Clinical Predictors of Culprit Plaque Rupture Assessed on Intravascular Ultrasound in Acute Coronary Syndrome

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Background: Acute coronary syndrome (ACS) commonly results from vulnerable plaque rupture, and occasionally results from thrombus formation in lesions without plaque rupture. The aim of the present study was to clarify the clinical features of different etiology of ACS and clinical predictors of culprit plaque rupture assessed on intravascular ultrasound (IVUS).

Methods and Results: One hundred and ten ACS patients with emergent coronary angiography were classified into 2 groups based on the presence or absence of culprit plaque rupture assessed on IVUS. Clinical characteristics were compared between the 2 groups. Culprit coronary plaque rupture was observed in 60 patients (55%). Patients with plaque rupture were younger and were more likely to be male (P<0.03 and P<0.02, respectively). In the rupture group, the prevalence of metabolic syndrome was higher (P<0.002), and among the components of metabolic syndrome, waist circumference was greater and serum high-density lipoprotein cholesterol level was lower (P<0.0001 and P=0.0004, respectively). IVUS-assessed lesion remodeling index was greater in the rupture group (P<0.0001). On multivariate analysis metabolic syndrome was an independent predictor of culprit plaque rupture (odds ratio=5.26, 95% confidence interval=1.49–21.40, P<0.02).

Conclusions: Abdominal obesity and low high-density lipoprotein-cholesterol level are the characteristics of metabolic syndrome that seem to be the key factors for vulnerable plaque rupture with coronary compensatory enlargement. (Circ J 2010; 74: 1936–1942)

Key Words: Acute coronary syndrome; Intravascular ultrasound; Plaque rupture
2 or more leads. Among them, acute myocardial infarctions were diagnosed by increased serum levels of the creatine kinase (more than twice the upper limit of normal) and creatine kinase-MB fraction (>10% of the total creatine kinase), and other patients with no elevation of the creatine kinase-MB fraction were classified as having unstable angina. All patients underwent angiography to document the responsible coronary lesions within 24 h after the onset of chest pain. Patients with a history of myocardial infarction or coronary artery bypass grafting were excluded. Patients with heavily calcified lesions, left main disease, tortuous lesions expected to cause difficulty in advancing the IVUS catheter were also excluded. We identified the plaques based on coronary angiography and analyzed each plaque using IVUS. Among them, lesions with massive thrombi were thrombolysed with a pulse infusion thrombolysis (PIT) system (Nemoto Kyorindo, Tokyo, Japan), or a thrombectomy was performed with an aspiration system (Thrombuster, Kaneka Medix, Osaka, Japan) before IVUS.

The patients were divided into 2 groups based on the presence or absence of culprit coronary plaque ruptures identified on IVUS. We assessed the patient characteristics, including the age, gender, body mass index, waist circumference, and the presence of coronary risk factors (hypertension, diabetes mellitus, hyperlipidemia, current smoking, and ischemic family history). Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of anti-hypertensive drugs. Hyperlipidemia was defined as low-density lipoprotein (LDL) level ≥140 mg/dl, fasting triglyceride level ≥150 mg/dl, or use of anti-hyperlipidemia drugs. Diabetes mellitus was defined as any of the following: fasting serum glucose level ≥126 mg/dl, non-fasting glucose level ≥200 mg/dl, self-reported use of medications for diabetes, or a self-reported previous physician diagnosis. High LDL-cholesterolemia was defined as a serum LDL-cholesterol level >140 mg/dl.

The characteristics of metabolic syndrome were based on the third report of the National Cholesterol Education Program’s Adult Treatment Panel III criteria. Among those criteria, the waist circumference might not be suitable for Japanese, and it was modified. A previous study demonstrated that a visceral fat area of 100 cm² assessed on abdominal computed tomography at the level of the umbilicus was identified in Japanese men with a waist circumference of 85 cm and in Japanese women with that of 90 cm. According to the report, we defined metabolic syndrome as the presence of ≥3 of the following factors: (1) waist circumference ≥85 cm in men and ≥90 cm in women; (2) fasting triglyceride level >150 mg/dl; (3) high-density lipoprotein (HDL)-cholesterol level <40 mg/dl in men and <50 mg/dl in women; (4) hypertension (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg) or use of anti-hypertensive drug therapy; and (5) fasting glucose level ≥110 mg/dl. The blood sampling was examined at a hemodynamically steady state 5–7 days after the onset of the ACS. Informed consent was obtained from all patients after receiving an explanation of the study.

Coronary Angiography
Oral aspirin (100 mg), clopidgrel (300 mg), and iv heparin (5,000–7,000 U) were administered before the coronary intervention. Coronary angiography was performed according to the standard Judkins technique, using a 6-F sheath and catheters. The images were analyzed as previously described, with substantial lesions (vessel diameter narrowed by >50%) being measured quantitatively.

