Relationship of Clinical Presentation and Calcification of Culprit Coronary Artery Stenoses

Joshua A. Beckman, Jason Ganz, Mark A. Creager, Peter Ganz, Scott Kinlay

Abstract—Coronary artery calcification is increased in the presence of atherosclerosis. However, there is great variability in the calcification of individual coronary stenoses, and the clinical significance of this finding remains unknown. We tested the hypothesis that culprit lesions associated with myocardial infarction or unstable angina are less calcified than are stenoses associated with stable angina. The study consisted of 78 patients who underwent intravascular ultrasound imaging of culprit stenoses after the placement of a stent. Seventeen patients presented with stable angina; 43, with unstable angina; and 18, with myocardial infarction. The extent of coronary calcification was measured by the angle of its arc and was quantified with a computer-based protractor. The arc of calcium was measured in the stented area at the point of maximal calcification and also as an average of the calcification found at proximal, middle, and distal stent segments. The maximal arc of calcium decreased progressively from patients with stable angina (91°±10°) to those with unstable angina (59°±8°) and to those with myocardial infarction (49°±11°, P=0.014). Similarly, the average arc of calcium was greatest (32°±7°) in patients with stable angina, less (15°±4°) in patients with unstable angina, and least (10°±5°) in patients with acute myocardial infarction (P=0.014). These associations remained significant after adjustment for other factors that potentially affect arterial calcification. Acute coronary syndromes are associated with a relative lack of calcium in the culprit stenoses compared with stenoses of patients with stable angina. These findings have implications for the understanding of the biology of acute coronary syndromes as well as for the identification of coronary stenoses by methods that rely solely on the presence of calcium. (Arterioscler Thromb Vasc Biol. 2001;21:1618-1622.)

Key Words: calcinosi s ■ calcium ■ coronary vessels ■ ultrasonography, interventional ■ myocardial infarction

Coronary artery calcification is an active process that is commonly observed in the setting of atherosclerosis.1-3 Previous reports have found that arterial calcification is proportional to the overall burden of the atherosclerotic plaque but not necessarily to the severity of luminal narrowing.3-7 Acute coronary syndromes, including myocardial infarction and unstable angina, arise from rupture or erosion of atherosclerotic plaques.4 The relationship of lesional calcium toward propensity to plaque rupture and, thus, to the pathogenesis of acute coronary syndromes remains uncertain.5

In the present study, we tested the hypothesis that calcification of culprit lesions responsible is reduced for acute coronary syndromes compared with lesions associated with stable angina. Accordingly, we used intravascular ultrasound (IVUS) to assess the extent of calcification of culprit lesions in patients with stable angina, unstable angina, and myocardial infarction.

Methods

Patient Selection

We selected all 78 patients with de novo native lesions causing angina or myocardial infarction who underwent IVUS imaging of coronary arteries after stent placement at Brigham and Women’s Hospital between January 1997 and January 2000. At this institution, IVUS imaging is performed at the discretion of the attending interventional cardiologist to assess the adequacy of stent deployment. We excluded patients who had interventions for in-stent restenosis or for bypass graft disease. We also excluded patients who underwent directional or rotational atherectomy.

Clinical Demographics

Clinical information and laboratory results were collected from the medical record by 1 author unaware of the IVUS characteristics. Diabetes mellitus and hypertension were defined by medical treat-
ment for these conditions. Current smoking included at least 1 cigarette per day in the previous month. The definition of unstable angina was based on the criteria of Braunwald6 as new onset (<2 months) of severe angina, accelerated angina, or angina at rest. Myocardial infarction was defined by requiring at least 2 of the following criteria: (1) chest discomfort typical of ischemic pain lasting for at least 30 minutes, (2) the presence of ST-segment elevations or new Q waves in ≥2 contiguous leads, and (3) the elevation of creatine kinase to more than twice the upper limit of our reference range obtained before catheterization. A vessel was defined as having significant atherosclerosis by the presence of a ≥50% stenosis. The culprit lesion was defined as the stented segment and was identified by the interventional cardiologist according to standard clinical, ECG, and noninvasive imaging and angiographic criteria.

**IVUS Imaging Protocol**

All IVUS studies were performed after intracoronary nitroglycerin (100 to 200 µg). One of 2 IVUS systems was used: a 30-MHz mechanical ultrasound catheter (Ultracross, Cardiovascular Imaging System) or a 25-MHz, 64-element, solid-state catheter (Visions Five-64 F/X, Endosonics). In all cases, an automated (0.5-mm/s) or slow manual pullback was recorded on high-resolution super-VHS tape for offline analysis.

**Analysis of IVUS Images**

Six frames from each IVUS study were grabbed from the super-VHS tape for measurement. These included 4 frames in the culprit lesion corresponding to the proximal, middle, and distal part of the stent and the frame showing the widest arc of calcification. Two reference segment frames were grabbed (a proximal and distal reference) within 10 mm of the ends of the stent and before any intervening branch.

