

## CLINICAL RESEARCH

## Atheroma Morphology

# Assessment of Culprit Lesion Morphology in Acute Myocardial Infarction

## Ability of Optical Coherence Tomography Compared With Intravascular Ultrasound and Coronary Angioscopy

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- Objectives** The aim of the present study was to evaluate the ability of optical coherence tomography (OCT) for assessment of the culprit lesion morphology in acute myocardial infarction (AMI) in comparison with intravascular ultrasound (IVUS) and coronary angioscopy (CAS).
- Background** Optical coherence tomography is a new intravascular imaging method with a high resolution of approximately 10  $\mu\text{m}$ . This may allow us to assess the vulnerable plaques in detail in vivo.
- Methods** We enrolled 30 patients with AMI, and analyzed the culprit lesion by OCT, CAS, and IVUS.
- Results** The average duration from the onset of symptom to OCT imaging was  $3.8 \pm 1.0$  h. The incidence of plaque rupture observed by OCT was 73%, and it was significantly higher than that by CAS (47%,  $p = 0.035$ ) and IVUS (40%,  $p = 0.009$ ). Furthermore, OCT (23%) was superior to CAS (3%,  $p = 0.022$ ) and IVUS (0%,  $p = 0.005$ ) in the detection of fibrous cap erosion. The intracoronary thrombus was observed in all cases by OCT and CAS, but it was identified in 33% by IVUS (vs. OCT,  $p < 0.001$ ). Only OCT could estimate the fibrous cap thickness, and it was  $49 \pm 21$   $\mu\text{m}$ . The incidence of thin cap fibroatheroma (TCFA) was 83% in this population by OCT.
- Conclusions** Optical coherence tomography is a feasible imaging modality in patients with AMI and allows us to identify not only plaque rupture, but also fibrous cap erosion, intracoronary thrombus, and TCFA in vivo more frequently compared with conventional imaging techniques. (J Am Coll Cardiol 2007;50:933-9) © 2007 by the American College of Cardiology Foundation

It is generally accepted that culprit lesions of acute myocardial infarction (AMI) typically have severe stenosis secondary to superimposed thrombus at the time of the event but not necessarily severe stenosis before the event (1,2). Patho-

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logically, AMI is provoked by sudden rupture or ulcer formation of vulnerable plaque followed by subsequent thrombosis (3,4). The pathological characteristics of vulnerable plaques include a thin fibrous cap with macrophage infiltration and a large lipid pool (4). These findings were based on the postmortem histological examination, and the

imaging of the vulnerable plaque characteristics was limited in vivo. Coronary angiography provided the first in vivo imaging of the coronary arteries. Pathohistological correlations of angiographic lesion morphologies have demonstrated that lesions with irregular borders and intraluminal lucencies corresponded to complex plaque with thrombosis (5). Intravascular ultrasound (IVUS) has become standard invasive method for diagnosing coronary artery disease. Recent reports have suggested that the presence of the positive vascular remodeling and hypochoic regions corresponding to lipid-rich tissue in coronary plaques on IVUS images were related to acute coronary events (6). Coronary angioscopic (CAS) investigations have indicated that AMI occurs more frequently in patients with glistening yellow plaques than in those with white plaques (7). Moreover, thrombus arising from the ruptured identical plaques was confirmed in the culprit lesion of the AMI by CAS.

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Manuscript received December 20, 2006; revised manuscript received April 12, 2007, accepted April 17, 2007.

