Impact of Coronary Artery Remodeling on Clinical Presentation of Coronary Artery Disease: An Intravascular Ultrasound Study

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OBJECTIVES
We examined the association between the features of the culprit lesion in coronary artery disease (CAD) and clinical presentation as shown by intravascular ultrasound (IVUS).

BACKGROUND
The association between coronary remodeling pattern and clinical presentation of CAD is unclear.

METHODS
We analyzed 125 selected patients who underwent preintervention IVUS. Acute myocardial infarction (AMI) and unstable angina pectoris (UAP) were categorized as an acute coronary syndrome (ACS), and stable angina pectoris (SAP) and old myocardial infarction (OMI) as stable CAD. Coronary remodeling patterns and plaque morphology of the culprit lesion obtained by IVUS were analyzed in terms of their association with clinical presentation or angiographic morphology.

RESULTS
Angiographically complex lesions were associated with ACS and OMI. In patients with a complex lesion, positive remodeling was observed more frequently than in those with a simple lesion. In AMI and UAP, positive remodeling was observed more frequently than in SAP and OMI (82% vs. 78% vs. 33% vs. 40%, respectively, p < 0.0001). The remodeling ratio was greater in AMI and UAP than in SAP and OMI (1.26 ± 0.15 vs. 1.11 ± 0.10 vs. 0.94 ± 0.11 vs. 0.96 ± 0.13, respectively, p < 0.0001). Furthermore, within ACS, the remodeling ratio was greater in AMI than in UAP (1.26 ± 0.15 vs. 1.11 ± 0.10, respectively, p < 0.05), whereas the frequency of positive remodeling was not different.

CONCLUSIONS
Positive remodeling was more frequently observed in ACS than in stable CAD. Moreover, the degree of positive remodeling was greater in AMI than in UAP. These results may reflect the impact of remodeling types and its degree in the culprit lesion of CAD on clinical presentation.

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An acute coronary syndrome (ACS), which presents as either unstable angina pectoris (UAP) or acute myocardial infarction (AMI), is a common clinical manifestation of coronary artery disease (CAD) and is often associated with catastrophic clinical results. The precise mechanism behind the progression of ACS is thought to be the development of a plaque rupture, with subsequent thrombus formation and fibrotic organization (1). Previous angiographic studies have suggested this mechanism (2) and have reported the possibility that AMI frequently developed from a nonsevere lesion (3).

Pathologic and intravascular ultrasound (IVUS) studies have shown that compensatory enlargement occurs in order to delay the development of coronary artery stenosis (4–6). Also, using IVUS, several studies have shown various morphologic and associated clinical characteristics of coronary atherosclerosis (7–10). However, the exact mechanism leading to the progression of different morphologies and its pathologic contribution to the development of different clinical expressions of CAD are not clear. Although compensatory enlargement, described as positive or adaptive remodeling (11,12), was suggested as a major remodeling pattern in the culprit lesion of CAD (13), and the presence of soft plaque was thought to be more prevalent in UAP (14,15), few studies using IVUS reported further details of morphologic features of atherosclerotic plaque, which was likely to progress to ACS, including AMI. Besides, few reports examined the correlation between angiographic and IVUS plaque morphology, including remodeling patterns. The aim of this study was to examine the characteristics of the culprit lesion in severe CAD, as shown by IVUS versus angiography, or according to its clinical presentation.

METHODS

Patients. Between May 1996 and November 1998, 442 consecutive patients had IVUS during their coronary interventions. Of these, 152 patients (121 men and 31 women; mean age 63 ± 10 years, range 40 to 82) were considered for analysis, in accordance with the following angiographic criteria: 1) new lesion developed in vessel without previous
angioplasty; and 2) single, well-defined focal lesion <10 mm in length, observed before or just after passage of a 0.014-in. (0.035-cm) guide wire across the lesion. Patients with the following criteria were excluded: 1) ostial lesion within 3 mm of the coronary ostia or <3 mm distal to a major proximal side branch (n = 21); 2) bifurcated lesion (n = 31); 3) culprit lesion in a small vessel (<2 mm in diameter) (n = 7); and 4) chronic total occlusion (n = 20); 5) lesion at left main trunk (n = 6) or bypass graft (n = 14). Patients with restenosis (n = 66), a long lesion (n = 56) and multiple lesions in a single vessel (n = 6) were also excluded. Angiographic measurements used for selection criteria were made by visual assessment of the coronary angiogram. In addition, 15 patients in whom the IVUS catheter did not pass across the lesion before angioplasty, 11 patients with a previous MI <1 month before the IVUS study and the remaining 37 patients in whom IVUS was not performed before angioplasty (because of the operator’s preference) were also excluded.