Calcium was defined as a bright echogenic signal with an accompanying acoustic shadow in the arterial wall and was quantified in 2 ways for each patient: (1) by the widest arc of calcium found in the stented segment and (2) as the average angle of the arc of calcium in the proximal, middle, and distal stented segments. The arc of calcium was chosen as the descriptor because of the demonstrated relationship between arc of calcium defined by IVUS and pathological calcium content and because it was less likely to be changed by stenting than were other lesional components (Figure 1).

One author, who was unaware of the clinical data, measured the vessel, lumen, and plaque areas in the reference segments, the lumen area in the stented segment, and the angle of the arcs of calcium by using computer planimetry (TapeMeasure, INDEC Systems). Vessel area was not reported in the stented segment because acoustic shadowing from calcium in the vessel wall partly obscured the external elastic membrane in many frames.

**Statistical Analysis**

All analyses compared patients presenting with myocardial infarction, unstable angina, and stable angina with the use of Stata statistical software (Statcorp). Descriptive statistics are presented as mean±SD or proportions, as appropriate. Experimental measures are presented as mean±SE. Fisher’s exact test was used to compare categorical data and regression analysis for continuous data across the 3 groups. The main hypothesis was tested by comparing the amount of culprit lesion calcium between the 3 patient groups, with stable angina patients used as the reference, and by performing an analysis of trend across increasing instability of the presenting syndrome (stable to unstable angina to myocardial infarction). Similar analyses were used to compare the risk factors between the 3 groups and to adjust the main analysis for other potential confounding variables.

**Results**

**Baseline Characteristics**

IVUS studies from 78 patients met the inclusion criteria for the present study. Of these, 17 patients presented with stable angina; 43, with unstable angina; and 18, with myocardial infarction. Their clinical characteristics are presented in Table 1. Among risk factors for coronary artery disease and arterial calcification, only hypertension was distributed unevenly among the 3 groups (P=0.03).

**Angiographic Characteristics**

The angiographic characteristics are presented in Table 2. The left anterior descending coronary artery was the vessel most commonly imaged, and the left circumflex coronary artery was the least imaged vessel. The average number of vessels with a >50% stenosis did not differ significantly between groups.

**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>SAP</th>
<th>UAP</th>
<th>AMI</th>
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</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>17</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±10</td>
<td>65±11</td>
<td>64±13</td>
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<tr>
<td>Sex, % male</td>
<td>72</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>191±62</td>
<td>178±27</td>
<td>165±45</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>36±10</td>
<td>41±16</td>
<td>34±11</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>22</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>33</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>44</td>
<td>73*</td>
<td>40</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
<td>1.0±0.4</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*P=0.03.
Coronary artery calcification scores reported in several large EBCT studies of patients at varying risks of coronary artery disease suggest that, on average, calcification increases with the overall plaque burden. Detrano et al12 demonstrated that subjects with risk factors but no ischemic symptoms had a mean calcification score of 44. In a multicenter study, symptomatic patients undergoing clinically indicated cardiac catheterization for coronary disease had a mean score of 336.13 Patients with angiographic evidence of left main or 3-vessel coronary disease had a mean calcium score of 491.14 These and other studies15–17 suggest that calcification is more likely a feature of advanced obstructive coronary atherosclerosis. Increasing coronary calcinosis is likely related to an increasing burden of atherosclerosis and, therefore, implies an associated incremental risk of cardiovascular events. Nonetheless, the important findings from CT studies cannot be extrapolated to indicate that calcium, per se, contributes to the development of acute coronary syndromes.

Arterial Calcification in Acute Coronary Syndromes

Recent studies have suggested that myocardial infarction and unstable angina usually arise from the disruption of mildly stenosed atherosclerotic lesions.16,19 For half of all patients with myocardial infarction, this event constitutes the initial clinical presentation of coronary artery disease, suggesting that severe stenoses that are likely to cause preexisting symptoms are frequently absent in this patient population.20 The characteristics of plaques vulnerable to rupture and thereby likely to cause acute coronary syndromes have been elucidated in postmortem studies.4,21,22 These studies have confirmed the angiographic observations that the mild stenoses are more frequently disrupted. Such vulnerable plaques typically contain a large amount of lipid and have a preponderance of inflammatory cells at the shoulders of the plaque and a thin fibrous cap. The large lipid core is soft and bears the circumferential stresses less well than fibrous components of the arterial wall.21,23,24 Calcium is found infrequently in the culprit lesions of ruptured plaques.23 In contrast to the destabilizing effects of the lipid core, it has been demonstrated theoretically by Huang et al,25 who used large-strain finite-element analysis, that calcium is a stabilizing force, similar to the fibrous plaque.25 Because only a minority of myocardial infarcts are fatal and even fewer are subject to postmortem examination, it is not clear whether inferences derived by postmortem examination apply to the general population of patients with coronary atherosclerosis.