**Abbreviations and Acronyms**

- AMI** = acute myocardial infarction
- CAS** = coronary angiography
- IVUS** = intravascular ultrasound
- OCT** = optical coherence tomography
- TCFA** = thin cap fibroatheroma
- TIMI** = Thrombolysis In Myocardial Infarction

Intravascular optical coherence tomography (OCT) has recently been proposed as a high-resolution imaging method for plaque characterization (8–12). Optical coherence tomography is an optical analogue of IVUS, and its resolution is approximately 10 to 20  $\mu\text{m}$ , which is about 10 times higher than IVUS. The histology-controlled studies have shown that the OCT can resolve microstructure of atherosclerotic plaque such as thin fibrous cap, lipid core, and intracoronary thrombus, which are thought to be responsible for plaque vulnerability (13,14). Therefore, we hypothesized that this new technique might allow us to observe vulnerable plaques in detail compared with conventional imaging modalities. The aims of this study were: 1) to assess the ability of OCT for visualization of vulnerable plaque features in comparison with IVUS and CAS; and 2) to evaluate the characteristics of culprit lesions in living patients with AMI by OCT.

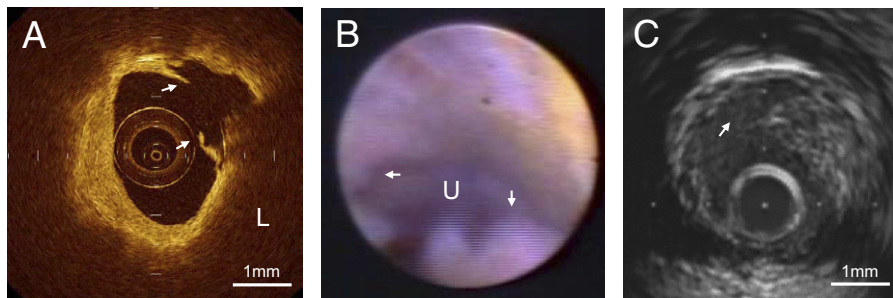
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**Methods**

**Study population.** The AMI patients, who had continuous chest pain lasting >30 min, arrival at our hospital within 6 h from the onset of the symptom, ST-segment elevation  $\geq 0.1$  mV in 2 or more contiguous leads on 12-lead electrocardiogram (ECG), and an identifiable culprit lesion in a native coronary artery by coronary angiography, were enrolled in this study. Exclusion criteria were presence of left bundle-branch block or pacemaker rhythm, a culprit lesion in the left main coronary artery, history of myocardial infarction, cardiogenic shock, unsuccessful reperfusion of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 by initial aspiration thrombectomy before the imaging, and the failure in advancing the CAS, IVUS, or OCT catheter to the

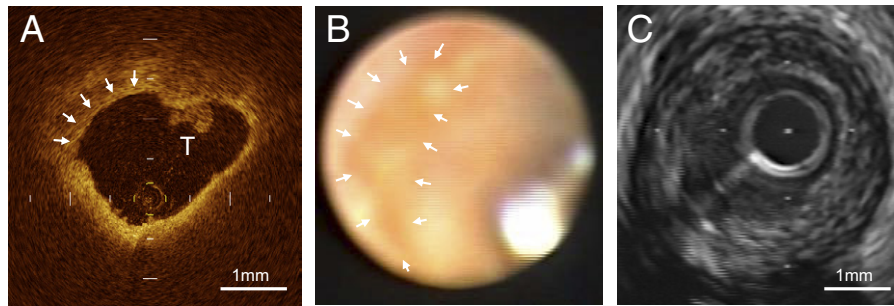
culprit lesion. After observation by various imaging modalities, percutaneous coronary intervention was performed. Demographic and clinical data were prospectively collected. This protocol was approved by the Wakayama Medical University Ethics Committee, and all patients provided informed consent before participation.

