Intravascular Ultrasound Assessment of Ulcerated Ruptured Plaques
A Comparison of Culprit and Nonculprit Lesions of Patients With Acute Coronary Syndromes and Lesions in Patients Without Acute Coronary Syndromes

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Background—It is not clear why some plaque ruptures lead to acute coronary syndromes (ACS) but others do not.

Methods and Results—We analyzed 80 plaque ruptures in 74 patients and compared culprit lesions of ACS patients with nonculprit lesions of ACS patients and lesions of non-ACS patients; both culprit and nonculprit plaque ruptures were studied in 6 of 54 ACS patients. Intravascular ultrasound findings suggesting thrombus were observed more frequently in culprit lesions of ACS patients (n = 35) compared with nonculprit lesions of ACS patients (n = 19) and lesions of non-ACS patients (n = 26): 60% versus 32% versus 8% (P < 0.001). At the minimal lumen site, smaller lumen areas (3.3 ± 1.5 versus 5.4 ± 2.6 versus 6.1 ± 2.0 mm², P < 0.001) and greater area stenosis (61 ± 15% versus 50 ± 14% versus 46 ± 18%, P = 0.002) and plaque burden (80 ± 8% versus 71 ± 8% versus 69 ± 10%, P < 0.001) were observed in culprit lesions of ACS patients compared with nonculprit lesions of ACS patients and lesions of non-ACS patients. Lesions were longer (18.7 ± 6.4 versus 154.9 ± 6.1 versus 12.0 ± 4.9 mm, P < 0.001) and rupture site remodeling indices were greater (1.26 ± 0.21 versus 1.24 ± 0.21 versus 1.09 ± 0.05, P = 0.002). Independent predictors of culprit plaque ruptures in ACS patients were smaller minimum lumen areas (P = 0.02) and presence of thrombus (P = 0.01).

Conclusions—Ruptured plaques in culprit lesions of ACS patients have smaller lumens, greater plaque burdens, area stenosis, and remodeling indices; and more thrombus. Plaque rupture itself does not lead to symptoms. The association of plaque rupture with a smaller lumen area and/or thrombus formation causes lumen compromise and leads to symptoms. (Circulation. 2003;108:2473-2478.)

Key Words: ultrasonics ▪ atherosclerosis ▪ coronary disease

Plaque rupture or endothelial erosion with subsequent thrombus formation are the most frequent cause of acute coronary syndromes (ACS). One intravascular ultrasound (IVUS) study reported a high incidence of multiple plaque ruptures in ACS patients. Another IVUS study showed that plaque ruptures occur not only in ACS patients but also in patients with stable angina or asymptomatic ischemia. Furthermore, pathological studies reported plaque ruptures in coronary arteries of patients with noncardiac death. Thus, it is not clear why some plaque ruptures lead to clinical manifestations, whereas others remain asymptomatic and heal, perhaps leading to disease progression. Therefore, we undertook the present study to compare ruptured plaques in culprit lesions of ACS patients with ruptured plaques in nonculprit lesions of ACS patients and ruptured plaques in lesions of non-ACS patients. We used IVUS to identify anatomic features that lead to the development of culprit lesions causing ACS after plaque rupture.

Methods

Patient and Lesion Population
Between December 1999 and December 2002, 983 patients (1325 lesions) underwent preintervention IVUS. One investigator reviewed all IVUS studies to identify high-quality images showing ulcerated plaque ruptures in de novo native coronary lesions. Clinical demographics were obtained by hospital chart review. Unstable angina was new-onset severe angina, accelerated angina, or rest angina. Recent myocardial infarction (MI) occurred within 4 weeks. Stable angina was no change in frequency, duration, or intensity of symptoms within 4 weeks. Asymptomatic patients were typically studied because of positive stress tests. Patients with unstable angina...
or recent MI were categorized as ACS, whereas non-ACS patients had stable angina or asymptomatic ischemia.

