Extent and Direction of Arterial Remodeling in Stable Versus Unstable Coronary Syndromes

An Intravascular Ultrasound Study

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Background—The morphological characteristics of coronary plaques in patients with stable versus unstable coronary syndromes have been described in vivo with intravascular ultrasound, but the relationship between arterial remodeling and clinical presentation is not well known.

Methods and Results—We studied 85 patients with unstable and 46 patients with stable coronary syndromes using intravascular ultrasound before coronary intervention. The lesion site and a proximal reference site were analyzed. The remodeling ratio (RR) was defined as the ratio of the external elastic membrane (EEM) area at the lesion to that at the proximal reference site. Positive remodeling was defined as an RR > 1.05 and negative remodeling as an RR < 0.95. Plaque area (13.9 ± 5.5 versus 11.1 ± 4.8 mm²; P = 0.005), EEM area (16.1 ± 6.2 versus 13.0 ± 4.8 mm²; P = 0.004), and the RR (1.06 ± 0.2 versus 0.94 ± 0.2; P = 0.008) were significantly greater at target lesions in patients with unstable syndromes than in patients with stable syndromes. Positive remodeling was more frequent in unstable than in stable lesions (51.8% versus 19.6%), whereas negative remodeling was more frequent in stable lesions (56.5% versus 31.8%) (P = 0.001).

Conclusions—Positive remodeling and larger plaque areas were associated with unstable clinical presentation, whereas negative remodeling was more common in patients with stable clinical presentation. This association between the extent of remodeling and clinical presentation may reflect a greater tendency of plaques with positive remodeling to cause unstable coronary syndromes. (Circulation. 2000;101:598-603.)

Key Words: coronary disease • remodeling • ultrasonics • imaging

A cute coronary syndromes, including acute myocardial infarction, unstable angina, and sudden cardiac death, represent a major cause of morbidity and mortality. Available data suggest that rupture of coronary plaques with subsequent thrombosis represents the principal pathophysiology underlying acute coronary syndromes.1–3 Most of our understanding of the anatomy of plaques underlying acute coronary syndromes has evolved from necropsy studies that examined patients who died of acute coronary syndromes.4–8 However, it has been difficult to investigate the anatomy of plaques in patients with acute coronary syndromes because until recently, no imaging technique could visualize coronary plaques in vivo.

Arterial remodeling of the vessel wall at the site of coronary plaques was originally described in a necropsy study by Glagov et al9 and later confirmed in vivo with intravascular ultrasound.10 Positive remodeling is defined as a compensatory increase in local vessel size in response to increasing plaque burden.11 Negative remodeling is defined as the local shrinkage of vessel size and has been implicated in the development of native atherosclerosis12–14 and restenosis after PTCA.15,16

The development of intravascular ultrasound has enabled the investigation of plaque morphology in patients with coronary artery disease. In comparative histological studies, echolucent appearance by intravascular ultrasound was correlated with the lipid content of plaques.17 In other studies, plaque echolucency has been associated with the clinical presentation of unstable angina.18 Intravascular ultrasound also provides excellent boundary definition for 2 important interfaces in the vessel wall, the blood-intimal border and the external elastic membrane (EEM). This allows the measurement of the extent and direction of arterial remodeling. The relationship of acute coronary syndromes and positive remodeling has become a focus of investigation.19 However, the association between clinical presentation and the direction and extent of remodeling has not been fully described. In the present study, we performed intravascular ultrasound before coronary intervention and sought to describe the pattern of remodeling at the culprit lesion site in patients with stable versus unstable coronary syndromes.
Methods

Patient Population
Preinterventional intravascular ultrasound images of 216 consecutive patients were identified. The intravascular ultrasound examinations were performed between January 1993 and May 1998. All patients had a single culprit lesion in native coronary arteries. Eighty-five of these patients were excluded from analysis for technical reasons. In 34 patients, no proximal reference site could be defined because the lesion involved the ostium (n = 15) or a bifurcation (n = 19). Calculation precluded accurate measurement of the vessel size in 9 patients. Finally, the images of 42 patients could not be analyzed because of poor image quality.

The remaining 131 patients constituted the study population. Clinical data including age, sex, risk factor for coronary artery disease (diabetes mellitus type I and II, hypertension, total cholesterol, smoking history, and family history) and information about the clinical presentation (stable versus unstable symptomatology and angina class according to the Canadian Cardiovascular Society [CCS]) were collected from the interventional database at our institution and from patient charts.