Patients were diagnosed as having AMI according to the presence of chest pain lasting >30 min, accompanied by ST-T segment elevation in two or more related electrocardiographic (ECG) leads or pathologic Q waves and subsequent elevation of creatine kinase greater than twice the upper limit of normal or an elevated creatine kinase, MB fraction value. Unstable angina was diagnosed if the patient’s chest pain, which was accompanied by ECG ST-T segment changes, was either new or worse in frequency, severity or duration, superimposed on a preexisting pattern of anginal pain. Stable angina pectoris (SAP) was defined as a clinically constant pattern of severity being treated in the outpatient clinic for more than two months. Patients with an old myocardial infarction (OMI) were those who had an MI more than one month before the IVUS study. Acute MI and UAP were categorized as ACS, and SAP and OMI were categorized as stable CAD.

The culprit lesion was determined on the basis of a combination of clinical and angiographic results. In patients with single-vessel disease, the ischemia-related (culprit) artery was considered to be the diseased vessel. In patients with multivessel disease, the culprit vessel was identified by coronary anatomy and localization of ST-T segment changes on the ECG during the anginal episode at rest or during exercise, or both. If there were no documented ST-T segment changes, the culprit lesion was considered to be the most severely stenotic lesion or to indicate the presence of angiographic thrombus, or both. Written, informed consent was obtained from each patient before the IVUS procedure, and the protocol was approved by our institutional Review Board.

**Coronary angiography and determination of angiographic morphology.** All cine films were reviewed, and the culprit lesions were qualitatively analyzed by a single angiographer who was unaware of the diagnoses and IVUS results. Coronary morphology of the culprit lesions was quantitatively categorized as previously reported (2,16,17). The culprit lesions were classified into two categories as either simple or complex, according to the symmetry and irregularity of their borders. Complex lesions also included any culprit lesion with intracoronary filling defects or total occlusion, both of which suggested existence of intracoronary thrombus. Intra-arterial flow was graded (grades 0 to 3) according to the Thrombolysis in Myocardial Infarction trial (TIMI) classification (18). Collateral flow was graded according to Rentrop’s score (19).

**Intravascular ultrasound imaging.** All patients were premedicated with aspirin and received heparin (100 U/kg) before routine catheterization procedures. Immediately after diagnosis, patients with ACS underwent coronary angiography and subsequent IVUS, without antithrombotic therapy or continuous intravenous administration of heparin. In particular, all patients with AMI had IVUS imaging within 6 h from the onset of clinical symptoms. A commercially available imaging system (Cardiovascular Imaging Systems, Natick, Massachusetts) with a catheter size of 3.2F and a center frequency of 30 MHz (n = 144), or 2.6F and 40 MHz, respectively (n = 8), was used for the ultrasound study. After intracoronary administration of 300 μg of nitroglycerin, the imaging catheter was inserted into an 8F guiding catheter and advanced along a 0.014-in. guide wire as distally as possible, using fluoroscopic guidance. With slow, manual pullback (n = 147) or auto pullback (0.5 mm/s, n = 5) of the IVUS catheter, ultrasound images were obtained at the aorto-ostial junction and were recorded on 0.5-in. S-VHS videotape for quantitative data analysis. In cases using slow, manual pullback, the IVUS catheter was withdrawn as constantly and slowly as possible for careful examination of the diseased vessel.

**Intravascular ultrasound analysis.** After the procedure, off-line analysis of the recorded images at the target and reference site was performed by two individuals who had no knowledge of the diagnoses and angiographic results. Quantitative measurements of the ultrasound images were obtained from the frames at the end-diastolic phase.