The coronary artery and lesion underlying the atherosclerotic event (ie, culprit) were identified by the association of precrisis and intercisis ECGs, left ventricle wall motion abnormalities, and angiographic lesion appearance. Two experienced cardiologists (K.F. and Y.K.) independently reviewed all clinical and angiographic data to decide angina status and culprit lesions. There was no disagreement on angina status or culprit lesion assignment.

Ulcerated ruptured plaques and thrombus required the agreement of 2 independent experienced observers (K.F. and H.T.). The rate of agreement for ulcerated ruptured plaques was 0.98 (80/82). Disagreements were reviewed by the third observer (Y.K.). The rate of agreement for thrombus was 0.94 (30/32). The 2 cases of thrombus disagreement were excluded. Finally, 80 ulcerated ruptured plaques in 74 patients (54 with ACS) were included. In ACS patients, IVUS was performed in only culprit lesions in 32 patients, only nonculprit lesions in 12, and both in 6 patients (ulcerated ruptured plaques were observed in 3 culprit and 7 nonculprit lesions). Multiple ruptures were observed in 3 of 6 ACS patients (2 in both culprit and nonculprit lesions and 1 in 2 nonculprit lesions). There were no non-ACS patients with multiple ruptures. Ulcerated ruptured plaques were divided into 3 groups: culprit lesions of ACS patients (n=35), nonculprit lesions of ACS patients (n=19), and non-ACS patients (n=26).

**Angiographic Analysis**

Cineangiograms were analyzed with a computer-assisted, automated edge detection algorithm (CMS, MEDIS) by a core laboratory using standard qualitative and quantitative definitions and measurements. The outer diameter of the contrast-filled catheter was used for calibration, and the minimal lumen diameter was obtained from the single "worst" view.

**IVUS Imaging Protocol**

Before all procedures, written informed consent was obtained. All IVUS studies were performed before any intervention (after intracoronary administration of 100 to 200 μg nitroglycerin) with a commercially available system (Boston Scientific). The 30- or 40-MHz IVUS catheter was advanced >10 mm beyond the lesion, and an imaging run (using automated transducer pullback at 0.5 mm/s) was performed to a point >10 mm proximal to the lesion. IVUS imaging was recorded only during transducer pullback onto 1/2-inch high-resolution s-VHS videotape for offline analysis.

**IVUS Analysis**

Qualitative and quantitative IVUS measurements were performed using published definitions, especially for ruptured plaque. Two observers (K.F. and H.T.) blinded to clinical and angiographic information (including ACS versus non-ACS) performed all IVUS analysis. An ulcerated ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment (A). Schema shows measurements of EEM CSA, lumen CSA, and ruptured plaque cavity area (CA) (B). IVUS image at minimal lumen site (C). Note thrombus (arrowheads). Lumen was compromised by thrombus (arrow) at minimum lumen site (C). Schema demonstrates EEM CSA, lumen CSA, and thrombus (arrow) (D).

**Statistical Analysis**

Statistical analysis was performed with StatView 5.0 software (SAS Institute). Continuous variables were reported as mean±SD and
TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ACS Culprit (n=35)</th>
<th>ACS Nonculprit (n=19)</th>
<th>Non-ACS (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±12</td>
<td>56±8</td>
<td>64±12</td>
<td>NS</td>
</tr>
<tr>
<td>Male, %</td>
<td>83</td>
<td>89</td>
<td>85</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>54</td>
<td>63</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>74</td>
<td>79</td>
<td>77</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>34</td>
<td>37</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>History of smoking, %</td>
<td>67</td>
<td>47</td>
<td>73</td>
<td>NS</td>
</tr>
<tr>
<td>Previous coronary angioplasty, %</td>
<td>34</td>
<td>21</td>
<td>27</td>
<td>NS</td>
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<tr>
<td>Previous coronary bypass, %</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>17</td>
<td>21</td>
<td>19</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results

Baseline patient characteristics and angiographic findings are presented in Tables 1 and 2. Five non-ACS patients had a previous MI; 2 underwent culprit-lesion percutaneous coronary intervention during the MI. In 2 of the other 3 patients, the culprit lesion was in another vessel; in the third patient, the culprit lesion was in the same vessel. No patient received thrombolytic therapy. Before IVUS, glycoprotein IIb/IIIa inhibitors were given to 6 patients in the culprit-lesion ACS group, 1 patient in the nonculprit-lesion ACS group, and no non-ACS patient (P=NS).