The location of the culprit lesion was determined by correlating the presence of a complex lesion with the electrocardiographic and wall motion abnormalities. In each patient, the coronary vasculature was reviewed to identify any anatomically remote complex lesions. An anatomically remote lesion was defined as a lesion in an artery different from that containing the culprit lesion, in a different branch of the same artery, or in the same branch, but at least 5 cm from the culprit lesion with an intervening disease-free segment. The angiograms were analyzed by 2 independent angiographers.
Figure 2. Non-ruptured culprit lesion on coronary angiography and intravascular ultrasound. No ulceration was observed after pulse infusion thrombolysis on coronary angiography and intravascular ultrasound. Intravascular ultrasound showed a significant luminal narrowing without a plaque rupture (Right).

Table 1. Clinical Characteristics of ACS Patients vs Plaque Rupture

<table>
<thead>
<tr>
<th>Coronary plaque rupture</th>
<th>+ (n=60)</th>
<th>- (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-elevation myocardial infarction</td>
<td>51 (85)</td>
<td>27 (54)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>5 (8)</td>
<td>15 (30)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>TIMI flow grade 0/1/2/3</td>
<td>46/2/8/4</td>
<td>16/5/20/9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.4±10.7</td>
<td>67.1±11.0</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Old age (≥65 years)</td>
<td>24 (40)</td>
<td>30 (60)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>51/9</td>
<td>33/17</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1±4.0</td>
<td>22.5±2.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>87.1±7.5</td>
<td>80.8±8.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>39 (65)</td>
<td>17 (34)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>36 (60)</td>
<td>16 (32)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Low HDL-cholesterolemia</td>
<td>29 (48)</td>
<td>13 (26)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>51 (85)</td>
<td>40 (80)</td>
<td>0.49</td>
</tr>
<tr>
<td>High triglyceridemia</td>
<td>27 (45)</td>
<td>12 (24)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>High blood glucose</td>
<td>30 (50)</td>
<td>22 (44)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (75)</td>
<td>36 (72)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (37)</td>
<td>17 (34)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>35 (58)</td>
<td>23 (46)</td>
<td>0.20</td>
</tr>
<tr>
<td>Current smoking</td>
<td>34 (57)</td>
<td>25 (50)</td>
<td>0.49</td>
</tr>
<tr>
<td>Ischemic family history</td>
<td>13 (22)</td>
<td>4 (8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>197±31</td>
<td>197±37</td>
<td>0.94</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>43±9</td>
<td>50±12</td>
<td>0.0004</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>124±28</td>
<td>120±31</td>
<td>0.44</td>
</tr>
<tr>
<td>Fasting triglycerides (mg/dl)</td>
<td>146±53</td>
<td>133±70</td>
<td>0.27</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>118±38</td>
<td>111±35</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Data are mean±SD or n (%).
ACS, acute coronary syndrome; TIMI, Thrombolysis In Myocardial Infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
and S.S.). The results were compared, and a final decision was made by consensus when there was disagreement.

Intracoronary Image Acquisition
Lesions with a Thrombolyis In Myocardial Infarction (TIMI) flow grade of ≤2 with thrombi were treated with aspiration thrombectomy and/or PIT\(^1\) before the intracoronary imaging, but pre-dilatation with a balloon catheter was not allowed. After reperfusion with a TIMI flow grade 3, the culprit lesion was observed using IVUS. IVUS (Atlantis SR Pro 2.5 F, 40 MHz; Boston Scientific, Natick, MA, USA) was performed utilizing an anatomic pullback device at a rate of 0.5 mm/s. The entire length of the culprit lesion was imaged with an automatic pullback device moving at 1 mm/s.

Image Analysis
All images were recorded digitally and analyzed by 2 independent investigators (T.N. and Y.W.) who were blinded to the clinical presentation. The corresponding image from the IVUS was identified by the distances from 2 landmarks, such as side branches. The change in the lesion site external elastic membrane cross-sectional area was the direct measure of arterial remodeling. The remodeling index was calculated as the lesion site divided by the reference external elastic membrane cross-sectional area and used to classify lesions into positive remodeling (remodeling index >1.1).

The presence of a plaque rupture was also noted. Plaque ruptures were identified as a plaque containing a cavity that communicated with the lumen with an overlying residual fibrous cap fragment on IVUS (Figure 1).\(^16\) Culprit lesions without plaque ruptures were identified as lesions without any fibrous cap disruption or cavity formation (Figure 2).

Statistical Analysis
The results are presented as mean±SD. Univariate analysis was performed using Student’s t-test. Categorical data were compared against a chi-square distribution. The clinical variables were entered into a multivariate logistic regression model of a coronary plaque rupture to test their independent effects. The independent clinical variables included old age (≥65 years), male gender, TIMI flow grade 0, and the presence of hypertension, diabetes mellitus, dyslipidemia, current smoking, ischemic family history (only including coronary artery disease), metabolic syndrome, and IVUS parameters. The odds ratios (OR) and 95% confidence intervals (95%CI) were calculated to assess the predictive value. P<0.05 was considered statistically significant.