Lesion Calcification

The maximal culprit lesion calcium (maximal width of the calcium arc) was greater in patients with stable angina (91±10°) than in patients with unstable angina (59±8°) and was smallest in patients with acute myocardial infarction (49±11°), as shown in Figure 2 (test of trend \( P = 0.014 \)). Similarly, the average angle of the arc of calcium in the culprit lesions was greater in patients with stable angina (32±7°), less in patients with unstable angina (15±4°), and least in patients with acute myocardial infarction (10±5°), as shown in Figure 3 (test of trend \( P = 0.014 \)). Subject age, sex, total and HDL cholesterol, diabetes, smoking, hypertension, and serum creatinine were not related to the amount of calcification by univariate or multivariate analysis.

Reference and Stented Segments

The maximal reference segment calcium was 20±32° in patients with stable angina, 25±35° in patients with unstable angina, and 4±10° in patients with acute myocardial infarction (test of trend \( P = \text{NS} \)). There were no significant relationships between the clinical presentation and vessel area, lumen area, or calcification in the reference segments.

Discussion

In the present study, we used IVUS to assess calcification of culprit coronary artery stenoses in patients with coronary artery disease and a range of clinical presentations. The novel finding in the present study is that culprit lesions of patients with stable angina are more extensively calcified than are those in patients with unstable angina and are least calcified in patients with myocardial infarction.

Arterial Calcification in Coronary Artery Disease

The introduction of EBCT has stimulated interest in the relationship between arterial calcification and atherosclerosis.
Detection of Coronary Calcium by Noninvasive Approaches in Patients With Anginal Syndromes

Studies using double-helical CT support the observation that coronary arteries containing stable stenoses are more heavily calcified than are those containing unstable plaques. Shemesh et al26 demonstrated that patients with stable angina had higher calcium scores than did patients with acute myocardial infarction and that the infarct-related arteries tended to have less calcium than did the other coronary arteries. Interestingly, African Americans with similar coronary risk factor profiles had less coronary artery calcification yet more coronary events than did white subjects.27 IVUS extends these findings by focusing on the calcification of a single culprit stenosis and associating culprit lesion calcification with clinical stability.

Findings in the Present Study

We used IVUS because it is accepted as the most sensitive method for the detection of arterial wall calcium in vivo.1,7,28–31 IVUS methods of quantifying arterial calcium rely on measuring the arc of calcium because the acoustic shadowing prohibits any measurement of the area of calcification. The ability of this approach to quantify the amount of calcium was confirmed by careful histological correlation.7 Although there are likely many factors that contribute to plaque rupture, the difference in average calcium allows us to study the effect of the variable of interest (calcium).

Calcium is more prevalent in older individuals and in some studies is more prevalent in patients with hypertension.23 We found no relationship between calcium and these variables in the present study. However, most of our subjects were older, and a wider age range may be required to find this relationship. Because there were more hypertensive individuals among our subjects with unstable angina, any effect of hypertension would have only underestimated the difference with stable angina. Finally, the vessel causing the intervention was most commonly the left anterior descending coronary artery, yet the extent of coronary artery disease was similar among the 3 groups. Adjustment for these and other factors did not change the results of the present study.

Implications

Calcium is stiffer than the surrounding components of atherosclerotic plaques. Potentially, it can concentrate stresses and serve as a nidus for plaque disruption.33 Nevertheless, histological studies of postmortem specimens have demonstrated that intimal tears localized to the junction of calcium with adjacent fibrous tissue are infrequent and observed in only 4% of all disrupted lesions.23 Furthermore, a recent publication by Huang et al25 provides mechanistic insight by demonstrating that the lipid core is a destabilizing force, whereas calcium provides the stability of the fibrous cap. Our results, derived from a broad range of patients undergoing coronary intervention, support the concept that calcium is not a critical substrate for plaque disruption and is, in fact, associated with more stable plaques.

Interestingly, some have postulated that calcium in adjacent sections may act as a rigid arterial segment and decrease arterial flexibility, creating a nidus for plaque rupture in culprit lesions.24 Our data indicate that calcium in adjacent segments is not related to clinical presentation or the calcium extent of the culprit lesion. Thus, it seems that only calcium found in a specified lesion conveys information specific to clinical presentation.

Limitations of the Study

We have excluded patients who underwent rotational and directional atherectomy because those procedures remove tissue along with calcium. Inasmuch as rotational atherectomy (majority of excluded patients) is usually performed because of extensive lesion calcium and is typically confined to patients with stable angina, the findings of the present study would have only been strengthened had these patients not been excluded.

Patients at our institution do not regularly undergo IVUS examination, and these patients may not be an exact representation of the whole; however, the patients in the present study were similar in age, sex ratio, and indication for intervention as the entire population of patients undergoing intervention at our hospital.

Conclusions

In summary, we found that acute coronary syndromes are associated with a relative lack of calcium in the culprit stenoses compared with stenoses of patients with stable angina. These findings have implications for the understanding of the biology of acute coronary syndromes as well as for the identification of coronary stenoses by methods that rely on the presence of calcium.

References


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