Definition of Clinical Presentation
Clinical presentation was defined according to the severity of symptoms and the time that elapsed between onset of symptoms and intravascular ultrasound examination. The unstable group included patients with unstable angina (new onset or changed pattern of angina over the previous 2 months and CCS class IV angina at presentation), recent myocardial infarction (myocardial infarction <14 days before the intravascular ultrasound examination), or acute myocardial infarction (within 24 hours of chest pain with ST-segment elevation and/or elevated levels of creatine kinase–MB isoenzymes). The patients with unstable angina were further classified according to the Braunwald classification.20 The stable group included patients with stable angina (CCS class I or II angina unchanged over ≥2 months) or patients with a positive stress test.

Coronary Intravascular Ultrasound Imaging
The method of intravascular ultrasound imaging has been reported in detail previously.21 Briefly, a 30-MHz 3.5F monorail ultrasound catheter (Boston Scientific) interfaced with a scanner (Hewlett-Packard) was used. After antiaggregation with heparin, intracoronary nitroglycerin was administered, and the ultrasound catheter was placed over the guidewire beyond the target lesion site. The ultrasound catheter was then withdrawn manually during continuous imaging. The ultrasound images were recorded on 0.5-in Super VHS videotape. Cineangiographic documentation of the lesion location and verbal annotation were used for site identification.

Image Analysis
A single operator blinded to the clinical presentation analyzed the intravascular ultrasound images. For every patient, the target (culprit) lesion site and a proximal reference site were selected for measurement. The culprit lesion was defined as the site with the smallest lumen diameter (MLD). The proximal reference segment was chosen as the site with the least amount of plaque proximal to the culprit lesion without any intervening side branch. For each site, a short segment (10 to 20 seconds) of videotape was digitized at 30 frames per second into a 640×480-pixel matrix image with an 8-bit gray scale for further analysis.

Quantitative Intravascular Ultrasound Measurements and Calculations
At each selected site, the intimal leading edge boundary and the leading edge of the adventitia were used to manually trace the lumen and EEM areas, respectively. Plaque area was calculated as the difference between lumen and EEM area. Percent cross-sectional narrowing (%CSN) was calculated as:

\[ \%\text{CSN} = \left(\frac{\text{plaque area}}{\text{EEM area}}\right) \times 100 \]

Intravascular Ultrasound Definitions of Remodeling
The remodeling ratio (RR) was defined as the ratio of the EEM area at the lesion site to the EEM area at the proximal reference site. Three remodeling categories were defined as follows: positive remodeling, an RR > 1.05; absence of remodeling, an RR between 0.95 and 1.05; and negative remodeling, an RR < 0.9522 (Figure 1).

Qualitative Intravascular Ultrasound Analysis
The operator visually classified plaque morphology according to commonly used definitions.18,23 Echolucent plaques were defined as lesions with an echodensity less than that of the adventitia for >75% of plaque area. Echodense plaques were defined as a plaque echodensity equivalent to or greater than the adventitia (over >75% of plaque area) without acoustic shadowing. Calcified plaques were defined as an echodensity exceeding that of the adventitia with acoustic shadowing occupying >90% of the vessel wall circumference. All other lesions were defined as mixed plaques.

Statistical Analysis
The mean±SD and median values are presented for continuous data. If the data were normally distributed, the 2 groups were compared with an unpaired t test. Otherwise, a Mann-Whitney U test was used. Categorical variables were compared with the χ² test. A value of P < 0.05 was considered statistically significant. The association of the RR with clinical presentation was tested after adjustment for

| TABLE 1. Clinical and Demographic Characteristics |
|---|---|---|---|
| | Unstable Syndrome (n = 85) | Stable Syndrome (n = 46) | P |
| Age, y | 59.5±10.4 (59.6) | 62.6±9.6 (64.5) | 0.1 |
| Male sex | 55 (65) | 33 (72) | 0.4 |
| Diabetes | 15 (20) | 12 (26) | 0.4 |
| Hypertension | 48 (63) | 22 (48) | 0.1 |
| Hypercholesterolemia | 34 (50) | 21 (47) | 0.7 |
| Smoking | 46 (61) | 24 (52) | 0.4 |
| Family history | 22 (29) | 12 (26) | 0.7 |
| Lesion location | 0.5 |
| LAD | 44 (52) | 26 (57) | |
| LCX | 15 (18) | 10 (22) | |
| RCA | 26 (31) | 10 (22) | |

LAD indicates left anterior descending artery; LCX, circumflex artery; and RCA, right coronary artery. Values are n (%) except for age, which is mean±SD (median).
Results

Patient Population

Demographic characteristics were similar between the stable and unstable angina groups. There was no significant difference in the frequency of conventional risk factors for coronary artery disease (Table 1).