Qualitative IVUS Findings

Table 3 shows qualitative lesion site findings. IVUS findings suggesting thrombus were observed more frequently in culprit lesions of ACS patients compared with nonculprit lesions of ACS patients (P=0.04) and lesions of non-ACS patients (P<0.001) as well as in nonculprit lesions of ACS patients compared with lesions of non-ACS patients (P=0.03). Five of 7 patients who received glycoprotein IIb/IIIa inhibitors had IVUS findings suggesting thrombi. Most of the ulcerated ruptured plaques in culprit lesions of ACS patients were proximal to the minimal lumen site, compared with half of the ulcerated ruptured plaques in lesions of non-ACS patients (P=0.02).

Quantitative IVUS Findings

Quantitative analyses are presented in Table 4. Proximal reference measurements were similar in the 3 groups. The distal reference lumen CSA was smaller in culprit lesions of ACS patients than nonculprit lesions of ACS patients and lesions of non-ACS patients (P=0.03 and P=0.004, respectively).

Rupture site EEM CSA was greater than at the minimum lumen site in culprit lesions of ACS patients (P=0.01) but not in nonculprit lesions of ACS patients or non-ACS patients. Rupture site lumen CSA was greater than at the minimum lumen site in all groups (P<0.001, P=0.02, and P=0.02, respectively). Rupture site remodeling index was greater than the minimal lumen site in all groups (P=0.008, P<0.001, and P<0.001, respectively). There was no significant difference in plaque + media CSA, plaque burden, plaque + media eccentricity, and arc of calcium comparing the rupture site versus the minimal lumen site in each group.

At the minimal lumen site, a smaller lumen CSA and greater plaque burden and area stenosis were observed in culprit lesions of ACS patients compared with nonculprit lesions of ACS patients (P=0.003, P=0.006, and P=0.03, respectively) and lesions of non-ACS patients (P<0.001 for all). Remodeling index was greater in culprit lesions of ACS patients than in lesions of non-ACS patients (P=0.02). Lesions were longer in (1) culprit lesions of ACS patients than nonculprit lesions of ACS patients (P=0.02) and lesions of non-ACS patients (P<0.001) and (2) in nonculprit lesions of ACS patients than lesions of non-ACS patients (P=0.04). Similar quantitative IVUS findings were observed at the rupture site. Cavity area and cavity length were similar among the groups.
plaque burden and remodeling index, and more frequent plaques leading to ACS have smaller lumen CSA, greater

The present study demonstrates that ulcerated ruptured ulcerated plaque ruptures in ACS patients: smaller minimum lumen CSA (P=0.02) and presence of thrombus (P=0.01).

When patients who received glycoprotein IIb/IIIa inhibitors were excluded from analysis (n=7), the results of qualitative and quantitative IVUS shown in Tables 3 and 4 were virtually identical. Multivariate logistic regression analysis showed that independent predictors of culprit ulcerated plaque ruptures in ACS patients were the minimum lumen CSA (P=0.02) and thrombus (P=0.07); 5 of 6 with culprit ulcerated plaque ruptures in ACS patients who received glycoprotein IIb/IIIa inhibitors had IVUS evidence of thrombus.

### Discussion
The present study demonstrates that ulcerated ruptured plaques leading to ACS have smaller lumen CSA, greater plaque burden and remodeling index, and more frequent IVUS evidence of thrombus formation. Independent predictors of ACS in association with ulcerated plaque rupture were (1) smaller lumen CSA and (2) IVUS evidence of thrombus.

