Coronary Plaque Morphology and Frequency of Ulceration Distant From Culprit Lesions in Patients With Unstable and Stable Presentation

Paul Schoenhagen, Gregg W. Stone, Steven E. Nissen, Cindy L. Grines, John Griffin, Barry S. Clemson, D. Geoffrey Vince, Khaled Ziada, Timothy Crowe, Carolyn Apperson-Hanson, Samir R. Kapadia, E. Murat Tuzcu

Objective—Intravascular ultrasound studies describe ruptured coronary plaques at sites remote from the culprit lesion in patients with acute myocardial infarction (MI), suggesting multifocal plaque vulnerability. However, the role of intravascular ultrasound in the diagnosis of lesion vulnerability before rupture is unclear.

Methods and Results—We compared morphology and frequency of ulceration of additional plaques proximal to the culprit lesion in 105 patients treated with emergent stenting during an evolving, acute MI in the CADILLAC study and 92 patients with stable/subacute presentation who underwent elective stenting. Additional plaques proximal to the culprit lesion were found in 52 (50%) and 54 (59%) patients in the acute MI and stable/subacute group, respectively. The prevalence of ulceration was significantly higher in the acute MI than in the stable/subacute group (19% versus 4%; \(P=0.014\)). However, there was no significant difference in other morphological lesion characteristics.

Conclusions—Additional plaques are frequently found adjacent to the culprit lesions in patients undergoing percutaneous coronary intervention independent of clinical presentation. The increased prevalence of plaque ulceration but otherwise similar morphology of additional lesions in patients with acute MI versus stable/subacute presentation demonstrates the limitations of imaging in the assessment of plaque vulnerability. (Arterioscler Thromb Vasc Biol. 2003;23:1895-1900.)

Key Words: acute coronary syndromes ● plaque vulnerability ● intravascular ultrasound ● atherosclerosis imaging ● plaque rupture

Rupture or superficial erosion of vulnerable coronary atheromata are the major pathologic events initiating acute myocardial infarctions (MIs). However, recent histologic investigations demonstrate that episodes of plaque rupture are frequent and only occasionally result in acute coronary syndromes (ACS). Clinical, in vivo imaging studies in patients presenting with ACS have demonstrated lesions with characteristics of plaque rupture at multiple sites other than the culprit lesion. Presumably, such patients have a temporary underlying milieu conducive to the development of multifocal plaque ulceration. This systemic vulnerability at the time of acute MI is associated with evidence of systemic inflammation and may explain the high propensity for recurrent acute coronary events.

Intravascular ultrasound (IVUS) can reliably identify overall plaque burden and morphological characteristics of individual lesions in the entire coronary tree. Culprit lesions in patients with ACS are consistently associated with plaque echolucency, ulceration, and positive arterial remodeling. However, it is unknown if multifocal plaque vulnerability in patients with acute MI is associated with specific morphological characteristics of plaques distant from the culprit lesion. We therefore compared morphology and frequency of ulceration of additional plaques proximal to the culprit lesion in patients with acute MI and stable/subacute clinical presentation. The high-risk patient group, with a high anticipated frequency of vulnerable lesions, was enrolled from a prospective multicenter study of stenting or balloon angioplasty during acute, evolving MI. A low-risk group, with a low anticipated frequency of vulnerable lesions, included patients with stable/subacute clinical presentation undergoing elective stenting.

Methods

Patient Population

The acute MI subgroup was derived from the CADILLAC trial, a randomized comparison of the Guidant Multi-Link and MultiLink Duet coronary stent system versus balloon angioplasty with and without abciximab in patients with acute, evolving MI. The control...
group included patients with stable/subacute clinical presentation undergoing elective stent placement. Postinterventional IVUS examinations of 148 patients treated with emergent stenting for acute MI (November 1997 to September 1999) and 173 patients treated with elective stenting (May 1994 to June 1997) were analyzed. A total of 124 patients (43 in the acute MI group and 81 in the stable/subacute group) were excluded from analysis for the following technical reasons: incomplete imaging of the proximal segment precluded analysis of 26 patients; calcification precluded accurate assessment of the segment in 16 patients; IVUS images of 22 patients could not be analyzed because of poor image quality, and, to match inclusion criteria of the acute MI group, 32 lesions involving the coronary ostium and 28 lesions at bifurcation sites were excluded in the control group.