The unstable syndrome group (n=85) included 21 patients with Braunwald class 1B unstable angina, 20 with Braunwald class 2B, 16 with Braunwald class 3B, 2 with Braunwald class 2C, 2 with Braunwald class 3C, 15 with recent myocardial infarction, and 9 with acute myocardial infarction.

The stable syndrome group (n=46) included 37 patients with stable angina and 9 patients with a positive stress test.

Quantitative Intravascular Ultrasound Measurements

At the proximal reference site, there was no significant difference between the stable and unstable groups with respect to lumen area, EEM area, plaque area, or %CSN. At the lesion site, %CSN and lumen area were similar between the stable and unstable groups. However, EEM area (16.1±6.2 versus 13.0±4.8 mm²; P=0.004) and plaque area (13.9±5.5 versus 11.1±4.8 mm²; P=0.005) were significantly larger in the unstable angina group (Table 2).

Measurements of Remodeling

The RR was significantly greater in the unstable group than in the stable group (1.06±0.2 versus 0.94±0.2; P=0.008) (Figures 2 and 3). The frequency of the remodeling categories was significantly different between the stable and unstable syndrome groups (P=0.001) (Figure 4). Positive remodeling was more common in the group with unstable syndrome (51.8% versus 19.6%). Conversely, negative remodeling was more common in the stable angina group (56.5% versus 31.8%).

In the unstable syndrome group, the RR was calculated for the subgroups of patients with different acuity of symptoms (unstable angina according to Braunwald classification, recent myocardial infarction, and acute myocardial infarction). No significant difference was found between the subgroups. In further analysis with a multiple regression model that adjusted for age, sex, diabetes mellitus, hypertension, smoking, and hypercholesterolemia, clinical presentation continued to be a significant predictor of the RR (β=0.13, SE=0.04, P=0.002).

Qualitative Intravascular Ultrasound Analysis

Compared with the 3 other morphology groups, echolucent plaques were more frequent in the unstable than in the stable angina group (19% versus 4%; P=0.02). The frequency of echodense, mixed, and calcified plaques was not different between the unstable and stable angina groups (Figure 5).

Discussion

The results of our study demonstrate a clear relationship between the direction and extent of arterial remodeling and clinical presentation of patients with coronary artery disease. Target lesion sites in patients with acute coronary syndromes more frequently exhibited positive remodeling and a large plaque area, whereas patients with a stable clinical presentation more frequently showed negative remodeling and a smaller plaque area. Echolucent plaques were also more common in the unstable than in the stable angina group. The difference in the prevalence of positive remodeling was

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**TABLE 2. Intravascular Ultrasound Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Unstable Syndrome</th>
<th>Stable Syndrome</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal reference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>9.1±3.6 (8.4)</td>
<td>7.9±2.8 (7.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Plaque area, mm²</td>
<td>6.1±2.6 (5.6)</td>
<td>6.2±3.5 (5.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>EEM area, mm²</td>
<td>15.2±5.2 (14.5)</td>
<td>14.1±5.2 (13.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>%CSN</td>
<td>40.3±10.9 (39.4)</td>
<td>42.3±13.0 (44.1)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Culprit lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>2.3±1.1 (1.9)</td>
<td>1.9±0.4 (1.9)</td>
<td>0.34*</td>
</tr>
<tr>
<td>Plaque area, mm²</td>
<td>13.9±5.5 (13.9)</td>
<td>11.1±4.8 (11.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>EEM area, mm²</td>
<td>16.1±6.2 (15.5)</td>
<td>13.0±4.8 (13.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>%CSN</td>
<td>85.0±6.4 (86.4)</td>
<td>83.1±6.7 (84.4)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*P by Mann-Whitney U test. Values are mean±SD (median).
particularly striking, occurring in 52% of the unstable syndrome group and only 20% of the stable angina cohort. Importantly, in a multivariate analysis, the relationship between remodeling and clinical presentation was independent of known risk factors for coronary artery disease.

These observations help explain an important conundrum in interpreting the literature regarding the size of plaques that cause acute coronary syndromes. Postmortem studies have consistently shown that these culprit lesions harbor large atherosclerotic plaques.5–8 On the other hand, several investigators24–26 have studied patients with myocardial infarction in whom an angiogram was performed within 1 year before the coronary event. Each of these studies reported that prior angiography most frequently demonstrated a stenosis of <50% at the culprit lesion site responsible for subsequent acute occlusion. On the basis of these observations, some investigators have proposed that plaques that cause acute coronary syndromes are small, “early” plaques. This assumption does not take into account that positive remodeling attenuates the encroachment of the plaque into the lumen, thereby maintaining the lumen area. The observed association between positive remodeling and unstable presentation may therefore explain the discrepancies in histological and angiographic assessments of the size of plaques that underlie acute coronary syndromes.

