Morphology of Exertion-Triggered Plaque Rupture in Patients With Acute Coronary Syndrome
An Optical Coherence Tomography Study

Atsushi Tanaka, MD, PhD; Toshio Imanishi, MD, PhD; Hironori Kitabata, MD; Takashi Kubo, MD, PhD; Shigeho Takarada, MD, PhD; Takashi Tanimoto, MD; Akio Kuroi, MD; Hiroto Tsujioka, MD; Hideyuki Ikejima, MD; Satoshi Ueno, MD; Hideaki Kataiwa, MD; Keishi Okouchi, MD; Manabu Kashiwaghi, MD; Hiroki Matsumoto, MD; Kazushi Takemoto, MT; Nobuo Nakamura, MD; Kumioko Hirata, MD, PhD; Masato Mizukoshi, MD, PhD; Takashi Akasaka, MD, PhD

Background—Plaque rupture and secondary thrombus formation play key roles in the onset of acute coronary syndrome (ACS). One pathological study suggested that the morphologies of plaque rupture differed between rest-onset and exertion-triggered rupture in men who experienced sudden death. The aim of the present study was to use optical coherence tomography to investigate the relationship in patients with ACS between the morphology of a ruptured plaque and the patient’s activity at the onset of ACS.

Methods and Results—The study population was drawn from 43 consecutive ACS patients (with or without ST-segment elevation) who underwent optical coherence tomography and presented with a ruptured plaque at the culprit site. Patients were divided into a rest group and an exertion group on the basis of their activities at the onset of ACS. The thickness of the broken fibrous cap correlated positively with activity at the onset of ACS. The culprit plaque ruptured at the shoulder more frequently in the exertion group than in the rest group (rest 57% versus exertion 93%, P = 0.014). The thickness of the broken fibrous cap in the exertion group was significantly higher than in the rest-onset group (rest onset: 50 μm [interquartile median 15 μm]; exertion: 90 μm [interquartile median 65 μm], P < 0.01).

Conclusions—The morphologies of exertion-triggered and rest-onset ruptured plaques differ in ACS patients. Our data suggest that a thin-cap fibroatheroma is a lesion predisposed to rupture both at rest and during the patient’s day-to-day activity, and some plaque rupture may occur in thick fibrous caps depending on exertion levels. (Circulation. 2008;118:2368-2373.)

Key Words: imaging ■ acute coronary syndrome ■ plaque ■ tomography, optical coherence

Plaque rupture and secondary thrombus formation play key roles in the onset of acute coronary syndrome (ACS). In a previous intravascular ultrasound (IVUS) study, we reported that this catastrophic event frequently occurred suddenly, at rest and early in the morning. It has also been reported that exertion is a possible trigger for plaque rupture. One pathological study has suggested that morphologies of plaques that rupture on exertion may differ from morphologies of those that rupture without exertion in men experiencing sudden death; however, there are few in vivo studies regarding the relationship between patient activity at the onset of ACS and the morphology of the ruptured plaque in patients with ACS.

Clinical Perspective p 2373

The recent development of intravascular optical coherence tomography (OCT) has provided a high-resolution imaging method suitable for plaque characterization. OCT is an optical analogue of IVUS with a resolution of approximately 10 to 20 μm. Histological studies have shown that OCT can identify the microstructure of atherosclerotic plaque, including thin-cap fibroatheroma and lipid core. The aim of the present study was to use OCT to investigate the relationship between the morphology of the ruptured plaque and the patient’s activity at the onset of ACS in ACS patients.

Methods

Subjects
The present study population was drawn from 72 consecutive ACS patients (with or without ST-segment elevation) who were admitted...
to Wakayama Medical University Hospital (Wakayama, Japan) and who underwent OCT. Of these 72 ACS patients, OCT identified plaque rupture in 43 (60%), who were accordingly included for analysis in the present study. The exclusion criteria were presentation of congestive heart failure, history of prior myocardial infarction, cardiogenic shock, and unsuccessful reperfusion of Thrombolysis In Myocardial Infarction (TIMI) flow grade III by initial aspiration thrombectomy before OCT imaging. 

Demographic and clinical data were collected prospectively. Patient activity at the time of the onset of ACS was determined precisely from an interview with an expert cardiologist blinded to the OCT data. The intensity of activity was estimated and the patient assigned a resting metabolic rate (MET) score.16 Patients were divided into rest and exertion groups determined by the cutoff value of 4 METs.