The remaining 197 patients constituted the study population, 105 with an acute, evolving MI and 92 with stable/subacute presentation. Clinical data, including age, sex, hypercholesterolemia (total cholesterol ≥200), family history (coronary artery disease in male first-degree relative <55 years of age, coronary artery disease in female first-degree relative <65 years of age), and diabetes (treatment with oral medications or insulin), were collected.

**Definition of Clinical Presentation**
Acute MI in the CADILLAC study was defined as clinical symptoms consistent with acute MI and ST elevation of ≥1 mm in ≥2 contiguous leads or a nondiagnostic ECG with angiographically high-grade stenosis and associated regional wall motion abnormalities. The elective stent group included patients with an initial clinical presentation of either unstable angina (Braunwald classification IIIB-Tn, n=56) or stable angina (Canadian class I or II angina unchanged over at least 2 months, n=36), but no acute electrocardiographic or enzymatic evidence of ischemia was present before intervention.20,21

**Coronary Intravascular Ultrasound Imaging**
IVUS imaging in the CADILLAC centers was performed according to a prespecified protocol using 30-MHz 3.5F monorail ultrasound catheters or 2.9F solid-state systems. After anticoagulation 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 during continuous imaging.22 The ultrasound images were recorded on 1/2-inch Super-VHS videotape.

**Image Identification and Analysis**
The vessel segment proximal to the culprit lesion was examined for presence of additional focal atherosclerotic lesions with or without plaque ulceration. We included only patients treated with coronary stents, eliminating patients treated with balloon angioplasty, to ensure precise identification of the culprit lesion. 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 additional analysis. All measurements were performed using the standards of the consensus panel of the American College of Cardiology and European Society of Cardiology.23 Focal atherosclerotic lesions were defined as sites with an intimal thickness of at least 0.5 mm, separated from the culprit lesion by a normal vessel segment (intimal thickness <0.3 mm) (Figure 1). Plaque ulceration was defined as a cavity in the vessel wall with disruption of the intima and flow observed within the plaque cavity. Features supporting intimal disruption were irregular surface of ulcerated plaques and visible torn edges in video sequences (Figure 2).

**Quantitative Intravascular Ultrasound Measurements and Calculations**
At each selected site, the lumen and external elastic membrane (EEM) areas were traced manually using the intimal leading-edge boundary and the leading edge of the adventitia, respectively. The plaque area was calculated as the difference between lumen and EEM area. Percent cross-sectional narrowing (%CSN) was calculated as follows: %CSN=(Plaque area/EEM area)×100.

**Qualitative Intravascular Ultrasound Analysis**
The operator visually classified plaque morphology according to commonly used definitions as recommended by ACC/AHA guidelines.22 Echolucent plaques were defined as lesions with an echodensity less than the adventitia for >75% of plaque area. Echodense plaques were defined as a plaque echodensity equivalent or greater than the adventitia (greater than >75% of plaque area) without acoustic shadowing. Calcified plaques were defined as echodense lesions with areas of acoustic shadowing occupying >90 degrees of the vessel wall circumference. All other lesions were defined as mixed plaques. For ulcerated lesions, plaque echodensity was classified by the appearance of the plaque adjacent to the ulceration.

Plaque eccentricity was defined as follows: (maximum−minimum atheroma thickness)/maximum atheroma thickness. Using this definition, a perfectly concentric plaque would have a value of 0, and a maximal eccentric plaque would have a score of 1.0.

**Statistical Analysis**
Simple descriptive statistics were used to summarize the data. These included frequencies and percentages for categorical variables and mean±SD for continuous variables.

Selected clinical, demographic, and lesion characteristics were compared for the 2 groups (acute MI and stable/subacute) using a 2-group independent t test for continuous data and a contingency table analysis (χ² or Fisher’s exact test) for categorical data. In addition, the prevalence of ulceration was compared between the 2
groups after adjusting for conventional cardiovascular risk factors in a multivariable logistic regression model.

Hypothesis testing was conducted using 2-sided alternatives with a significance level of 0.05. The Statistical Analysis System package (SAS) was used to generate data summaries and statistical analyses.

Results

Patient Population
The demographic characteristics of the patients are shown in Table 1. The patients in the stable/subacute group were older and had a lower prevalence of smoking history. Sex as well as the prevalence of diabetes, hypertension, hypercholesterolemia, and family history were similar in the stable/subacute and acute MI groups.