**Image acquisition.** Oral aspirin (162 mg) and intravenous heparin (100 U/kg) were administered before coronary intervention. Thrombolysis was not performed for any patient. Cardiac catheterization was performed by the conventional femoral approach, using a 7-F sheath and catheters. The culprit lesion was identified on the basis of the findings by a coronary angiogram as well as an ECG and transthoracic echocardiogram. In patients with TIMI flow grade  $\leq \text{II}$ , aspiration thrombectomy was performed by an aspiration catheter (Export catheter, Medtronic Japan, Tokyo, Japan) before intracoronary imaging, but predilatation by balloon catheter was not allowed. After reperfusion with TIMI flow grade 3, the culprit lesion was observed by IVUS, CAS, and then OCT as described previously (8,13,15). First, IVUS (Atlantis SR Pro 2.5F, 40-MHz; Boston Scientific, Natick, Massachusetts) examination was performed with an automatic pullback device at a rate of 0.5 mm/s. Second, the observation by CAS (Vecmova, Clinical Supply Co., Gifu, Japan) was made while blood was cleared away from view by the injection of 5 to 10 ml saline. Lastly, a 0.016-inch OCT catheter (ImageWire, LightLab Imaging, Westford, Massachusetts) was advanced to the distal end of the culprit lesion through a 3-F occlusion balloon catheter. In order to remove the blood from the field of view, occlusion balloon was inflated to 0.6 atm at proximal site of the culprit lesion, and lactate Ringer’s solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 ml/s. The entire length of the culprit lesion was imaged with an automatic pullback device moving at 1 mm/s, and the OCT image clearly visualized the culprit lesion.



**Figure 1** Images of Typical Fibrous Cap Disruption

Fibrous cap disruption in corresponding images of optical coherence tomography (A), coronary angiography (B), and intravascular ultrasound (C). (A) Lipid-rich plaque (L) with localized disruption of a fibrous cap with a flap protruding into lumen (arrow). (B) Yellow lesion with fibrous cap disruption (arrows) and large ulceration (U). (C) Eccentric plaque ruptured at the shoulder (arrow).



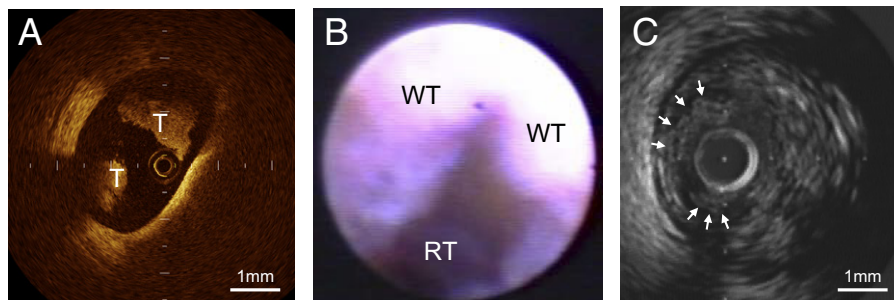
**Figure 2** Images of Typical Fibrous Cap Erosion

Fibrous cap erosion in corresponding images of optical coherence tomography (A), coronary angiography (B), and intravascular ultrasound (C). (A) Erosion located on the surface of a plaque (arrows) with intraluminal thrombus (T). (B) Rough surface erosion without disrupted fibrous cap protruding into lumen (arrows). (C) No identification of fibrous cap erosion.

**Image analysis.** All images were recorded digitally and were analyzed by 2 independent investigators who were blinded to the clinical presentation. When there was discordance between the observers, a consensus reading was obtained. The corresponding images of IVUS, CAS, and OCT were identified by the distances from 2 landmarks, such as side branches. The presence of fibrous cap disruption, fibrous cap erosion, or an intracoronary thrombus was also noted. Fibrous cap disruption was identified by a presence of fibrous cap discontinuity and a cavity formation of the plaque (Fig. 1). Fibrous cap erosion was characterized by loss of the endothelial lining with lacerations of the superficial intimal layers and without “trans-cap” ruptures (Fig. 2). Intracoronary thrombus was identified by the mass images protruding into the vessel lumen from the surface of the vessel wall (Fig. 3). Furthermore, OCT images were analyzed using validated criteria for plaque characterization, and fibrous cap thickness was determined as reported previously (13,14). Briefly, fibrous cap thickness in nonruptured plaque was defined as the minimum distance from the coronary artery lumen to inner border of lipid pool, which