This study complies with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Wakayama Medical University. We also obtained written informed consent from all participants before initial coronary angiography.

**Coronary Angiography**

In all patients, coronary angiography was performed with a 5F Judkins-type catheter via the femoral approach. All patients received an intravenous bolus injection of 2000 IU of heparin and intracoronary isosorbide dinitrate (2 mg) before angiography. The culprit lesion was identified on the basis of the findings of coronary angiography, as well as an ECG and transthoracic echocardiogram. Coronary angiograms were reviewed separately by 2 independent observers (HK and TT) unaware of the OCT findings.

**OCT Imaging Protocol**

Oral aspirin (162 mg) and intravenous heparin (8000 U) were administered before coronary intervention. No patient received any thrombolytic therapy before angioplasty. After completion of diagnostic coronary angiography, aspiration thrombectomy was performed with the aspiration catheter (Export, Medtronic Japan, Tokyo, Japan) before OCT imaging if the patient had TIMI grade 0, I, or II coronary flow. After thrombectomy, OCT was used to observe the culprit coronary artery. A 0.016-in OCT catheter (ImageWire; LightLab Imaging, Westford, Mass) was advanced to the distal end of the culprit lesion through a 3F (distal) occlusion balloon catheter (Helios; Goodman Co Ltd, Nagoya, Japan). To remove blood cells from the imaging field, the occlusion balloon was inflated to 0.5 atm proximal to the culprit lesion, and lactated Ringer’s solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at a rate of 0.5 mL/s.

For proximal lesions, we used a continuous-flushing (nonocclusive) technique of OCT image acquisition, which is a newly developed alternative to the balloon-occlusion technique. To flush the vessel, we infused a mixture of commercially available dextran 40 and lactated Ringer’s solution (low-molecular-weight Dextran L Injection, Otsuka Pharmaceutical Factory, Tokushima, Japan) direct from the guiding catheter at a rate of 2.5 to 4.5 mL/s with an injector pump (Mark V, Medrad Inc, Warrendale, Pa). Regardless of the OCT technique used, in all cases, the culprit lesion was imaged with an automatic pullback device traveling at 1 mm/s. The OCT images were digitalized and analyzed by an M2CV (MIDI [musical instrument digital interface] to CV [control voltage] converter) OCT console.

**OCT Image Analysis**

All OCT images were analyzed by 2 independent investigators (AT and MM) who were blinded to the clinical presentations. When there was any discordance between the observers, a consensus reading was obtained. Presence of plaque rupture, intracoronary thrombus, or thin-cap fibroatheroma was recorded. Plaque rupture was defined as the presence of fibrous-cap discontinuity and a cavity formation in the plaque (Figure 1). Intracoronary thrombus was identified as a mass that protruded into the vessel lumen from the surface of the vessel wall (Figure 2). OCT images were analyzed with previously validated criteria for plaque characterization, and fibrous-cap thickness was determined as reported previously.14,15 Lipid was semi-quantified according to the number of involved quadrants on the cross-sectional OCT image. When lipid was present in ≥2 quadrants in any of the images within a plaque, the plaque was deemed to be lipid rich. For each patient, the cross-sectional image with the highest number of lipid quadrants was used for analysis. A thin-cap fibroatheroma was defined as a plaque with lipid content in ≥2 quadrants and the thinnest part of the fibrous cap measuring <70 μm (Figure 2).

**High-Sensitivity C-Reactive Protein Assay**

Blood was collected in the emergency department. Blood samples were centrifuged, and serum was removed and stored at −80° until assays could be performed. High-sensitivity C-reactive protein (hs-CRP) was analyzed with a commercially available testing kit (N-Latex CRP II, Dade Behring Marburg GmbH, Marburg, Germany).

**Figure 1.** Representative cases of plaque rupture occurring at rest or with exertion. Left, Plaque rupture that occurred at rest. Fibrous cap was broken at the midportion, and a thin fibrous cap could be observed. Right, Plaque rupture that occurred during heavy farm work. Thick fibrous cap was broken at shoulder of plaque.
Statistical Analysis
Statistical analysis was performed with StatView 5.0.1 (SAS Institute, Cary, NC). Results are expressed as mean±SD for approximately normally distributed variables and median (interquartile median) for skewed variables. Qualitative data are presented as number (%). Differences between the 2 groups were tested by the unpaired t test for approximately normally distributed variables, by Mann-Whitney test for skewed variables, and by Fisher’s exact test for categorical variables. The Spearman rank correlation test was used in analysis for the correlation between the thickness of the broken fibrous cap and activity at the onset of ACS. A P value <0.05 was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics
The patient characteristics of both groups are summarized in Table 1. There were no statistically significant differences in terms of age, gender, or classic coronary risk factors between the 2 groups. There were no patients who developed ACS after obvious emotional triggers or particular situations, such as postearthquake stress, in the present study. ST-segment elevation myocardial infarction was observed significantly more frequently in the group that developed ACS at rest (46% versus 13%, P=0.03).

