Is Pre-Intervention Intravascular Ultrasound Necessary in Evaluating Target Lesion Calcification in Patients Undergoing Transcatheter Therapy?

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To identify a subset of patients with a high probability of extensive calcification for further intravascular ultrasound (IVUS) examination, the frequency and extent of target lesion calcification as assessed by IVUS and its correlations with age, gender and risk factors as well as the value of angiography in identifying ultrasound calcification were analyzed in 88 patients undergoing balloon angioplasty for significant coronary atherosclerotic stenosis. The extent of calcification was semi-quantitatively graded as 0: no calcification; +: calcification arc < 90°; ++: calcification arc from 90° to 180°; +++: calcification arc > 180°. The distribution pattern of calcification was classified as superficial, deep or mixed. The results indicate: (1) the frequency of target lesion calcification was 38.6%, of which 52.9% showed a superficial pattern and 56.0% had a calcification arc < 90°; and (2) only age was significantly associated with target lesion calcification in all of the patients. The frequency of calcification was remarkably higher in patients ≥ 60 years old than in patients ≤ 60 years old (61.9% vs 17.4%, p < 0.001); (3) among patients less than 60 years old, those with calcification had a higher average number of risk factors than those without; and (4) the total sensitivity of angiography in identifying ultrasound calcification was 43.6%, with a significantly higher sensitivity for calcification arc > 180° and mixed pattern. In conclusion, pre-intervention IVUS may be necessary in patients ≥ 60 years old and in those < 60 years old with more than two risk factors in selecting devices to optimize interventional strategies.

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Coronary artery calcification, particularly target lesion calcification, has been shown to be an important determinant of the arterial response to transcatheter therapy: balloon angioplasty causes dissection in calcified lesions1,2 directional atherectomy cuts calcified plaque poorly3,4 and rotational atherectomy causes preferential ablation of calcium5,6 Therefore, detailed information regarding target lesion calcification is necessary in selecting devices for transcatheter therapy. Intravascular ultrasound (IVUS), a highly sensitive technique for the detection of plaque calcification7,8 has been used pre-intervention to evaluate features of target lesions and to guide transcatheter treatment strategies in coronary artery disease.

Key words: Target lesion calcification Age Risk factors Intravascular ultrasound Balloon angioplasty

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However, the practical limitations of pre-intervention IVUS examination, such as significant complications, technical difficulty and high cost, preclude its routine use in clinical settings. To identify a subset of patients with a high probability of extensive calcification for further IVUS examination, the frequency, extent and distribution of target lesion calcification as assessed by IVUS and its correlations with age, gender, smoking, hypertension, diabetes mellitus and hyperlipidemia, as well as the value of angiography in identifying ultrasound calcification, were analyzed in patients undergoing balloon angioplasty for significant atherosclerotic stenosis.

METHODS

Subjects
The study population consisted of 88 patients (80 men and 8 women, mean age 58.5±8.1 years) who underwent balloon angioplasty for significant atherosclerotic stenosis. Sixty two patients had previous myocardial infarction and 26 had a history of angina pectoris. The target lesions included 57 in the left anterior descending artery, 29 in the right coronary artery and 2 in the left circumflex artery.

We examined risk factors for coronary artery disease in all of the patients. The risk factors included smoking (> about 1 pack/day), hypertension (>160/95 mmHg), hyperlipidemia (cholesterol >240 mg/dl) and diabetes mellitus.

Angiographic calcification was graded as none, mild or severe by the consensus of 2 investigators after angiographic films were reviewed by visual inspection without knowledge of IVUS findings.

All of the patients gave their informed consent before the study.

Intravascular Ultrasound Imaging
IVUS was performed before and after balloon angioplasty in 8 patients and only after balloon angioplasty in 80 patients using a commercially available mechanical scanner (CVIS Inc, Sunnyvale, CA) with a 30 MHz transducer. Since this is a manual retrieve system rather than a motorized retrieve system, we could not evaluate the length of calcification. Ultrasound images were updated with fluoroscopic images and audio annotation to ensure correct location and interpretation, and all of the studies were recorded on high-resolution videotape for offline analysis.

Image Analysis
Calcification was defined as bright dense echoes (brighter than the reference adventitia) with distal acoustic shadowing. The extent of calcification was semi-quantitatively graded as 0 no calcification; +calcification arc <90°; ++calcification arc from 90° to 180°; +++calcification arc >180° (Fig 1). If there was more than 1 calcific deposit in a given imaging slice, the angles of the calcification arc were added. The distribution pattern of calcification was classified as: (1) superficial, if it involved the lumen-intimal interface and was localized within the inner 1/2 layer of the plaque; (2) deep, if it was within the outer 1/2 layer of plaque; or (3) mixed, if both superficial and deep were present or if it extended from the inner to the outer 1/2 layer of the plaque (Fig 2).