The total vessel area (VA) was measured by tracing the
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January 2001:63–9

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Table 1. Baseline Characteristics of Study Group (n = 125)

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<tr>
<th></th>
<th>ACS (n = 54)</th>
<th>Stable CAD (n = 71)</th>
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<tbody>
<tr>
<td>AMI (n = 22)</td>
<td>UAP (n = 32)</td>
<td>SAP (n = 51)</td>
</tr>
<tr>
<td>OMI (n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61 ± 12</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>Men (82%)</td>
<td>18 (66%)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>10 (54%)</td>
<td>17 (53%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (50%)</td>
<td>20 (63%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (32%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13 (59%)</td>
<td>15 (47%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>3 (14%)</td>
<td>11 (34%)</td>
</tr>
<tr>
<td>Previous MI*</td>
<td>2 (9%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Intervention to IRA*</td>
<td>22 (100%)</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

*The difference is significant at p < 0.0001 in a four-way comparison. Data are presented as the mean value ± SD or number (%) of patients.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; IRA = infarct-related artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; OMI = old myocardial infarction; RCA = right coronary artery; SAP = stable angina pectoris; UAP = unstable angina pectoris.

Intraobserver and interobserver variabilities of IVUS analysis. Quantitative measurements of the ultrasound images of VA were reanalyzed at least eight weeks apart and used to assess the reliability of off-line IVUS analysis. The correlation coefficient obtained from linear regression analysis and the percent error obtained by taking the absolute difference divided by the initial measurements were used to express the intraobserver and interobserver variabilities (22). In our institution, the intraobserver correlation coefficient and percent error for VA were 0.99 and 5.1 ± 4.5%, respectively, and the interobserver correlation coefficient and percent error for VA were 0.97 and 4.1 ± 3.9%, respectively.

Statistical analysis. Statistical analysis was performed using StatView 4.5 (Abacus Concepts). The results are expressed as the mean value ± SD for each measurement. Categorical variables were assessed by using the chi-square test. Continuous variables were compared by using the unpaired Student t-test, the Mann-Whitney U test or analysis of variance. Statistical significance in all comparisons was p < 0.05.

RESULTS

Patient characteristics. Of the 152 patients, 27 were excluded from the analysis because their side branches >1 mm were observed between the lesion and the proximal reference site on IVUS images. The baseline characteristics of the four groups are listed in Table 1. There were no significant differences in demographic data and clinical
Correlation of angiographic results with clinical presentation or IVUS results. The angiographic lesion morphology of the enrolled patients is summarized in Table 2. The complex culprit lesion was observed more frequently in ACS and OMI than in SAP and UAP (p < 0.0001). As shown in Table 3, in patients with an angiographically complex lesion, VA, PA, percent PA and eccentricity of the lesion site, as shown by IVUS, were larger than those values in patients with simple lesion. In addition, positive remodeling was more significant, in either frequency or degree, in patients with a complex lesion. In patients with TIMI flow grade <3, the remodeling ratio was larger than that in patients with normal coronary flow (1.15 ± 0.16 vs. 1.01 ± 0.12, p < 0.05). Compared with the patients without collateral vessels, the patients with collateral vessels to the target vessel had a larger PA (13.0 ± 2.6 vs. 15.7 ± 3.1, p < 0.05) and eccentricity (2.11 ± 0.27 vs. 2.49 ± 0.38, p < 0.01) at the culprit lesion. However, there was no significant difference in frequency of positive remodeling and remodeling ratio between those two groups.

Correlation of IVUS results with clinical presentation. A comparison of IVUS variables between ACS (AMI and UAP) and stable CAD (SAP and OMI) is summarized in Table 4. In the culprit lesion, VA, PA and the eccentricity index were significantly larger in patients with ACS than in those with stable CAD. The frequency of fibrofatty plaque in the culprit lesion in patients with ACS was greater than that in patients with stable CAD (57% vs. 39%, p < 0.05 by the unpaired Student t test). Positive remodeling was observed more frequently in patients with AMI or UAP than in those with SAP or OMI (p < 0.0001) (Fig. 1A). The remodeling ratio of AMI and UAP was also significantly larger than that of SAP and OMI (1.26 ± 0.15 vs. 1.11 ± 0.10 vs. 0.94 ± 0.11 vs. 0.96 ± 0.13, p < 0.0001) (Fig. 1B).