Angiographic Results
Angiographic findings are summarized in Table 2. There were no significant differences in angiographic findings between the groups. Thrombectomy was performed in 23 patients (53%).

OCT Findings
Culprit sites were successfully observed in all patients with OCT without any serious procedural complications. There were no incidences of critical arrhythmia. The balloon-occlusion technique for OCT image acquisition was applied for 11 patients (26%). OCT findings are summarized in Table 3. Analysis of the distribution of broken fibrous-cap thickness is shown in Figure 3. There were 29 patients (67%) presenting with broken fibrous-cap thickness <70 μm. Broken fibrous-cap thickness correlated positively with activity at the onset of ACS (Figure 4). We also observed that plaques ruptured more frequently at the shoulder in the exertion group (rest 57% versus exertion 93%, P=0.014). Representative cases of plaque rupture that occurred at rest and at exertion are shown in Figure 1. The thickness of the broken fibrous cap in the ruptured plaques also showed a weak inverse correlation with hs-CRP levels (r=-0.31, P<0.01; Figure 5). If we exclude patients with ST-elevation myocardial

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rest Group (n=28)</th>
<th>Exertion Group (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.2±11</td>
<td>65.2±14</td>
<td>0.80</td>
</tr>
<tr>
<td>Male</td>
<td>21 (75)</td>
<td>11 (73)</td>
<td>0.99</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>19 (68)</td>
<td>13 (87)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (29)</td>
<td>8 (53)</td>
<td>0.18</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>14 (50)</td>
<td>8 (60)</td>
<td>0.83</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (61)</td>
<td>7 (47)</td>
<td>0.52</td>
</tr>
<tr>
<td>Obesity</td>
<td>2 (7)</td>
<td>4 (27)</td>
<td>0.16</td>
</tr>
<tr>
<td>ST-elevation myocardial infarction</td>
<td>13 (46)</td>
<td>2 (13)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data presented are mean±SD or n (%).

Table 2. Angiographic Findings

<table>
<thead>
<tr>
<th></th>
<th>Onset at Rest (n=28)</th>
<th>Onset With Exertion (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culprit artery</td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>12 (43)</td>
<td>6 (40)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>2 (7)</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>14 (50)</td>
<td>6 (40)</td>
<td></td>
</tr>
<tr>
<td>TIMI flow grade at initial angiograms</td>
<td>0.27</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (32)</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (7)</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (21)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (39)</td>
<td>9 (60)</td>
<td></td>
</tr>
<tr>
<td>Reference lumen diameter, mm</td>
<td>3.3±0.7</td>
<td>3.4±0.5</td>
<td>0.38</td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>0.10 (1.0)</td>
<td>0.58 (0.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>% Diameter stenosis</td>
<td>97 (32)</td>
<td>82 (25)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Data presented are mean±SD, median (interquartile median), or n (%).
infarction from the original study population, the main findings of the present study with regard to the relationship between activity levels at the onset of ACS and fibrous-cap thickness \( (r=0.65, P=0.0001) \) and the difference in frequency of cap rupture at the plaque shoulder between the 2 groups (rest 53% versus exertion 92%, \( P=0.037 \)) do not change.

**Discussion**

In the present study, we have demonstrated that the morphology of plaque rupture is different depending on what the patient was doing at the time of onset of ACS.

