 mg) and intravenous bolus injection of heparin (100 U/kg) and intracoronary isosorbide dinitrate (2 mg) before angiography. Patients did not receive any thrombolytic therapy before angiography. The culprit lesions were identified by the findings of coronary angiogram and those of electrocardiogram, transthoracic echocardiogram, and stress test. Coronary angiograms were analyzed by observers (T.T. and I.K.) who were blinded to clinical and OCT information. Qualitative analysis included assessment of previously used angiographic descriptors [7]. Ulceration was defined as a small crater consisting of a discrete luminal widening with luminal irregularity. Intimal flap was defined as a radiolucent extension of the vessel wall into the arterial lumen. Lumen irregularity was defined as an irregular lumen border that was not classified as ulceration. Thrombus was defined as a discrete intraluminal filling defect. Lesions were considered as complex if they had one or more of the following specific morphologies: ulceration, intimal flap, lumen irregularity, and thrombus [8]. Otherwise, they were considered as simple. Quantitative coronary angiography analysis was performed using the Cardiovascular Measurement System (CMSMEDIS Medical Imaging System, Leiden, The Netherlands). The reference vessel diameter, minimal luminal diameter, and percent diameter stenosis was measured in the culprit lesion.

OCT imaging and analysis

After completion of diagnostic coronary angiography, OCT (the M2 OCT imaging system, LightLab Imaging, Inc, Westford, Massachusetts, USA) was performed before any intervention. We used a continuous-flushing (non-occlusive) method for OCT image acquisition. A 0.016-inch wire-type imaging catheter was positioned distal to the culprit lesion. To remove blood cells from the field of view, a mixture of commercially available dextran 40 and lactated Ringer solution was infused from the guiding catheter at 2.5 to 4.5 ml/s with an injector pump. The culprit lesion was imaged with a motorized pull-back device travelling at 1 mm/s. Continuous OCT images were stored digitally for subsequent analysis. The OCT analysis was performed by observers (K.H. and I.Y.) who were blinded to clinical and angiographic information. As reported previously [9], fibrous tissues were defined as homogeneous signal-rich regions, calcifications as signal poor regions with sharp borders, and lipidic tissues as signal-poor regions with diffuse borders. Plaque rupture was identified by a presence of fibrous-cap discontinuity and a cavity formation in the plaque [4,5]. The location of the rupture site in accordance with the site of minimal lumen area (MLA), and the distance between the 2 sites was estimated [10,11]. We also studied in the cross-sectional view whether the plaque was ruptured at the shoulder or at the center [12]. The longitudinal morphological features of plaque rupture were classified into 3 types according to the previous OCT report [13]. Proximal-type rupture was defined as the ruptured plaque of which aperture was open-wide against the direction of coronary flow. Distal-type rupture was defined as the ruptured plaque of which aperture opened along the direction of coronary flow. Mid-type rupture was defined as the ruptured plaque of which aperture opened at the center of the plaque. The lumen area and the ruptured cavity area was measured at the site of largest intra-plaque cavity. Lipid was semiquantified as the number of involved quadrants on the cross-sectional image. When lipid was present in ≥2 quadrants in any of the images within a plaque, it was considered a lipid-rich plaque [4,5]. Intracoronary thrombus was defined as a protrusion inside the lumen of the artery with signal attenuation [4,5].

Statistical analysis

Statistical analysis was performed using Statview 5.0.1 (SAS Institute, Cary, North Carolina, USA). Categorical variables were presented as absolute numbers and percentages, with comparison using chi square statistics or Fisher exact test if there was an expected cell value <5. Continuous variables were presented as mean ± standard deviation and were compared using Student t test. All analyses required a $P<0.05$ for statistical significance.

Results

Patient clinical characteristics

Baseline clinical characteristics of 67 UAP patients and 35 SAP patients who had plaque rupture detected by OCT are shown in Table 1. There were no significant differences in age, gender and coronary risk factors between the patients with UAP and SAP.

Angiographic findings

Angiographic findings are shown in Table 2. There were no differences in distribution of culprit lesion between UAP and SAP. Although the frequency of ulceration, intimal flap and lumen irregularity was similar in UAP and SAP, the frequency of thrombus (12% vs. 0%, p=0.048) and complex lesion (37% vs. 17%, p=0.030) was significantly high in UAP compared with SAP. Minimal lumen

	UAP (n=67)	SAP (n=35)	*p*-value
Age, y	69 ± 9	71 ± 8	0.339
Male	46 (69)	20 (57)	0.248
Hypertension	56 (84)	23 (66)	0.196
Diabetes mellitus	20 (30)	13 (37)	0.455
Hypercholesterolemia	44 (66)	19 (54)	0.263
Current smoker	16 (24)	8 (23)	0.908
Family history of coronary disease	14 (21)	11 (31)	0.240

Values are given as n (%) or mean ± standard deviation. UAP = unstable angina pectoris; SAP = stable angina pectoris

Table 1: Patient clinical characteristics.