In stable CAD, there was no difference in IVUS measurements at the reference site and culprit lesion between the SAP and OMI groups. In 54 patients with ACS, although the frequency of positive remodeling was not different between the AMI and UAP groups, the remodeling ratio for AMI was significantly higher than that for UAP (1.26 ± 0.15 vs. 1.11 ± 0.10, p < 0.05) (Fig. 1B).

DISCUSSION
Several studies using IVUS before the intervention have described various characteristics of coronary remodeling and plaque morphology in the culprit lesion of CAD (8,13–15). Although the precise mechanisms leading to these different remodeling morphologies were discussed (4,12,13) and the types of plaque morphology prevalent in UAP were reported (14,15), the features of the culprit lesion, especially the remodeling pattern, which is most vulnerable to ACS, are still unclear. The mechanism leading to ACS is believed to be rupturing or fissuring of the atheromatous plaques, with subsequent thrombus formation. Studies using angiography (23), angioscopy (24,25) and pathologic specimens (26–28) have supported this hypothesis. Thus, certain characteristics of coronary remodeling may be observed in the culprit lesion

**Table 2.** Angiographic Lesion Morphology of Study Group (n = 125)

<table>
<thead>
<tr>
<th></th>
<th>ACS (n = 54)</th>
<th>Stable CAD (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMI (n = 22)</td>
<td>UAP (n = 32)</td>
</tr>
<tr>
<td>Complex lesion*</td>
<td>19 (86%)</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>Intracoronary thrombus*</td>
<td>17 (77%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Total occlusion*</td>
<td>9 (41%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>TIMI flow grade &lt;3*</td>
<td>14 (64%)</td>
<td>7 (22%)</td>
</tr>
<tr>
<td>Collateral vessels to target vessel†</td>
<td>9 (41%)</td>
<td>6 (19%)</td>
</tr>
</tbody>
</table>

*The difference is significant at p < 0.001 in a four-way comparison. †The difference is significant at p < 0.05 in a four-way comparison. Data are presented as the number (%) of patients.

**Table 3.** Correlation of Angiographic Morphology and Ultrasound Variables

<table>
<thead>
<tr>
<th></th>
<th>Complex Lesions (n = 57)</th>
<th>Simple Lesions (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel area (mm²)</td>
<td>15.9 ± 3.1</td>
<td>14.9 ± 2.3</td>
</tr>
<tr>
<td>Lesion site*</td>
<td>17.2 ± 3.2</td>
<td>14.3 ± 2.4</td>
</tr>
<tr>
<td>Lumen area (mm²)</td>
<td>9.2 ± 2.6</td>
<td>8.5 ± 1.6</td>
</tr>
<tr>
<td>Lesion site</td>
<td>2.1 ± 0.5</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>Plaque area (mm²)</td>
<td>6.7 ± 1.3</td>
<td>6.4 ± 1.4</td>
</tr>
<tr>
<td>Lesion site*</td>
<td>15.1 ± 3.1</td>
<td>12.2 ± 2.3</td>
</tr>
<tr>
<td>Plaque area (%)</td>
<td>43 ± 6.2</td>
<td>44 ± 6.7</td>
</tr>
<tr>
<td>Lesion site†</td>
<td>87 ± 2.7</td>
<td>84 ± 3.1</td>
</tr>
<tr>
<td>Lesion eccentricity index*</td>
<td>2.36 ± 0.31</td>
<td>2.03 ± 0.27</td>
</tr>
<tr>
<td>Lesion calcification (degree)</td>
<td>51 ± 37</td>
<td>43 ± 26</td>
</tr>
<tr>
<td>Remodeling ratio*</td>
<td>1.12 ± 0.15</td>
<td>0.97 ± 0.10</td>
</tr>
<tr>
<td>Positive remodeling†</td>
<td>38 (67%)</td>
<td>30 (44%)</td>
</tr>
<tr>
<td>Calcified plaque</td>
<td>10 (18%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Mixed plaque</td>
<td>15 (26%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>Fibrous plaque</td>
<td>7 (12%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Fibrofatty plaque</td>
<td>25 (44%)</td>
<td>34 (50%)</td>
</tr>
</tbody>
</table>

*The difference is significant at p < 0.01. †The difference is significant at p < 0.05. Data are presented as the mean value ± SD or number (%) of patients.
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of ACS with IVUS, and, if so, it may be possible to predict the plaque instability leading to ACS.