### Plaque Rupture
Pathological studies have demonstrated that plaque rupture with subsequent thrombus formation is the initiating event of most ACS.\(^1\,\,^3\) Plaque rupture is a mechanical event that depends on an imbalance between stress imposed on the plaque cap and innate strength (resistance to fracture) of the cap.\(^1\,\,^11,\,\,^12\) The mechanical strength of the cap depends on the amount and organization of the collagen produced by smooth muscle cells.\(^1\,\,^3,\,\,^14\) The cap is increasingly recognized as a dynamic structure in which collagen synthesis is modulated by positive and negative growth factors produced by inflammatory cells and in which collagen is degraded by metalloproteinases derived from activated macrophages.\(^1\,\,^5,\,\,^17\)

Loss of smooth muscle cells because of apoptosis may be an important element in weakening of cap tissue.\(^1\,\,^18\) Intrinsic plaque instability may develop owing to the expansion of intraplaque contents (eg, lipid-pool swelling).\(^1\,\,^3,\,\,^19\) Thus, plaques vulnerable to rupture are described as those with a large lipid pool under a thin fibrous cap.

### TABLE 4. Quantitative IVUS Analysis

<table>
<thead>
<tr>
<th></th>
<th>ACS Culprit (n=35)</th>
<th>ACS Nonculprit (n=19)</th>
<th>Non-ACS (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM CSA, mm²</td>
<td>16.8±4.1</td>
<td>17.9±4.4</td>
<td>19.0±6.6</td>
<td>NS</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>9.8±2.3</td>
<td>11.9±3.9</td>
<td>11.9±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Distal reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM CSA, mm²</td>
<td>14.0±3.6</td>
<td>16.7±6.7</td>
<td>17.4±6.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>8.5±2.2</td>
<td>10.5±4.7</td>
<td>11.3±3.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Minimal lumen site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM CSA, mm²</td>
<td>17.0±4.3</td>
<td>19.0±5.9</td>
<td>19.7±6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>3.3±1.5</td>
<td>5.3±2.6</td>
<td>6.0±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumen CSA+thrombus, mm²</td>
<td>3.6±1.6</td>
<td>5.4±2.6</td>
<td>6.1±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque+media CSA, mm²</td>
<td>13.6±3.7</td>
<td>13.7±4.6</td>
<td>13.7±6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>80±8</td>
<td>72±8</td>
<td>70±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Area stenosis, %</td>
<td>61±15</td>
<td>51±14</td>
<td>47±18</td>
<td>0.002</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>1.12±0.23</td>
<td>1.10±0.18</td>
<td>1.02±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque+media eccentricity, %</td>
<td>72±18</td>
<td>77±18</td>
<td>74±18</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>18.7±6.4</td>
<td>14.9±6.1</td>
<td>12.0±4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arc of calcium, degrees</td>
<td>52.8±66.9</td>
<td>47.4±66.1</td>
<td>32.8±31.6</td>
<td>NS</td>
</tr>
<tr>
<td>Rupture site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM CSA, mm²</td>
<td>19.0±4.2</td>
<td>20.6±5.8</td>
<td>20.8±6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>4.6±1.7</td>
<td>6.6±2.8</td>
<td>7.3±3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque+media CSA, mm²</td>
<td>14.4±3.8</td>
<td>14.1±3.9</td>
<td>13.5±6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>76±17</td>
<td>68±9</td>
<td>65±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>1.26±0.21</td>
<td>1.22±0.23</td>
<td>1.09±0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Plaque+media eccentricity, %</td>
<td>75±19</td>
<td>81±16</td>
<td>80±13</td>
<td>NS</td>
</tr>
<tr>
<td>Cavity area, mm²</td>
<td>2.2±1.4</td>
<td>2.8±1.9</td>
<td>2.6±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cavity area/plaque ratio, %</td>
<td>15.3±6.2</td>
<td>19.9±10.0</td>
<td>19.3±8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Cavity length, mm</td>
<td>4.3±3.5</td>
<td>4.4±2.1</td>
<td>3.5±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Arc of calcium, degrees</td>
<td>37.6±47.1</td>
<td>29.4±45.0</td>
<td>29.2±38.8</td>
<td>NS</td>
</tr>
</tbody>
</table>
When plaque rupture occurs, it exposes tissue factor and collagen, promoting thrombosis. Plaque composition determines its thrombogenic potential. Tissue factor and plasminogen activator inhibitor-1 contents of vulnerable plaques are twice that of stable plaque and parallel the macrophage area. Increased activity of platelet and clotting factors in ACS patients intensifies the thrombogenic potential of ruptured plaques.