	UAP (n=67)	SAP (n=35)	*p*-value
Vessel			
LAD	28 (42)	14 (40)	0.862
LCX	9 (13)	7 (20)	0.387
RCA	30 (45)	14 (40)	0.644
Location			
Proximal	39 (58)	15 (37)	0.140
Mid	21 (31)	13 (31)	0.555
Distal	7 (10)	7 (31)	0.183
Qualitative analysis			
Ulceration	10 (15)	3 (9)	0.534
Intimal flap	1 (1)	0 (0)	0.999
Lumen irregularity	9 (13)	3 (9)	0.538
Thrombus	8 (12)	0 (0)	0.048
Complex lesion	25 (37)	6 (17)	0.030
Quantitative analysis			
Reference vessel diameter, mm	3.3 ± 0.4	3.2 ± 0.6	0.111
Minimal lesion diameter, mm	0.6 ± 0.2	0.8 ± 0.3	<0.001
Percent diameter stenosis, %	80 ± 7	74 ± 6	<0.001

Values are given as n (%) or mean ± standard deviation. UAP = unstable angina pectoris; SAP = stable angina pectoris; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery

Table 2: Angiographic findings.

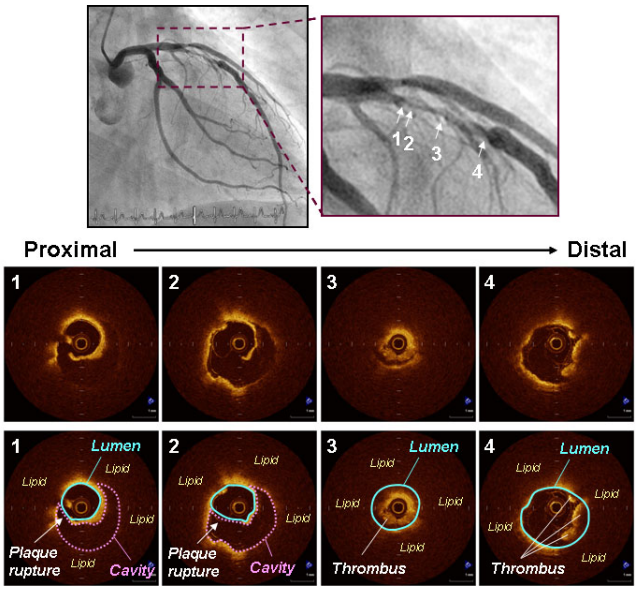

Figure 1: Representative OCT images of plaque rupture in unstable angina pectoris. Angiography showed a complex lesion in the left anterior descending coronary artery. OCT revealed a plaque rupture with a residual fibrous-cap and plaque cavity (#1 and #2), and intracoronary thrombi (#3 and #4). Schemas demonstrate plaque rupture, lumen, ruptured cavity, lipid, and thrombi. Plaque rupture was observed at the minimal lumen area site [minimal lumen area = 1.83 mm^2 (#1); maximal ruptured cavity area = 3.26 mm^2 (#2)]. The plaque was considered to contain abundant lipid (number of lipid quadrants = 4). Thrombi occupied coronary lumen distal to the plaque rupture.