was characterized by signal-poor region in OCT image. In the ruptured plaque, residual fibrous cap was identified as a flap between the lumen of coronary artery and the cavity of plaque, and its thickness was measured at the thinnest part (Fig. 4). Cap thicknesses for each image were measured at 3 different times, and the average value was computed. Lipid was semiquantified as the number of involved quadrants on the cross-sectional OCT image. When lipid was present in  $\geq 2$  quadrants in any of the images within a plaque, it was considered a lipid-rich plaque. For each patient, the cross-sectional image with the highest number of lipid quadrants was used for analysis. Thin cap fibroatheroma (TCFA) was defined as a plaque with lipid content in  $\geq 2$  quadrants and the thinnest part of a fibrous cap measuring  $\leq 65 \mu\text{m}$ . Interobserver and intraobserver variabilities were assessed by the evaluation of all images by 2 independent readers and by the same reader at 2 separate time points, respectively.

**Statistical analysis.** Data are expressed as mean  $\pm$  SD or median with range. The incidences of fibrous cap disruption, fibrous cap erosion, or intracoronary thrombus were compared between imaging modalities by use of chi-square



**Figure 3** Images of Typical Intraluminal Thrombi

Intraluminal thrombi in corresponding images of optical coherence tomography (A), coronary angiography (B), and intravascular ultrasound (C). (A) Thrombus with optical coherence tomography signal attenuation (T). (B) Large white thrombus (WT) and small red thrombus (RT) adhering to a rough surface of yellow plaque. (C) Thrombus (arrows) identified the mass images protruding into the vessel lumen from the surface of the vessel wall.

test or Fisher exact test. To control for multiple comparisons, pairwise tests of incidence were performed, if the contingency table for all 3 imaging techniques was significant. Intraobserver and interobserver variabilities were measured by  $\kappa$  test of concordance. All analysis required a value of  $p < 0.05$  for statistical significance.

**Results**

**Baseline characteristics.** A total of 41 patients with AMI were consecutively enrolled. Eleven patients were excused according to exclusion criteria, and 30 patients were presented in this study. The baseline characteristics are demonstrated in Table 1. The mean age in these patients was 69 years old. In coronary risk factors, the prevalence of diabetes mellitus and hypercholesterolemia was 30% and 53%, respectively. There are no patients with chronic renal insufficiency or hemodialysis. The culprit lesions were easily identified by coronary angiography. Averaged percent diameter stenosis of culprit lesions before intracoronary imaging was  $88 \pm 26\%$ , and TIMI flow grade 0 was most frequent. In 6 patients with TIMI flow grade 3, aspiration thrombectomy was not required. The average duration from the onset of symptom to OCT imaging was  $3.8 \pm 1.0$  h. In all cases, the corresponding OCT, CAS, and IVUS images were obtained by only 1 pullback procedure. Because reference vessel diameter was  $<4$  mm in this population, clear OCT images were provided in spite of limited penetration of OCT signal. The total coronary occlusion time necessary for CAS and OCT was  $18 \pm 7$  s and  $37 \pm 4$  s, respectively. The averaged procedure time required to complete imaging by 3 methods, including imaging catheters exchanges, was  $<13$  min. Although ST-segment re-elevation on ECG was

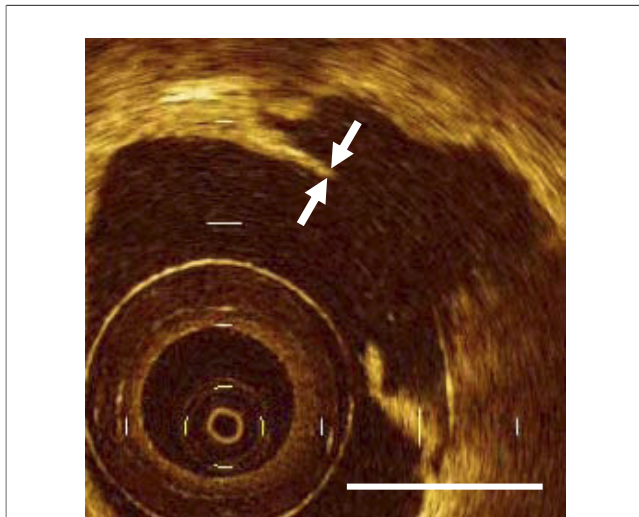
Number of patients	30
Age, yrs	69 $\pm$ 11
Male gender	19 (63)
Diabetes mellitus	9 (30)
Hypertension	25 (83)
Cigarette smoking	14 (47)
Hypercholesterolemia (total cholesterol $>220$ mg/dl)	16 (53)
Culprit vessel	
LAD	11 (37)
LCx	5 (16)
RCA	14 (47)
Percent diameter stenosis, %	88 $\pm$ 26
TIMI flow grade	
0	19 (63)
1	2 (7)
2	3 (10)
3	6 (20)
Duration from the onset of symptom to OCT imaging, h	3.8 $\pm$ 1.0