Prevalence of Additional Proximal Lesion Sites
In the overall group of 197 patients, a total of 106 atherosclerotic lesions proximal to the treated culprit lesion were identified (54%). Proximal focal lesions were identified in 52 of 105 (50%) patients presenting with acute MI and 54 of 92 (59%) patients in the stable/subacute group ($P=0.2$).

Plaque Ulceration of Additional Proximal Lesions
Considering the 2 cohorts, a total of 12 ulcerated lesions were identified within the 106 identified proximal lesions (11%). These 12 ulcerated lesions were unequally distributed. There were 10 ulcerated plaques in the proximal vessel segments of the acute MI group and only 2 ulcerations in the stable/subacute group. The prevalence of ulceration was significantly higher in the acute MI compared with the stable/subacute group (19% versus 4%; $P=0.014$, Fisher’s exact test; $P=0.012$, $\chi^2$) (Figure 3). After adjusting for age and smoking using a multivariable logistic regression model, the prevalence of ulceration in the acute MI group REMAINED statistically higher than in the stable/subacute group ($P=0.04$; OR, 5.6; 95% CI, 1.1 to 28.4).

Morphology of Additional Proximal Lesions
Other than the higher frequency of ulceration, additional plaques distant from the culprit lesion in patients with acute MI were indistinguishable from plaques in patients with stable/subacute presentation (Table 2 and Figure 4). Plaque area ($10.3\pm3.1$ versus $10.4\pm3.7$, $P=0.93$), EEM area ($19.2\pm5.2$ versus $18.2\pm5.4$, $P=0.33$), and %CSN ($53.6\pm8.9$% and $56.6\pm9.1$, $P=0.09$) were similar at additional lesions in the acute MI and elective stent group, respectively. A trend toward larger lumen area in the acute MI group ($8.9\pm3.1$ versus $7.9\pm2.7$, $P=0.06$) was observed.

**Figure 2.** Example of an ulcerated lesion proximal to the stented segment. Plaque ulceration is demonstrated by the interruption of the fibrous cap and flow in the lesion cavity, which is best seen on video sequences.

**Figure 3.** Comparison of the prevalence of plaque ulceration in lesions proximal of the culprit lesion between patients with acute, evolving MI and stable/subacute clinical presentation. In patients with acute MI, these plaques had a significantly higher frequency of ulceration, suggesting multifocal plaque vulnerability.

**Table 1.** Clinical and Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Acute MI n=105</th>
<th>Stable/Subacute n=95</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.1±11.1</td>
<td>60.9±10.0</td>
<td>0.017</td>
</tr>
<tr>
<td>Male, %</td>
<td>76</td>
<td>73</td>
<td>0.62</td>
</tr>
<tr>
<td>Artery, %</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>LAD</td>
<td>29</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>59</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>18</td>
<td>23</td>
<td>0.40</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>46</td>
<td>49</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>38</td>
<td>47</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>73</td>
<td>56</td>
<td>0.02</td>
</tr>
<tr>
<td>Family history, %</td>
<td>40</td>
<td>30</td>
<td>0.14</td>
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LAD indicates left anterior descending; LCX, left circumflex; RCA, right coronary artery.
The eccentricity index was 0.78±0.9 and 0.82±0.1 in the acute MI and elective stent groups (P=0.1). Plaque echolucency was not significantly different (P=0.14).

**Discussion**

Regardless of clinical presentation with either acute, evolving MI, or stable/subacute coronary syndromes, we found a high prevalence (54%) of additional atherosclerotic lesions with mild to moderate stenosis in vessel segments proximal to the culprit lesion. In patients with acute MI, these plaques distant from the culprit lesion had a 5-fold higher frequency of ulceration, suggesting multifocal plaque vulnerability. However, additional plaques were otherwise indistinguishable in patients with acute MI and stable/subacute presentation.