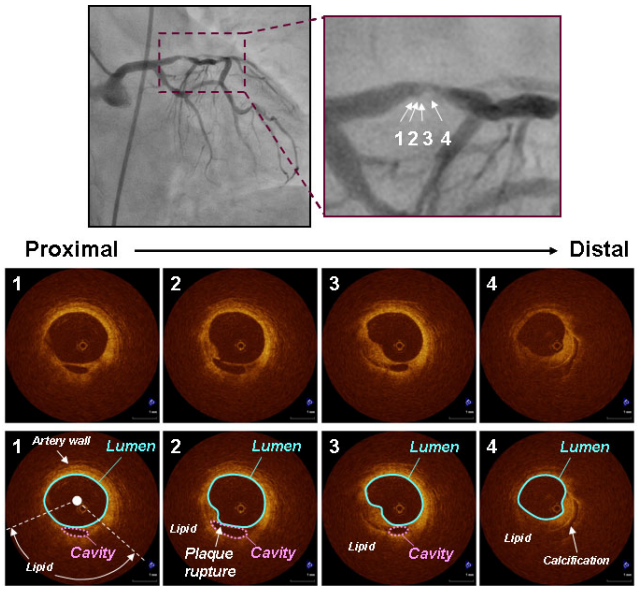

Figure 2: Representative OCT images of plaque rupture in stable angina pectoris. Angiography showed an eccentric stenosis in the left anterior descending coronary artery. OCT revealed a plaque rupture with a residual fibrous-cap and plaque cavity (#1, #2, and #3). Schemas demonstrate plaque rupture, lumen, ruptured cavity, 3-layered coronary artery wall, lipid, and calcification. Plaque rupture was located proximally to the minimal lumen area site [maximal ruptured cavity area = 0.45 mm^2; (#2) minimal lumen area = 2.59 mm^2 (#4)]. The plaque contained lipdic tissue (number of lipid quadrants = 2) and calcium. Intracoronary thrombi were not detected in the lesion with plaque rupture.

	UAP (n=67)	SAP (n=35)	*p*-value
Rupture at plaque shoulder	45 (67)	25 (71)	0.660
Location of rupture			
Proximal to the MLA site	33 (49)	20 (57)	0.449
MLA site	24 (36)	11 (31)	0.657
Distal to the MLA site	10 (15)	4 (11)	0.626
Distance between rupture site and MLA site, mm	2.64 ± 1.45	2.99 ± 1.70	0.280
Longitudinal morphological features of plaque rupture			
Proximal-type	30 (45)	14 (40)	0.644
Mid-type	29 (43)	17 (49)	0.610
Distal-type	8 (12)	4 (11)	0.939
Maximal ruptured cavity area, mm^2	1.57 ± 0.54	1.30 ± 0.72	0.032
Lumen area at rupture site, mm^2	3.00 ± 0.86	3.45 ± 1.18	0.030
MLA, mm^2	2.69 ± 0.80	3.12 ± 1.14	0.029
Lipid-rich plaque	56 (84)	22 (63)	0.019
Thrombus	63 (94)	1 (3)	<0.001

Values are given as n (%) or mean ± standard deviation. UAP = unstable angina pectoris; SAP = stable angina pectoris; MLA = minimal lumen area

Table 3: Optical coherence tomography findings.

diameter was smaller (0.6 ± 0.2 mm vs. 0.8 ± 0.3 mm, p<0.001) and percent diameter stenosis was greater (80 ± 7% vs. 74 ± 6%, p<0.001) in UAP compared with SAP.

OCT findings

Representative OCT images of plaque ruptures in UAP and SAP are shown in Figure 1 and Figure 2, respectively. OCT findings are listed in Table 3. In the cross-sectional view, rupture was observed at plaque shoulder in 67% of UAP and 71% of SAP (p=0.660). In the longitudinal view, plaque rupture was located proximally to the MLA site in 49% of UAP and 57% of SAP (p=0.449). Distance between the rupture site and the MLA site was similar in UAP and SAP (2.64 ± 1.45 mm vs. 2.99 ± 1.70 mm, p=0.280). The longitudinal morphological features of plaque rupture were not different between UAP and SAP (proximal-type: 45% vs. 40%, p=0.644; mid-type: 43% vs. 49%, p=0.610; and distal-type: 12% vs. 11%, p=0.939). Maximal ruptured cavity area was significantly greater in UAP compared with SAP (1.57 ± 0.54 mm^2 vs.1.30 ± 0.72 mm^2, p=0.032). Lumen area at rupture site (3.00 ± 0.86 mm^2 vs. 3.45 ± 1.18 mm^2, p=0.030) and MLA (2.69 ± 0.80 mm^2 vs. 3.12 ± 1.14 mm^2, p=0.029) was significantly smaller in UAP compared with SAP. The frequency of lipid-rich plaque (84% vs. 63%, p=0.019) and intracoronary thrombus (94% vs. 3%, p<0.001) was significantly higher in UAP compared with SAP.

Discussion

The present OCT study demonstrated the differences of lesion morphologies between symptomatic plaque rupture in UAP and silent plaque rupture in SAP. The main findings are summarized as follows: ruptured plaques in UAP had larger ruptured cavity area, smaller lumen area, higher frequency of lipid-rich plaque and intracoronary thrombus compared with those in SAP. Our results suggest that these morphologies in plaque rupture might be associated with clinical presentation of coronary artery disease.