Statistical Analysis
Continuous variables are expressed as mean±SD and categoric data are expressed as absolute values and percentages. Chi-square and Fisher exact tests, Student's t-test and multivariate analysis were used where appropriate.

RESULTS
Target Lesion Calcification by IVUS
IVUS was performed both before and after percutaneous transluminal coronary angioplasty (PTCA) in 8 patients. We observed the effects of PTCA on the extent and distribution patterns of target lesion calcification in these 8 patients, and found that there was no change in extent or distribution pattern after PTCA.

Target lesion calcification was found only in 34 patients (38.6%), of whom 20 patients (21.6%) had a calcification arc <90°, 11 (12.5%) from 90° to 180° and 3 (4.5%) >180° (Fig 3). In these 34 patients, calcification was superficial in 18 patients (52.9%), deep in 8 (17.7%) and mixed in 10 (29.4%) (Fig 4).
Clinical Correlates

The 34 patients with target lesion calcification were assigned to the calcification (+) group while the 54 without calcification were placed in the calcification (−) group. Age, gender, history of coronary artery
disease, and risk factors including smoking, hypertension, hyperlipidemia and diabetes were compared between the 2 groups (Table I). Only age was significantly associated with target lesion calcification.

Fig 5 shows the frequency of target lesion calcification in different age groups. We took 60 years as a cut-off to obtain the most significant difference between the 2 age groups and found that the frequency and extent of target lesion calcification were significantly different between the 2 age groups (p<0.001) (Fig 6). In patients ≤60 years old, the frequency was 17.4% and a calcification arc of >180° was not detected, while in patients ≥60 years old, the frequency was 61.9% and a calcification arc >180° was found in 9.5%. There was no difference in the distribution patterns of calcification between the 2 age groups (Fig 7).

The differences in the average number of risk factors between patients with calcification and those without in the 2 age groups are shown in Fig 8. Patients <60 years old with calcification had a higher average number of risk factors compared not only to those <60 years old without calcification but also to those ≥60 years old with calcification (p<0.001). Of the 8 patients <60 years old with calcification, six had 3 or 4 risk factors while two had 1 or 2 risk factors. There was no significant difference in the average number of risk factors between patients ≥60 years old with calcification and those without.

**TABLE I CLINICAL CORRELATES OF THE STUDY GROUPS**

<table>
<thead>
<tr>
<th></th>
<th>calcification (+) (n=34)</th>
<th>calcification (-) (n=34)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>31/3</td>
<td>49/5</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>62.6±6.9</td>
<td>55.9±7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI/AP</td>
<td>23/11</td>
<td>39/15</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>19/15</td>
<td>31/23</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>12/22</td>
<td>11/43</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia (yes/no)</td>
<td>10/24</td>
<td>12/42</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes Mellitus (yes/no)</td>
<td>5/29</td>
<td>9/45</td>
<td>NS</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; AP: angina pectoris; NS: differences not significant

**Sensitivity of Angiography in Identifying Ultrasound Calcification**

Calcified lesions detected by IVUS included 34 target lesions and 38 lesions located in other segments. The total sensitivity of angiography in identifying ultrasound calcification was 43.6%. According to the extent of calcification, the sensitivity was 33.3% for +, 44.8% for ++ and 100% for +++, respectively, with a higher sensitivity for calcification arc >180°(p<0.01) (Table II). The sensitivity of angiography in identifying different patterns of ultrasound calcification was 36.0% for superficial, 45.5% for deep and 80% for mixed, indicating a higher sensitivity for the mixed pattern (p<0.05) (Table III). However, the grades of angiographic calcification were not associated with
Fig 5. Frequency of target lesion calcification in different age groups.

Fig 6. Differences in the extent of calcification between patients ≤60 years old and patients ≥60 years old.

Fig 7. Differences in distribution patterns of calcification between patients ≤60 years old and patients ≥60 years old.
either the extent grades or the distribution pattern of calcification by IVUS.