Coronary remodeling and plaque morphology. The major finding of this study was the significantly higher frequency and greater degree of positive remodeling in ACS as shown by IVUS. Also, the high prevalence of soft plaque, greater eccentricity and lesser degree of calcium were observed in the culprit lesion of ACS. These findings suggest that coronary atherosclerosis with these characteristics obtained by IVUS are vulnerable to ACS. The significant correlation of positive remodeling and eccentricity observed with IVUS with an angiographically complex lesion further supports this hypothesis, because an angiographically complex lesion was observed predominantly in ACS rather than stable CAD.

Although the current study does not address the exact pathologic process for these findings, several possible explanations can be made. Previous studies suggest that positive remodeling occurs in the early stage of atherosclerosis to delay the progression of lumen narrowing (4,5) in the early stage of atherosclerosis. Moreover, the deposition of calcium may be associated with advanced atherosclerosis (21,29,30), and from histologic studies, eccentric and lipid-rich plaques are considered to be vulnerable to rupture (28,31). In contrast, ruptured plaque allows blood from the lumen into the lipid pool of the plaque and forms the thrombus, which leads to considerable expansion of the plaque (26). Thus, positive remodeling observed predominantly in ACS may be caused by rapid expansion of the vessel either toward the inside or the outside due to thrombus formation in the ruptured atherosclerotic plaque. Although there was no difference in percent PA between ACS and stable CAD in this study, PA in the culprit lesion might have been overestimated by including the area of thrombus rather than real PA, because the patients with ACS in this study had IVUS imaging without previous thrombolytic therapy, and it is difficult to determine the border of plaque and thrombus (32). Recent studies suggested the coronary atherosclerosis with positive remodeling and large plaque burden but less severe stenosis might be vulnerable to ACS (33,34). Considering these results, the findings observed in this study, which showed that ACS tends to have more eccentric, soft plaque and less calcium with positive remodeling, may further support the concept that ACS is likely to develop in the relatively early stages of atherosclerosis. Because this hypothesis is also supported by the angiographic evidence suggesting that ACS develops frequently from relatively mild or moderate coronary lesions (3,35), positive remodeling predominantly observed in ACS seems to occur more likely from the progression of coronary atherosclerosis rather than as the result of “rapid expansion of VA.”

It is interesting to note that even in ACS, there was a significant difference in the degree, but not the frequency, of positive remodeling between the AMI and UAP groups. This finding may reflect the impact of the degree of positive remodeling on severity of CAD, even in ACS.
Clinical impact of positive remodeling in ACS. A recent study has suggested that the lesion with positive remodeling has more revascularization events, despite a larger final IVUS LA after the nonstent coronary intervention (36). It has been recognized that UAP and post-MI lesions have a higher rate of clinical and angiographic restenosis (37). The predominance of positive remodeling in ACS observed in this study further supports the high rate of restenosis in the unstable coronary lesion. Thus, in revascularization of such an unstable lesion, it appears to be more preferable to use other interventions, such as stent implantation or a debulking device, or a combination of both, to reduce the rate of restenosis.

Study limitations. There are several limitations of the present study. This study was a retrospective analysis of a limited number of patients who underwent IVUS-guided angioplasty. In addition, the indication to perform IVUS may not have been uniform. Thus, the results of this study represent only a selected group of patients. To confirm the results of this study, a prospective study with a larger population needs to be conducted. We excluded patients in whom the IVUS catheter was not used before the intervention, because coronary remodeling is affected by the catheter intervention, and the accurate interpretation of the original atherosclerotic characteristics is difficult in such cases. However, the number of such cases is relatively small and would not likely have an impact on the results of this study. There is a possibility that the determination of the single culprit lesion may not be accurate, because we determined the lesion morphology by visual assessment, not by the qualitative angiographic results. We selected and analyzed a single cross-sectional image at the proximal reference site and at the culprit lesion site in each case, as described in the Methods. Because these images were only part of the diseased vessel, the results of this study may not reflect the entire morphologic features of each lesion.

Conclusions. Positive remodeling and soft plaque were observed more frequently in the culprit lesion of ACS than in stable CAD. Besides, in patients with an angiographically complex lesions, positive remodeling was observed more frequently by IVUS. These results suggest that, in addition to plaque morphology, coronary remodeling patterns might be associated with the clinical presentation of CAD.

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