Results
Clinical Characteristics in ACS Patients With and Without Culprit Plaque Ruptures
A prospective but non-consecutive series of 139 ACS patients whose culprit lesions were observed on IVUS were enrolled. We could not obtain clear images for an exact analysis in 29 patients and in the remaining 110 patients we were able to analyze the IVUS images. Among them, culprit plaque ruptures were identified in 60 patients (55%). The clinical characteristics of the patients with and without plaque ruptures are listed in Table 1. Patients with culprit plaque rupture were younger and had a higher proportion of men. The prevalence of an acute myocardial infarction in the patients with plaque...
ruptures was higher than that in the patients without plaque ruptures. The body mass index and waist circumference in the patients with plaque ruptures were significantly greater than that in the patients without plaque ruptures. The prevalence of metabolic syndrome diagnosed with the revised ATP III criteria was higher in the rupture group. The serum HDL-cholesterol level in the rupture group was significantly lower than that in the non-rupture group. In ACS men, the prevalence of metabolic syndrome was significantly higher than in women (54% vs 32%, P<0.03).

**IVUS Findings of Culprit Lesions With and Without Culprit Plaque Rupture**

The IVUS findings of the culprit lesions with and without plaque ruptures are given in Table 2. Both the elastic membrane cross-sectional area and minimum lumen area in the culprit lesions with plaque ruptures were significantly greater than that in the lesions without plaque ruptures. On receiver operating characteristic analysis, 13.9 mm² was the optimal cut-off of the lesion elastic membrane cross-sectional area in this population to predict culprit plaque rupture (area under the curve of 0.71, P=0.0004; sensitivity 77%, specificity 62%). Furthermore, in the ruptured lesions, the vascular remodeling index was significantly greater and significant positive remodeling was observed. In patients with IVUS-assessed positive remodeling, body mass index was significantly greater (24.7 kg/m² vs 23.3 kg/m², P<0.05) and the prevalence of low HDL-cholesterolemia tended to be higher (48% vs 30%, P=0.053) than in patients without positive remodeling.

**Independent Predictors for Culprit Plaque Rupture**

The strongest independent predictor of a culprit coronary plaque rupture was the presence of metabolic syndrome, TIMI flow grade 0, elastic membrane cross-sectional area ≥14 mm², and positive remodeling at the culprit lesion (Table 3). Among the components of metabolic syndrome, abdominal obesity and a low serum HDL-cholesterol level were significant independent predictors for culprit coronary plaque rupture (OR=2.98, 95%CI=1.28–7.22, P=0.02; and OR=2.94, 95%CI=1.25–7.30, P<0.02, respectively).

**Discussion**

In the present study on ACS we clarified that the prevalence of metabolic syndrome was significantly greater in ACS patients with culprit plaque rupture. Among the metabolic variables, abdominal obesity and low serum HDL-cholesterol were important predictors of plaque rupture. Furthermore, the incidence of culprit plaque rupture was significantly higher in ACS men. As found in previous pathology studies, the features of the lesions with plaque ruptures were positive remodeling with a large plaque burden, whereas no vascular remodeling was observed in the lesions without any plaque ruptures.3,17,18 The previous study demonstrated that the luminal cross-sectional area in ruptured culprit plaque was larger than that in the non-ruptured plaque. In fact, a pooling of the angiography studies showed that a myocardial infarction may arise most frequently from mild–moderate stenosis.19–23 Furthermore, a thin cap fibroatheroma is one of the important characteristics for representing vulnerable plaque.5,7,24 Previous studies demonstrated that intracoronary thrombi, and thin cap fibroatheromas could be identified more frequently on OCT than IVUS.5,24 OCT, however, could not detect the coronary vascular remodeling of the culprit plaque. Because the plaque instability is to be viewed not as a consequence of fibrous cap thickness alone but rather as a combination of cap thickness, necrotic core thickness, and the arterial remodeling index,5 OCT alone could not detect the vulnerable coronary plaque just before fibrous cap disruption. A combination of various coronary imaging modalities might be needed to detect the plaques easy to rupture.