Values are given as n (%) or mean  $\pm$  standard deviation.

AMI = acute myocardial infarction; LAD = left anterior descending coronary artery; LCx = left circumflex artery; OCT = optical coherence tomography; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

observed in all patients during imaging procedures, it disappeared soon after the procedures by releasing the coronary occlusion. The major complications and adverse events did not occur in the present study.

**OCT, CAS, and IVUS findings for corresponding images.** The OCT, CAS, and IVUS findings for corresponding images are summarized in Table 2. The incidence of fibrous cap disruption was significantly different among the imaging techniques (73%, 47%, and 40% in OCT, CAS, and IVUS, respectively;  $p = 0.021$ ). Difference in the incidence of fibrous cap disruption was significant between OCT and CAS ( $p = 0.035$ ) or OCT and IVUS ( $p = 0.009$ ), but not between CAS and IVUS ( $p = 0.602$ ). In the detection of fibrous cap erosion, there was a significant difference among the imaging techniques (23%, 3%, and 0% in OCT, CAS, and IVUS, respectively;  $p = 0.003$ ). Difference in the incidence of erosion was significant between OCT and CAS ( $p = 0.026$ ) or between OCT and IVUS ( $p = 0.005$ ), but not between CAS and IVUS ( $p = 0.500$ ). The intracoronary thrombus was observed in all cases by OCT and CAS, but it was identified only in 33% by IVUS ( $p < 0.001$ ). The incidence of thrombus was



**Figure 4 Measurement of Fibrous Cap Thickness**

Measurement of fibrous cap thickness in ruptured plaque using optical coherence tomography. Residual fibrous cap was identified as a flap between the lumen of the coronary artery and the cavity of plaque, and its thickness was measured at the thinnest part (arrows). Scale bar = 1 mm.

Finding	OCT (n = 30)	CAS (n = 30)	IVUS (n = 30)	p Value
Fibrous cap disruption	22 (73)*†	14 (47)	12 (40)	0.021
Fibrous cap erosion	7 (23)*†	1 (3)	0 (0)	0.003
Thrombus	30 (100)†	30 (100)‡	10 (33)	$<0.001$

Values are given as n (%). \* $p < 0.05$ , optical coherence tomography (OCT) versus coronary angiography (CAS); † $p < 0.01$ , OCT versus intravascular ultrasound (IVUS); ‡ $p < 0.01$ , CAS versus IVUS.

**Table 3** OCT Findings of the Culprit Lesion in 30 Patients With AMI

Fibrous cap thickness, $\mu\text{m}^*$	49 $\pm$ 21
Lipid-rich plaque (lipid $\geq$ 2 quadrants)	28 (93)
TCFA	25 (83)

Values are given as n (%) or \*mean  $\pm$  SD.

TCFA = thin-cap fibrothrombosis (lipid  $\geq$  2 quadrants and fibrous cap thickness  $\leq$  65  $\mu\text{m}$ ); other abbreviations as in Table 1.

significantly different between OCT and IVUS ( $p < 0.001$ ) or between CAS and IVUS ( $p < 0.001$ ), but not different between OCT and CAS ( $p = 1.000$ ). In addition, only OCT could estimate the fibrous cap thickness, and it was  $49 \pm 21 \mu\text{m}$  (Table 3). The lipid-rich plaque was observed in 93% and the frequency of TCFA was 83% of patients with AMI in the OCT findings.

