Editorial

The Mystery of Spotty Calcification
Can We Solve It by Optical Coherence Tomography?

Kazuyuki Yahagi, MD; Michael Joner, MD; Renu Virmani, MD

Spotty calcification has recently been introduced as a marker of plaque vulnerability in patients presenting with acute coronary syndrome undergoing invasive and noninvasive coronary imaging, and it has been suggested to be of predictive value for percent atheroma volume with greater progression. Several pathological and clinical studies applying computed tomography (CT) and intravascular ultrasound (IVUS) demonstrated that spotty calcification is more frequently observed in lesions with plaque rupture compared with stable plaque. Recently, optical coherence tomography (OCT) has emerged as the premier intracoronary imaging technology with a higher resolution (10–20 μm) than IVUS (100–200 μm) and also when compared with noninvasive CT and magnetic resonance imaging, both with a lower resolution (1 mm; Table). Indeed, OCT studies provided insights into coronary plaque morphology by the ability to discriminate macrophages, fibrous cap thickness, necrotic core/lipid pool, and calcium. However, not all agree that spotty calcification is a marker of plaque vulnerability, because high coronary artery calcium scores (>100 Agatston score) represent a powerful marker of future coronary events. It is therefore important to distinguish the positive association of overall coronary calcium score with cardiovascular mortality in the general population from focal or spotty calcification in selected subgroups presenting with acute myocardial infarction.

See Article by Ong et al

In this issue of Circulation: Cardiovascular Imaging, Ong et al investigated 53 patients presenting with ST-segment–elevation myocardial infarction (STEMI) undergoing invasive diagnostic assessment using OCT from a single center in Japan and compared the findings with 55 patients selected from their international multicenter OCT registry of 613 patients with stable angina pectoris (SAP). Spotty calcification was defined on a frame level basis with a length of calcium <4 mm and maximum arc <90°, and superficial calcium was based on depth threshold of 65 (superficial-65) and 100 (superficial-100) microns and calcification with overlying necrotic core was categorized separately and termed as lipid-interfacing deposits. This study showed that the frequency of spotty and large calcification was similar in patients with plaque rupture and stable lesions. Also, the frequency of calcification, for example, superficial-65 and superficial-100, was similar among patients presenting with STEMI versus SAP. Surprisingly, lipid-interfacing deposits were also not significantly different between the 2 cohorts. The baseline characteristics of the SAP were different from those of STEMI, with significant differences in age, previous myocardial infarction, lower incidence of diabetes mellitus, and current smoking status, making the comparison somewhat difficult. Because previous OCT and IVUS studies have reported that the location of calcification relative to the gravitational center of the vessel impacts on overall plaque vulnerability, this study seems an outlier. This study findings are hard to grasp because the pathological findings reported by our group in both postmortem radiography and histological sectioning of coronary arteries show obvious differences. We found that calcification was indeed less at the site of plaque rupture with the majority, that is, nearly three fourth of cases showing speckled calcification on radiography, which was defined as calcification <2 mm in length, whereas by histology we identified calcification as fragmented occupying 0.6±0.17mm², which equated as 6% to 8% of the plaque area.

It is important to distinguish speckled calcification, which can be derived from postmortem radiography and histological sections of human autopsy samples, with spotty calcification in this study. The 2 studies define speckled and spotty calcification differently. In this study, spotty calcification had to be <4 mm in length and <90° arc, which could involve as much as 50% of plaque area as illustrated by the OCT image shown in Figure 1 in the study by Ong et al, and could be located in the nonrupture site within 5 to 15 mm proximal and distal. Our definition of speckled calcification is <2 mm in size by radiograph at the site of rupture. Consequently, the definition of spotty calcification by OCT as adopted in this study may be more representative of overall calcium burden rather than the presence of speckled calcification in the proximity of ruptured plaque. Owing to differences in image resolution, 3-dimensional processing and the inherent limitation of penetration depth during OCT image acquisition, this technology may not be sensitive enough to assess smaller areas of calcification.