**Cap Thickness and Patient Activity at the Onset of ACS**

Previous studies from cross-sectional views have suggested that plaque rupture occurs most frequently at the point where the fibrous cap is thinnest and most heavily infiltrated by macrophage foam cells. These rupture-related macrophages are activated, which indicates ongoing inflammation at the site of plaque disruption. Macrophages are capable of degrading the extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and the family of matrix metalloproteinases, which may weaken the fibrous cap, predisposing it to rupture. These heavily infiltrated macrophages are observed frequently at the shoulder of plaques. The present data regarding an inverse correlation between hs-CRP and thickness of the broken fibrous cap may support the above theory. In addition, computational fluid-structure interaction models and finite-element models predict maximum tissue stresses at the shoulders of the lipid core.\(^{18–20}\) Therefore, the shoulder of the plaque is considered the weakest point and the most prone to rupture. Despite this, however, a large-scale in vivo IVUS study has suggested that \( \approx40\% \) of plaque ruptures occur at the central part of the cap.\(^{21}\)

The present data may provide an explanation for this paradoxical observation. In the exertion group, 93% of patients had cap rupture at the shoulder, where the computational models mentioned above, which assume that mechanical stress is a major determining trigger for rupture, predict maximum stress. The present data also show that the thickness of the broken cap is positively correlated with patient activity at the time of onset. We therefore consider that the present findings fit well with the predictions of computer models.

Alternatively, recent 3D finite-element calculations by Vengrenyuk et al\(^ {22}\) show that maximum stress actually occurs when microcalcifications are in close proximity to regions where background peak circumferential stress is high. If we

<table>
<thead>
<tr>
<th></th>
<th>Rest (n=28)</th>
<th>Exertion (n=15)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus</td>
<td>27 (96)</td>
<td>11 (73)</td>
<td>0.04</td>
</tr>
<tr>
<td>Thin-cap fibroatheroma at culprit site</td>
<td>16 (57)</td>
<td>6 (40)</td>
<td>0.35</td>
</tr>
<tr>
<td>Broken at plaque shoulder</td>
<td>16 (57)</td>
<td>14 (93)</td>
<td>0.017</td>
</tr>
<tr>
<td>Thickness of broken fibrous cap, ( \mu m )</td>
<td>50 (15)</td>
<td>90 (65)</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

Data presented are median (interquartile median) or \( n \) (%).
put our findings into this new model, cap thinning would occur primarily because of enzymes that are released by macrophages in the lipid pool, where their concentration is far greater than in the tissue at the cap shoulder. The inverse correlation between thickness of cap rupture and hs-CRP levels could be explained by the fact that inflammation might be triggered by background tensile stress and that this is reduced in thick caps.

Furthermore, most plaque ruptures in the exertion group in the present study appeared at the shoulder, where cap thickness can be as great as 140 μm and still result in rupture. The new 3D finite-element model by Vengrenyuk et al also reported that the shape of the microcalcification plays a critical role and that for an elongated calcification with aspect ratios between 2 and 4 in a region of high background stress at the shoulders, the thickness at which the plaque can rupture lies between 120 and 160 μm, in good agreement with the present in vivo OCT observations for rupture in thick caps.

In contrast, 57% of patients in the rest-onset group in the present study presented with rupture in the center of the cap. Cap thickness for ruptured plaque in the rest-onset group was also thinner than in the exertion-triggered group. Recently, Vengrenyuk et al reported that their theoretical model predicts that cap rupture can occur in the center of a fibrous cap with thickness <65 μm and the structure of which includes cellular microcalcifications. This prediction is in close agreement with pathological observations that Virmani et al have reported, namely, that a thin cap <65 μm is a more specific precursor of plaque rupture, and with the present study data showing that 90% of patients in the rest-onset group had caps with a thickness <70 μm. In other words, when a fibrous-cap rupture occurs at its center, the thickness of the cap may be less than the 65 μm described by pathological reports. The present results with OCT appear to support the hypotheses by Vengrenyuk et al that cellular-level microcalcifications in the cap and their shape could play a critical role in determining plaque stability in both thin and thick fibrous caps.

In the present study, nearly 70% of patients presented with broken fibrous caps of <70 μm thickness, but this figure was 93% in the rest-onset group. One pathological study reported that 95% of broken caps were <65 μm in men who experienced sudden death. This discrepancy may result from the patient’s background. Interestingly, the rest-onset group in the present study had a higher incidence of ST-elevation myocardial infarction than the exertion group. Our recent 3D IVUS study revealed that the longitudinal morphology of ruptured plaques affects the clinical presentation in ACS. We speculate that cap thickness also may correlate with the severity of the clinical presentation but accept that further study is needed to clarify this issue. Previous pathological studies assumed the activity at the onset of sudden death on the basis of the underlying situations of sudden death patients or on the basis of bystander’s comments, whereas we were able to take a detailed clinical history from the patients themselves and determine their precise activity at the onset of ACS. Therefore, there may be a possibility that such pathological studies misclassified the activity at the precise onset of sudden death in some patients because of the nature of their methodology.