DISCUSSION

With the rapid development of new devices, catheter-based interventional therapy has become a popular non-surgical method for the treatment of coronary artery disease. The significant impact of target lesion features (including lesion calcification, lesion severity and plaque distribution) on the outcome of different interventional strategies has drawn considerable attention, and precise information regarding target lesion pre-intervention is becoming increasingly important in selecting devices and guiding interventional therapy. IVUS has been shown to be useful for providing detailed transmural high-quality images of coronary artery in vivo, and plays an important role in evaluating and optimizing the results of catheter-based interventional strategies. However, practical factors, such as significant complications and high cost, preclude its unlimited use. Therefore, in the present study, we tried to identify a subset of patients with a high probability of target lesion calcification for further IVUS study based on clinical correlates and coronary angiography.

IVUS was performed both before and after PTCA in 8 patients. We found that there was no change in the extent or the distribution pattern of calcification after PTCA, and think that the findings after PTCA are credible.

The incidence of target lesion calcification as assessed by IVUS was 38.6%, of which 21.6% had a calcification arc <90° and extensive calcification (arc >180°) was detected in only 4.5% of the patients. It has been thought that, in most cases, extensive calcification has a significant impact on interventional strategy. In the present study, the incidence of extensive calcification was so low that little clinical implication could be considered. We think that this may be due to the age of the study population since the incidence increased remarkably up to 9.5% in patients >60 years old. This also suggested that pre-intervention IVUS may not be necessary in all patients, but the need may be greater in patients >60 years old.

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With regard to the distribution patterns, the most common type was superficial, which was found in 52.9% of the patients. The incidence of target lesion calcification reported by other studies has varied from 66% to 83%. This variation may be attributed to differences in the age or race of the study populations.

Age was the only variable that was significantly associated with target lesion calcification in all of the patients. When 60 years old was taken as a cut-off, target lesion calcification was rare in patients less than 60 years old despite the presence of significant stenotic coronary artery disease. In contrast, in patients ≥ 60 years old, the incidence of target lesion calcification was greatly increased. This finding may have 2 clinical implications.

First, the absence of calcification on angiography or IVUS, particularly in patients under the age of 60, does not preclude the clinically relevant coronary artery disease. Recently, screening techniques such as ultrafast computed tomography have been used to noninvasively evaluate the extent of atherosclerosis based on the quantitation of calcium in coronary arteries, and there is reportedly a close relation between the extent of coronary calcium and the extent of atherosclerosis. However, according to our findings, the frequency of target lesion calcification in patients < 60 years old was only 17.4% despite the presence of significant stenosis. Therefore, it may be improper to exclude significant coronary artery disease on the basis of a negative result in calcium-dependent screening techniques.

Second, in patients ≥ 60 years old, since target lesion calcification was common and more than half of the patients had superficial calcification, which has more impact on interventional strategies than deep calcification, there is a greater need for accurate information regarding target lesion calcification than in young subjects. We evaluated the sensitivity of coronary angiography in identifying ultrasound calcification. Although the total sensitivity was not very high (43.6%), the sensitivity for extensive calcification (calcified arc > 180° or mixed pattern) was significantly higher. However, the grade of angiographic calcification did not correlate with either the extent or the distribution pattern defined by IVUS. Thus, angiography was insensitive in detecting the presence and extent of coronary calcification compared with IVUS, and could not evaluate the extent and distribution of calcification correctly. If coronary calcification is important in clinical decision-making, IVUS rather than simply coronary angiography, should be performed.

Another interesting finding in this study is that the presence of target lesion calcification in patients < 60 years old was associated with a higher average number of risk factors. In patients ≥ 60 years old, there was no significant difference in the average number of risk factors between patients with target lesion calcification and those without. However, in patients < 60 years old with target lesion calcification, the average number of risk factors was significantly higher than that in those without calcification. This suggests that although target lesion calcification was not common in patients < 60 years old, patients with more than 2 of the risk factors, including smoking, hypertension, hyperlipidemia and diabetes, may have a high probability of target lesion calcification. In most cases, extensive calcification is one of the most important factors in determining device-selection. However, this does not mean that calcification < 180° has no clinical implications, especially in patients with eccentric stenosis. In addition, pre-intervention IVUS also provides other important information about plaque besides calcification. In this study, 30.9% of patients ≥ 60 years old and 50% of patients < 60 years old with more than 2 risk factors showed a calcified arc > 90°. Thus, we think that pre-intervention IVUS may be necessary in those patients.

In conclusion, pre-intervention IVUS may be particularly important in patients ≥ 60 years old and in those < 60 years old with more than 2 risk factors to observe the extent and the distribution pattern of calcification and other features of the target lesion and to aid in selecting devices to optimize interventional strategies.

REFERENCES
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