These results have important implications for the morphological assessment of plaque rupture and vulnerability with in vivo imaging modalities. Recent histologic studies suggest that episodes of plaque destabilization and rupture are common and most frequently not associated with clinical symptoms.6–8 Presumably, after an episode of rupture, the local balance between thrombosis and spontaneous thrombolysis prevents the occlusion in most vessel segments. However, at the time of an acute MI, the systemic inflammatory and procoagulant milieu seems to promote multifocal plaque vulnerability, increasing the probability of additional atheroma disruption at multiple sites other than the culprit lesion.1,13,14 Plaque vulnerability therefore describes a temporary biochemical stage of plaque activation with increased risk to rupture.2,23–25

The diagnosis of vulnerable lesions with in vivo imaging modalities could allow the identification and early treatment of high-risk patients before the initial or recurrent acute event. IVUS can reliably identify overall plaque burden and morphological characteristics of individual lesions in the entire coronary tree.16 Culprit lesions in patients with ACS are consistently associated with plaque echolucency, ulceration, and positive arterial remodeling.17–19 However, the role of IVUS and other imaging modalities in the diagnosis of vulnerability before rupture is controversial.26–28 Despite detailed morphological characterization of plaques with IVUS26,29 and angioscopy28–31 and more recently with computed tomography and MRI,32,33 none of these modalities presently allows the reliable prospective identification of vulnerable sites.27 The similarity of plaque dimension and morphology of additional lesions without ulceration in the acute MI and stable/subacute groups in our study demonstrates the limitations of identifying morphological characteristics of vulnerable plaques in vivo. In particular, characteristics previously associated with vulnerability at culprit lesion sites such as echolucency and eccentricity were present with similar frequency in the 2 groups.

A possible explanation for the negative findings could be that the spatial resolution of IVUS is insufficient for the assessment of the plaque structures, which are associated with vulnerability in postmortem studies. Advances in IVUS image analysis (eg, radiofrequency analysis) and imaging modalities with higher spatial resolution including optical coherence tomography may provide additional insights into plaque stability.34,35 However, an alternative hypothesis is that the paradigm about morphological changes of individual vulnerable plaques based on autopsy studies of fatal coronary events2–5,24,25 is not applicable in vivo imaging of nonfatal cases. It is conceivable that the temporal biochemical changes associated with plaque vulnerability are below the detection threshold of in vivo imaging in general. Therefore, the identification of vulnerability may need to rely on an assessment of plaque morphology and plaque burden with imaging modalities integrated with systemic markers of disease activity (eg, serum markers of inflammation).15,36–39

Because of the retrospective design and the unavailability of serum markers, we cannot examine this hypothesis in the present study. Another important limitation is that the acute MI and stable/subacute groups were derived from 2 distinct patient populations. Therefore, despite correction with multivariate analysis, selection bias or differences in unexamined baseline characteristics may have influenced our findings. The indication for IVUS imaging in the examined patient populations was guidance of percutaneous coronary intervention, limiting the value for the purpose of this study. In particular, preinterventional images and complete imaging of the coronary tree were not available. To differentiate additional lesions proximal to the stented segment from plaque

<table>
<thead>
<tr>
<th>TABLE 2. IVUS Characteristics of Plaques Proximal to the Culprit Lesion</th>
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<tr>
<td><strong>Prevalence of additional plaque, %</strong></td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Ulceration, %</td>
</tr>
<tr>
<td>Lumen area, mm²</td>
</tr>
<tr>
<td>Plaque area, mm²</td>
</tr>
<tr>
<td>EEM area, mm²</td>
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<tr>
<td>CSN, %</td>
</tr>
<tr>
<td>Eccentricity</td>
</tr>
<tr>
<td>Echolucent</td>
</tr>
<tr>
<td>Fibrous</td>
</tr>
<tr>
<td>Mixed</td>
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*χ² test. †Fisher exact test.
shifted axially during the percutaneous coronary intervention, we defined proximal lesions as those separated from the culprit stenosis by a relatively normal segment.

Conclusions

The role of in vivo imaging with IVUS and other imaging modalities for the identification of patients at risk for cardiovascular events is a subject of intense research. Morphological criteria of plaques vulnerable to initiate acute events have been derived from postmortem observation. Our results demonstrate significant limitations of IVUS and perhaps have been derived from postmortem observation. Our results demonstrate significant limitations of IVUS and perhaps morphological criteria in general for the in vivo identification of individual vulnerable lesions. Future studies comparing imaging criteria of individual lesions and diffuse plaque burden with systemic markers of vulnerability are necessary to define the clinical role of atherosclerosis imaging.

Acknowledgments

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References


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