**Intraobserver and interobserver variability.** Intraobserver variability yielded acceptable concordance for fibrous cap disruption ( $\kappa = 0.83$ ), erosion ( $\kappa = 0.77$ ), intracoronary thrombus ( $\kappa = 0.73$ ), and TCFA ( $\kappa = 0.79$ ). Interobserver variability showed slightly lower concordance: fibrous cap disruption ( $\kappa = 0.77$ ), erosion ( $\kappa = 0.67$ ), intracoronary thrombus ( $\kappa = 0.61$ ), and TCFA ( $\kappa = 0.71$ ).

## Discussion

This is the first report assessing the feasibility and safety of OCT, in comparison with CAS and IVUS, for evaluation of vulnerable coronary plaques in patients with AMI. The high resolution of OCT enabled visualization of the vulnerable plaque characteristics reported by pathohistological study. The fibrous cap disruption, fibrous cap erosion, intracoronary thrombus, and TCFA could be identified more frequently by OCT in comparison with IVUS or CAS. These results indicate that OCT would be an ideal method to identify the vulnerable plaques.

**Fibrous cap disruption and erosion.** The OCT allowed us to evaluate the fibrous cap disruption clearly in patients with AMI. Retrospective pathological studies in patients with coronary artery disease who died suddenly showed fibrous cap disruption in 70% of patients (16,17). One angioscopic evaluation revealed that the prevalence of fibrous cap disruption was 55.5% in patients with AMI (18). Intravascular ultrasound studies have reported varying frequencies of infarct-related fibrous cap disruption (15.8% to 66%) in AMI patients (19,20), and the durations from symptom onset to IVUS imaging were from 10 h to 4 weeks. In the present study using OCT, the time from symptom onset to OCT imaging was  $3.8 \pm 1.0$  h, and the prevalence of fibrous cap disruption was 73%, which was similar to that in postmortem pathohistological examinations and more frequent than those in vivo studies using CAS and IVUS. In addition, OCT was able to evaluate the fibrous cap erosion clearly, and the prevalence of fibrous cap erosion was 23% in patients with AMI in the present study, and this is also thought to be similar frequency compared with that in postmortem pathohistology.

**Intracoronary thrombus.** Intracoronary thrombosis might take a critical role in the pathogenesis and the clinical manifestations of AMI (21). But coronary angiography and IVUS could not reliably identify thrombus (22), and CAS was the only available technology to assess it in vivo (23,24). The present study demonstrated that OCT was able to visualize the intracoronary thrombus clearly in all cases as much as CAS. Jang et al. (13) reported that the frequency of thrombus using OCT imaging was only 20% in patients with recent myocardial infarction who had thrombolytic therapy and the average time interval between the onset of symptoms and OCT imaging was  $4.6 \pm 5.3$  days. These OCT investigations revealed that the intraluminal thrombus was an important characteristic of vulnerable plaque, and pharmacologic thrombolytic intervention could have dissolved some thrombi in the AMI patients. Furthermore, the present study would be more reliable in the incidence of the thrombus in the culprit lesion of AMI compared with the previous study because there was a time delay of up to 6 h between the onset and imaging acquisition.

**TCFA.** Pathohistologically, TCFA has a necrotic core with an overlying thin fibrous cap ( $\leq 65 \mu\text{m}$ ) infiltrated by macrophages, and they have been defined as precursors to lesions of rupture and erosion (25). Although the identification of TCFA is limited in the conventional imaging modalities in vivo, the high resolution of OCT allows us to identify it clearly (13,26). The present study using OCT demonstrates that the thin fibrous cap and large lipid core must be important characteristics to represent vulnerable plaque in AMI. Optical coherence tomography is a powerful modality for evaluation of vulnerable coronary plaque in vivo, and it may provide a great opportunity to understand the mechanism of AMI onset.