The present study demonstrated that vulnerable coronary plaque ruptures might be associated with metabolic syndrome, especially with an abdominal obesity and low HDL-cholesterol level. We previously reported that Japanese ACS men with metabolic syndrome are more susceptible to multiple, complex coronary lesions.26 Among the components of metabolic syndrome, abdominal obesity and low HDL-cholesterol levels were more frequently observed in patients with multiple, complex coronary lesions. The presence of multiple, complex coronary lesions identified on coronary angiography has been reported to be associated with an increased incidence of recurrent ACS.27,28 Furthermore, multiplicity of vulnerable plaques in non-target vessels was the important predictor of future critical cardiac events in 3-vessel IVUS.29 A recent study demonstrated that ST-segment elevation myocardial infarction caused by plaque rupture is associated with a large degree of myocardial damage and poor functional recovery as compared with that without plaque rupture, even after successful primary angioplasty.3 Therefore, the abdominal obesity and low HDL-cholesterol level seem to be the key factors for coronary plaque vulnerability and may be associated with the poor clinical outcomes of ACS patients.

Although metabolic syndrome has been acknowledged as a risk factor for cardiovascular disease and mortality,30–32 this syndrome was found to be more frequent in men than in women. The DECODE Study Group demonstrated that metabolic syndrome that fulfilled the 4 criteria predicted cardiovascular mortality in men, but the prediction was weak in women.31 The present study also demonstrated that the impact of this syndrome is lower in women than in men. In the present study 65% of culprit plaques in ACS women had no culprit plaque rupture. ACS women were older and the proportion of abdominal obesity was lower in ACS women than men. This syndrome, however, might be important for the secondary prevention of cardiovascular disease even in women, because the proportion of metabolic syndrome was significantly higher in ACS women with multiple complex coronary lesions than in patients with a single complex lesion in our previous study.33 Modified expression of metabolic syndrome by gender should be taken into consideration for risk stratification of ACS.

In the present study we examined the presence of plaque rupture in the culprit lesion and divided ACS patients into 2 groups. It has been suggested, however, that ACS patients had multiple plaque ruptures except for the culprit lesion.34,35 It is unclear when such silent plaque ruptures occurred before this acute coronary event and whether the lesions without thrombus formation are vulnerable. In the present study we identified the culprit lesion of acute coronary event with thrombus formation as vulnerable. In support of this view, previous studies using IVUS, OCT, and autopsy in ACS patients demonstrated that some of the vulnerable culprit lesions had no plaque rupture,5,7,35 and Naghavi et al noted in their review that rupture-prone plaques are not the only vulnerable plaque, and that all types of atherosclerotic plaques with a high likelihood of thrombotic complications and rapid progression should be considered as vulnerable plaques.35 The present results suggested that there might be 2 very dif-
different types of culprit plaques with thrombus formation in ACS. Ruptured culprit plaque might be associated with more massive thrombus formation than culprit plaque without rupture.

Study Limitations
There were several limitations associated with the present study. Because IVUS procedures have several limitations for coronary morphological disturbances, such as severely calcified arteries, tortuous lesions, or other complex lesions, only limited vessel areas could be observed.

PIT or thrombectomy were performed before IVUS. It is possible that those imaging procedures might have affected the culprit lesion morphologies. Furthermore, it is possible that the interventional procedure induced the plaque rupture during advance of the guidewire and catheter in vulnerable plaques. The thrombolysis and thrombectomy, however, were appropriate for achieving an ideal coronary reperfusion without any reflow phenomenon. The change of culprit lesion morphology might be small, because the chemical and mechanical thrombolysis with the PIT system was very gradual.19

Even after thrombolysis with the PIT system and/or aspiration thrombectomy, there might have been a residual thrombus in the culprit lesion. OCT has been proposed as a high-resolution imaging method for plaque characterization and its resolution is approximately 10–20 μm, which is approximately 10-fold higher than that of IVUS.5,6,15 Kubo et al demonstrated that the incidence of plaque rupture observed on OCT was 73%, and it was significantly higher than that observed on IVUS (40%) in patients with acute myocardial infarction.6 Although the incidence of culprit plaque rupture in the present study after aggressive thrombolysis was higher than that found in the previous IVUS study,7 the incidence was lower than that on OCT. Therefore, it is likely that the patients with culprit plaque rupture might have been included in the non-rupture group in the present study. Furthermore, not only plaque rupture but also thrombus formation is an important factor in the onset of ACS.13 Therefore, the assessment of intracoronary thrombus is important to elucidate the pathophysiological etiology of ACS. More detailed evaluation using OCT is needed.

Conclusions
There are 2 different clinical presentations of ACS related to the pathophysiology of culprit coronary lesions. Abdominal obesity and low HDL-cholesterol level were the characteristics of metabolic syndrome that seem to be the key factors for coronary vulnerable plaque ruptures. Furthermore, plaque rupture was more frequent in men. Not only the positive remodeling and large plaque burden, but also the large external elastic membrane cross-sectional area and luminal cross-sectional area were necessary for plaque ruptures. As a result, more massive thrombus formation might occur in ruptured culprit plaque. We should understand these different etiologies and clinical presentations of ACS for future prevention and delivery of optimal therapy.

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Disclosure
There were no conflicts of interest for any of the authors of our study.

References