From our sudden death registry, the extent of calcification assessed by both postmortem radiographic assessment and histological sectioning showed least calcification in plaque erosion, followed by plaque rupture and vulnerable plaque (thin-cap fibroatheroma); however, maximum calcification being observed in healed plaque ruptures (stable plaques). On radiographic assessment healed plaque ruptures mostly showed either fragmented (2–5 mm) or diffuse (>5 mm) calcification.
A large number of CT studies evaluating coronary calcification score have shown a positive relationship between high coronary artery calcification score and overall plaque burden as well as future events. However, broken down to individual atherosclerotic plaque types, recent studies have shown that positive remodeling, low attenuated plaque, and spotty calcification are predictors of plaque vulnerability. Motoyama et al demonstrated that in patients presenting with acute coronary syndrome compared with those presenting with SAP, the presence of above criteria was predictive of future events, whereas the presence of large calcification was a negative predictor. Also, large calcifications were more frequently observed in SAP lesions when compared with acute coronary syndrome lesions. Ehrara et al showed that IVUS-identified spotty calcification, which was defined as calcium deposits within an arc of <90°, was most frequently observed in acute myocardial infarction (51%), followed by unstable angina pectoris (40%), and SAP (30%; P < 0.001). The longitudinal extension of calcification was significantly greater in SAP (4.3 ± 3.2 mm) compared with unstable angina pectoris (1.9 ± 1.8 mm) and acute myocardial infarction (2.2 ± 1.6 mm; P < 0.0001), which is similar to results from our postmortem radiographic assessment.

OCT is a high resolution intravascular imaging technique; however, the depth of penetration is limited, especially in lesions with necrotic core with or without macrophages (Table). Calcific deposits are often located close to the media and consequently areas of calcification can be missed by OCT. Ong et al assessed not just the site of plaque rupture in STEMI and the site of maximal narrowing in SAP, but actually assessed 5 to 15 mm proximal and distal to the culprit site and showed no difference in extent of calcification between those with STEMI and SAP. This is surprising in many ways because lesions found in patients presenting with acute myocardial infarction were associated with less calcification compared with patients presenting with SAP, which is supported by similar assessment in IVUS13 and OCT studies.

More recently, Dweck et al have developed a novel non-invasive assessment of coronary plaque, using radiolabeled 18F-fluorodeoxyglucose (18F-FDG) and 18F-sodium fluoride (18F-NaF) to visualize regions of active inflammation and calcification on positron emission tomography–CT. The subsequent study showed that high 18F-NaF uptake was observed at sites of plaque rupture in carotid arteries. Moreover, high-risk features of coronary arteries based on IVUS (ie, positive remodeling, microcalcification, and necrotic core) were more frequently observed in plaques with 18F-NaF uptake as compared with those without. Noninvasive imaging by 18F-NaF positron emission tomography–CT, therefore, may be another option for the detection of vulnerable plaque and predict future events representing calcification as a marker of activity of plaques.

In summary, OCT has a higher resolution than other invasive or noninvasive modalities; however, the assessment of calcification in lesions with overlying thrombus or macrophage/necrotic core is limited and calcified areas are often missed within or behind necrotic core close to media and within macrophage-rich regions. We need to pay more attention to the various features of atherosclerotic plaques and also not collect data from highly selected patients that may lead us astray and off target in our quest to diagnose vulnerable lesions.

### Table. Assessment of Calcification

<table>
<thead>
<tr>
<th>Histology (Gold Standard)</th>
<th>Angiography</th>
<th>CT</th>
<th>IVUS</th>
<th>OCT</th>
<th>PET-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td>&lt;1 μm</td>
<td>100 μm</td>
<td>0.5–1.0 mm</td>
<td>100–200 μm</td>
<td>10–20 μm</td>
</tr>
<tr>
<td>Calcification in stable plaque</td>
<td>None</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Usefulness</td>
<td>+++++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Limitation</td>
<td>1. Low resolution</td>
<td>1. Low resolution</td>
<td>1. Low resolution</td>
<td>1. Invasive</td>
<td>1. Invasive</td>
</tr>
<tr>
<td></td>
<td>2. Invasive</td>
<td>2. Blooming artifact</td>
<td>3. Invisible with overlying necrotic core</td>
<td>2. Invisible when calcification coexists with macrophage/apoptosis/necrosis and when deep to necrotic core</td>
<td>1. No advantage over CT for the presence of spotty and diffuse Ca2+; however, blooming artifacts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Identifies active areas of calcification—needs more evidence</td>
<td></td>
</tr>
<tr>
<td>Calcification in plaque rupture</td>
<td>None</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++ (active Ca2+?)</td>
</tr>
<tr>
<td>Usefulness</td>
<td>+++++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<td>1. Invasive</td>
</tr>
<tr>
<td></td>
<td>2. Invasive</td>
<td>2. Blooming artifact</td>
<td>3. Invisible with overlying necrotic core</td>
<td>2. Penetration limited in the presence of red cell rich thrombus</td>
<td>1. Identifies active areas of calcification—needs more evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Invisible when calcification coexists with macrophage/apoptosis/necrosis and when deep to necrotic core</td>
<td></td>
</tr>
</tbody>
</table>

Ranking: +, possibly useful; ++, probably useful; ++++, useful; and ++++, definitely useful. CT indicates computed tomography; IVUS, intravascular ultrasound; OCT, optimal coherence tomography; and PET-CT, positron emission tomography–computed tomography.
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References

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