Autopsy studies have revealed pathohistological characteristics of plaque rupture in cases of sudden cardiac death [1]. Plaque rupture is characterized by a thin fibrous-cap heavily infiltrated by macrophages and an underlying necrotic core that is in communication with the flowing blood causing an overlying thrombus. A reliable study reported

that 95% of ruptured fibrous-cap was measured less than 65μm, and the necrotic core occupied nearly 35% of the plaque area [1]. Plaque ruptures cluster in the proximal left anterior descending coronary artery and left circumflex artery, and are more uniformly distributed in the right coronary artery [1]. Furthermore, some plaque ruptures occur silently without causing symptoms, and repetitive plaque rupture and healing could lead to inward remodeling. Indeed, pathohistological observations have demonstrated that acute ruptures overlying healed ruptures were more narrowed than de novo ruptures [14].

Intravascular ultrasound (IVUS) provides cross-sectional images of coronary vessel wall and allows us to identify plaque rupture in vivo. Three-vessel IVUS studies in ACS patients have reported that plaque rupture was observed not only in the culprit lesions but also in the non-culprit lesions (17%-38%) [2,15]. In addition, several IVUS studies showed that 11%-27% of SAP patients had plaque rupture in the culprit lesions [2,3]. Therefore, there is a great interest in the reason why some plaque ruptures lead to ACS but others do not. Hong et al compared IVUS features of ruptured plaques between acute myocardial infarction and SAP, and showed higher frequency of positive remodeling in infarct-related ruptured plaques compared with non-infarct-related ruptured plaques (68% vs. 46%, p=0.001) [2]. Fujii et al., demonstrated that ruptured plaques in culprit lesions of ACS had smaller lumens (3.3 ± 1.5 mm^2 vs. 5.4 ± 2.6 mm^2, p<0.001), and greater plaque burdens (80 ± 8% vs. 71 ± 8%, p<0.001) and area stenosis (61 ± 15% vs. 50 ± 14%, p<0.001) than those in non-culprit lesions of ACS [16]. Although angiographic studies showed that ACS frequently occur at sites that were previously only a mild-to-moderate stenosis [17,18], autopsy studies demonstrated that ruptured plaques leading to ACS were often within the segment of significant stenosis [19,20]. In the present OCT analysis, lumen area at rupture site was significantly smaller in UAP compared with SAP. Our result supports previous IVUS and pathological concept that smaller lumen might be an important risk factor linking plaque rupture to ACS.

Intravascular OCT is a recently developed intravascular imaging modality using near-infrared light to create images. The greatest advantage of OCT is its high-resolution, which is 10 times higher than that of IVUS. The high resolution of OCT allows a detailed assessment of plaque rupture and intracoronary thrombi and a precise measurement of ruptured cavity size in vivo. Ino et al used OCT to investigate the difference of ruptured plaque morphologies between ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS [10]. In their results, ruptured cavity area was significantly larger in STEMI compared with non-ST-segment elevation ACS (2.52 ± 1.36 mm^2 vs. 1.67 ± 1.37 mm^2, p=0.034) [10]. Subsequently, Toutouzas et al showed that culprit lesions of STEMI had greater plaque rupture (length of missing fibrous cap: 0.63 ± 0.27 mm vs. 0.46 ± 0.25 mm, p=0.020) than those of non-STEMI [11]. In the present OCT comparison between UAP and SAP, we found larger ruptured cavity area and higher frequency of lipid-rich plaque and intracoronary thrombus in UAP. Because the exposed necrotic core is highly thrombogenic [1], the greater degree of plaque rupture could provoke more increased thrombus formation, thus leading to development of ACS.

Limitations

The present study had several limitations. First, this was a retrospective study. We identified the cases with plaque rupture from the database of OCT registry at our institution; the OCT examinations were performed for guidance of coronary intervention in daily clinical practice. Hence, there is a possibility of bias in this study. Second, thrombus might affect analysis of the plaque behind, making it especially difficult to observe plaque rupture. Third, the relatively shallow imaging depth of the current time-domain OCT precludes the assessment of plaque burden and arterial positive remodeling, which are well-described characteristics of vulnerable plaque [1]. A second-generation OCT technology, termed Fourier-domain OCT, might eliminate these technical limitations of the present study [21,22]. Finally, the study population was relatively small. Therefore, the present results should be viewed as preliminary and await confirmation by larger clinical trials with a second-generation OCT use.

Conclusions

The present OCT study found 4 risk factors linking ruptured plaques to acute coronary syndromes: greater degree of plaque rupture, smaller lumen, lipid-rich plaque, and evidence of thrombus. It is conceivable that the greater degree of plaque rupture in the lipid-rich plaque provokes more increased thrombus formation and the smaller lumen requires less thrombus to precipitate an acute coronary event.

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