The relationship between negative remodeling and stable clinical presentation is also noteworthy. Negative remodeling has been implicated in the development of luminal stenosis in native atherosclerosis12–14 and after PTCA,15,16 but its association with clinical presentation has not been examined. The high prevalence of negative remodeling in patients with stable angina suggests that fibrosis and shrinkage associated with negative remodeling may have a duality of effect, both reducing lumen size, which leads to angina, and decreasing the tendency to develop acute coronary syndromes.

Prior data on remodeling and clinical presentation are limited. However, comparison of our study with previous investigations reveals a consistent pattern. A recent comparative angioscopic and intracoronary ultrasound study19 reported an association of angioscopic complex lesions with compensatory enlargement and unstable presentation. Other studies14 examining the extent and direction of remodeling in patients with stable coronary syndromes found a high proportion of negative remodeling. Previous intravascular ultrasound data show a weak relation between plaque morphology and clinical presentation. Compared with patients with stable angina, patients with unstable angina had more echolucent lesions but fewer calcified and mixed plaques.18

In a recent histological study by Pasterkamp et al,27 the relation between markers associated with plaque vulnerability and arterial remodeling was examined in femoral arteries. Histological evidence of plaque inflammation was associated

Figure 3. Intravascular ultrasound image from patient with unstable clinical presentation. Lesion shows positive remodeling with RR of 1.42.

Figure 4. Frequency of positive and negative remodeling in stable and unstable angina groups. Remodeling category is shown on horizontal axis, and frequency of each category in stable and unstable groups is shown on vertical axis. Frequency of remodeling categories was significantly different between stable and unstable angina groups (P=0.001).

Figure 5. Plaque morphology in stable and unstable angina groups. Predominant morphology is shown on horizontal axis, and frequency of each morphology in stable and unstable angina groups is shown on vertical axis.
with larger plaque and EEM areas but did not correlate with lumen size. The authors suggested that positive arterial remodeling may be associated with an increased risk of plaque rupture. Conversely, the fibrotic changes associated with negative remodeling may increase internal plaque resistance to rupture.

The biological implications of the relationship between positive or negative remodeling and clinical presentation are provocative. An attractive hypothesis is the concept that large, positive remodeled plaques are more susceptible to mechanical forces that lead to plaque rupture and an unstable clinical presentation. Thus, a paradox may exist in which positive remodeling protects against luminal narrowing but increases the likelihood of a cascade of events that lead to plaque rupture.

Study Limitations

The retrospective design of this study accounts for several limitations. The patients in the unstable coronary syndromes group had already experienced an acute coronary event, and accordingly, some of the observed plaque characteristics may have been the effect, rather than the cause, of the clinical presentation. However, histological studies indicate that plaque inflammation and remodeling precede plaque rupture and therefore support a causative role of remodeling. The target lesion was assumed to be the culprit lesion at the time of angiography, but we cannot exclude the possibility that the acute coronary event was in fact caused by another lesion in the same vessel. The cohort included only angiographically relatively severe lesions selected for preinterventional ultrasound imaging. Accordingly, these results may not be applicable to less severe obstructive lesions. The indications to perform intravascular ultrasound imaging may not have been uniform.

Other concerns include the possibility that the presence of the ultrasound catheter within severe lesions may have altered the vessel geometry. Although the effect of the intravascular catheter on lumen size has been described in the literature, the effect on the EEM area and the remodeling pattern is not well described. The definition of positive and negative remodeling is based on comparison of the proximal reference and lesion sites. Therefore, vessel tapering may have led to an overestimation of the number of negatively remodeled lesions, despite the definition of negative remodeling as an RR (RR) <0.95. Current intravascular ultrasound technology does not allow a definitive distinction to be made between plaque and thrombus. The classification of plaque morphology is based on a semiquantitative visual estimation of plaque echodensity.

Conclusions

This study demonstrates an association between the direction of arterial remodeling and the type of clinical presentation in patients with coronary artery disease. Positive remodeling of the culprit lesion was associated with unstable clinical presentation, whereas negative remodeling was more common in patients with stable clinical presentation. The biological relevance of this association is not clear, but it may reflect a greater tendency for large, positively remodeled plaques to cause acute coronary events. Future prospective studies are needed to determine whether the extent and direction of arterial remodeling can predict the risk of developing acute coronary syndromes.

References


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