Ruptured Plaque With ACS

Pathological studies have reported that plaque disruption can occur without symptoms and is found in 5% to 10% of noncardiac deaths. Recently, IVUS studies have demonstrated that ruptured plaques do not always cause ACS. One IVUS study showed a high incidence of ruptured plaques (79%) in coronary segments remote from the culprit lesion of ACS patients. Maehara et al reported that plaque ruptures occurred not only in patients with unstable angina (46%) or MI (33%) but also in stable angina (11%) or asymptomatic ischemia (11%). Plaque rupture may be a frequent event that only occasionally leads to an ACS. The present study found 2 risk factors linking ulcerated ruptured plaques to ACS: smaller lumens and evidence of thrombus. Angiographic studies have shown that MIIs often occur at sites that were previously only a mild-to-moderate stenosis. Conversely, postmortem examinations demonstrated that ruptured plaques leading to ACS were often within the segment of significant stenosis. When patients have increased thrombogenic potential, ruptured plaques in lesions with mild-to-moderate stenosis may lead to ACS. Conversely, because atherosclerosis is a progressive disease, angiography may not show the degree of stenosis immediately before plaque rupture.

In the present analysis, the size of the residual cavity was, if anything, smaller in culprit plaque ruptures. This suggests that it is not the size of the underlying lipid pool or necrotic core that leads to post–plaque rupture thrombus formation and ACS but rather the thrombogenicity of the resulting cavity. In addition, it is conceivable that a smaller “prerupture” lumen requires less thrombus to precipitate an acute event.

Ruptured Plaque Without ACS

Previous studies showed a high incidence of recurrent events in ACS patients. Because ACS correlates with systemic markers of inflammation, high recurrent events may be related to additional vulnerable lesions distant from the culprit lesion. These observations support the concept that plaque instability is not merely a local vascular accident but rather probably reflects more generalized pathophysiological processes with the potential to destabilize atherosclerotic plaques throughout the coronary tree. This may also explain the high incidence of multiple plaque ruptures in ACS patients reported by one IVUS study. Thus, it may be reasonable to prescribe platelet-receptor inhibitors to prevent thrombus formation and anti-inflammatory drugs and lipid-lowering medications to stabilize plaques in ACS patients.

Pathological studies have reported that healed ruptured plaque is associated with lesion progression. Subclinical episodes of plaque disruption, local thrombin activation, and subsequent healing with incorporation of thrombus into the vessel wall may represent one pathway for episodic progression superimposed on the slower systemic process. This concept is supported by previous angiographic studies showing rapid progression of stenosis with complex angiographic features.

Study Limitations

This was a retrospective study. IVUS was not performed in all segments of all coronary arteries in all patients. Some selection bias is inevitable, beginning with selection of patients to undergo cardiac catheterization and IVUS and which arteries are imaged before intervention. Thus, the frequency of plaque ruptures remains unknown. Some ruptured plaques with small cavities might be missed, especially when the cavity was filled by thrombus. The diagnosis of thrombus by IVUS is typically considered to be presumptive. Two different IVUS catheters were used during the study; thrombus detection may be dependent on transducer frequency. Finally, the lag between symptom onset and IVUS was not known and may have influenced both IVUS and angiographic findings. The distinction between culprit and nonculprit lesions in ACS patients is sometimes difficult.

Conclusions

Ulcerated ruptured plaques in culprit lesions of ACS patients have smaller lumens; greater plaque burdens, area stenosis, and remodeling indices; and more thrombus formation. Plaque rupture itself does not lead to symptoms. Instead, it is the association of plaque rupture with a smaller lumen area and/or thrombus formation causing lumen compromise that leads to symptoms.

References

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