**Clinical Implications**

The detection of vulnerable plaques and the prevention of ACS are key objectives for all cardiologists. The data in the present study strongly suggest that a thin-cap fibroatheroma is a lesion predisposed to rupture, both at rest and during the patient’s day-to-day activity. OCT can identify and quantify these thin-cap fibroatheromas in human subjects. Furthermore, in the clinical setting, some plaque rupture may occur in thick fibrous caps (70 to 140 μm) depending on exertion levels. We would like to emphasize the importance of further investigation into not only thin-cap atheroma but also thick-cap atheroma in the clinical setting. We believe that ≈30% of plaque ruptures develop from thick-cap atheromas.

**Study Limitations**

A number of limitations may be associated with the present study. The study population was relatively small. Thrombectomy was performed for reperfusion before OCT. A thrombectomy catheter may modify the morphology of ruptured plaques. In the present study, >90% of patients had thrombus even after thrombectomy. This intracoronary thrombus may also affect imaging analysis, especially the measurement of fibrous-cap thickness. We estimated activity levels at the onset of ACS by precise history taking, but the possibility remains that the onset of ACS is different from the onset of plaque rupture.

Mittleman et al reported that onset of ACS during heavy exertion (>6 METs) within 1 hour occurs in only 4.4% of myocardial infarctions. On the other hand, our previous IVUS study, which consisted of 174 acute myocardial infarction patients, revealed that plaque rupture occurred during exertion in 33% of the patients. Our present OCT data also showed a similar frequency of ACS caused by exertion-related plaque rupture (15 [35%] of 43 patients). We speculate that this difference is due to the time restriction on the historical data and extent of exertion. Mittleman et al also reported that emotional triggers such as anger could provoke ACS. In the present study, there were no patients who developed ACS due to obvious emotional triggers or particular situations, such as postearthquake stress; therefore, we could not investigate the plaque morphology of such cases with OCT. Although our previous IVUS studies reported that elevated hs-CRP is associated with the inflammatory activities of coronary plaques, plaque instabilities may exist elsewhere. Therefore, there is a possibility that serum hs-CRP levels may reflect the inflammatory activities of plaques throughout the systemic artery. Finally, Kume et al. in their comparative study of OCT and histological examination, suggest that OCT may slightly overestimate cap thickness. They argue that this discrepancy may be due to shrinkage that results from the processing of histological specimens in spite of the use of pressure fixation. If correct, this may have introduced bias into the results of the present study.

**Disclosures**

None.
References


CLINICAL PERSPECTIVE

Plaque rupture and secondary thrombus formation play key roles in the onset of an acute coronary syndrome. To prevent acute coronary syndrome events, many studies have focused on rupture-prone plaques. Until recently, thin-cap fibroatheromas proposed by pathological studies and computational models were considered to be the most rupture-prone plaques. The data from the present study suggest that thin-cap fibroatheromas would be predisposed to rupture, both at rest and during the patient’s day-to-day activity. Inflammation aggressively participates in the process of plaque instability, as suggested by the negative correlation between thickness of ruptured caps and high-sensitivity C-reactive protein levels. Furthermore, the data suggest that in the clinical setting, some plaque ruptures may occur in thick fibrous caps (70 to 140 μm) depending on exertion levels. Theses findings are consistent with new 3D finite-element models. Therefore, the present study suggests that broader thinking may be called for in the area of the mechanism of plaque rupture. Further investigation is required into not only thin-cap atheroma but also thick-cap atheroma in the clinical setting.
Morphology of Exertion-Triggered Plaque Rupture in Patients With Acute Coronary Syndrome: An Optical Coherence Tomography Study
Atsushi Tanaka, Toshio Imanishi, Hironori Kitabata, Takashi Kubo, Shigeho Takarada, Takashi Tanimoto, Akio Kuroi, Hiroto Tsujioka, Hideyuki Ikejima, Satoshi Ueno, Hideaki Kataiwa, Keishi Okouchi, Manabu Kashiwaghi, Hiroki Matsumoto, Kazushi Takemoto, Nobuo Nakamura, Kumiko Hirata, Masato Mizukoshi and Takashi Akasaka

_Circulation._ 2008;118:2368-2373; originally published online November 17, 2008; doi: 10.1161/CIRCULATIONAHA.108.782540
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/23/2368