**Possibility of OCT for assessing plaque vulnerability.** Optical coherence tomography may be a useful technique for assessing plaque vulnerability. Recent OCT study of culprit lesions demonstrated a higher prevalence of fibrous cap disruption (20% vs. 12%) and TCFA (55% vs. 18%) in patients with acute coronary disease than patients with stable coronary disease (13). The frequency of an intracoronary thrombus was not different in various clinical presentations; however, this unexpected finding may have resulted from a time delay of up to 2 weeks between the acute event and OCT imaging and antithrombotic therapy. These findings represent the observation of presentation-dependent plaque morphology in living human patients and confirm our current knowledge of the relationship between morphology and patient outcome that has been obtained in previous autopsy studies (4).

Arterial positive remodeling and abundant plaque burden are well-described characteristics of vulnerability (4). Several recent IVUS trials have established a relationship between changes in plaque burden and treatment effect with plaque stabilizing medications (e.g., statins) (27-29). Optical coherence tomography is limited in the assessment of plaque burden, because of the limited depth of imaging (2 mm).

Intravascular ultrasound is useful for the evaluation of entire vessel wall and plaque in comparison with current OCT system.

An advantage of OCT is the potential to assess macrophage distribution in the context of high-resolution cross-sectional images of plaque morphology. MacNeill et al. (30) demonstrated that increases in both multifocal and focal macrophage densities are highly correlated with symptom severity of coronary atherosclerosis. By providing a means of detecting increases in plaque macrophage content before an acute event, this technique may aid in determining prognosis and guiding preventive therapy.

An important controversy in the discussion about plaque vulnerability is the focal versus systemic nature. It is increasingly obvious that patients at the time of acute presentation have evidence of plaque instability at various sites in the coronary tree. Several imaging modalities including coronary angiography (31), IVUS (32,33), and CAS (34) have demonstrated evidence that plaque vulnerability is a multifocal process. The current OCT system is limited to focal lesion assessment. Simultaneous imaging with IVUS and CAS would allow us to identify additional vulnerable sites, which could then be evaluated by OCT. However, in the present study multifocal assessment was not performed by 3 modalities, because it would take too much time in the highly life-threatening patients. In addition, an inherent limitation of OCT is the need to occlude coronary artery by balloon catheter and to flush lactate Ringer's solution for imaging. Therefore nonculprit vessel occlusion was thought to increase risk in patients with AMI especially at the time of reperfusion. Although still in a relatively early stage of development, frequency domain OCT imaging has already been shown to be a powerful enabling technology, including improvements in interrupting blood flow, higher penetration depth, and faster image acquisition rates (35,36). Next-generation OCT systems may allow screening of long coronary segments and eliminate many of the technical limitations of the present study.

**Study limitations.** The coronary thrombectomy was performed for reperfusion before the observations. Although the morphologic feature of the culprit lesion might be affected by this procedure, imaging before treatment would not be appropriate ethically. And the thrombolysis might have been a better treatment before the imaging because it would not influence plaque morphology. Also, IVUS was always done before angiography, which was always before OCT, so it is possible that alteration from the IVUS catheter accounted for the findings on angiography or OCT. Performing imaging modalities in a random order would have been a better methodological approach. But it is thought that these procedures affect plaque morphology little, because the frequencies of fibrous cap disruption and erosion assessed by OCT were similar to those in postmortem pathohistological examinations.

In addition, the abilities to detect the characteristics of vulnerable plaques were compared between imaging modal-

ities in this study, but none of them serve as "the gold standard." Therefore, based on the pathohistological knowledge, it must be assessed which modality is better for evaluation of vulnerable plaque.

## Conclusions

Intracoronary OCT is a feasible and safe imaging modality in patients with AMI and allows us to identify plaque ruptures, fibrous cap erosions, TCFA, and intracoronary thrombus in vivo, which has been demonstrated only by histology, more frequently and clearly compared with conventional imaging techniques. The high resolution of OCT provides a greater understanding of the intrinsic morphologic features that determine plaque vulnerability.

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