Evaluation by Multislice Computed Tomography of Atherosclerotic Coronary Artery Plaques in Non-Culprit, Remote Coronary Arteries of Patients With Acute Coronary Syndrome

Taeko Kunimasa, MD; Yuichi Sato, MD*; Kaoru Sugi, MD; Masao Moroi, MD

Background Patients with acute coronary syndrome (ACS) frequently have vulnerable plaques in the remote coronary arteries, suggesting that ACS is part of the pan-coronary process. In the present study the computed tomography (CT) plaque density in non-culprit atherosclerotic coronary artery lesions was evaluated by multislice computed tomography (MSCT) in patients with ACS and non-ACS.

Methods and Results MSCT was performed in 21 patients with ACS and 53 patients with non-ACS: 16 of the 21 ACS patients (76%) and 30 of the non-ACS 53 patients (57%) had non-calcified plaques in the non-culprit coronary arteries (p=0.18). CT-low-density plaques (CT density <68 Hounsfield units (HU)) were more frequent in the ACS group (13/16 patients, 81%) than in the non-ACS group (13/30 patients, 43%, p=0.03). In addition, the CT density of the non-culprit lesion was significantly lower in patients with ACS than in those with non-ACS (44.1±22.9 and 77.3±33.7 HU, respectively).

Conclusion Patients with ACS more frequently had CT-low-density plaques in the non-culprit, remote arteries than those with non-ACS, which suggests that ACS treatment should focus not only on stabilizing the culprit lesion but also on systemic stabilization of non-culprit lesions. (Circ J 2005; 69: 1346–1351)

Key Words: Acute coronary syndrome; Coronary artery plaque; Multislice computed tomography
angiography was defined as typical precordial chest pain (Braunwald class IB, IIB, IIIb)\textsuperscript{16} angiographic evidence of a stenosis >50% in 1 or more principal coronary arteries, and no increase in the serum CK activity. Stable angina was defined by symptoms of typical precordial chest pain and coronary angiographic findings of a stenosis >50% in 1 or more principal coronary arteries. Nineteen patients had undergone percutaneous coronary intervention of the culprit lesion (stent implantation in 16, directional atherectomy in 2 and percutaneous balloon angioplasty in 1). The location of the culprit lesion was the left anterior descending artery in 11, the left circumflex artery in 1, and the right coronary artery in 7 patients. Exclusion criteria included (1) chronic atrial fibrillation, (2) deteriorating renal function, (3) pregnancy, hyperthyroidism, or a known allergic reaction to contrast media, (4) severe left ventricular dysfunction (left ventricular ejection fraction <30%), or (5) known history of bronchial asthma with a contraindication to \textsuperscript{2}-blocker use. The study was approved by the hospital’s ethics committee and informed consent was obtained from all patients.

**MSCT**

MSCT (Aquilion 16, Toshiba Medical, Tokyo, Japan) was performed within 4 weeks from the onset of chest pain in the ACS group and within 24.7±22.6 days (range 1–91 days) prior to and 29.9±17.6 days (range 12–63 days) after angiographic studies in the non-ACS group. Patients received metoprolol (20–60 mg) 1 h before the MSCT scan if the heart rate was >68 beats/min in order to perform the half-reconstruction algorithm. SUBLINGUAL nitroglycerin (0.3 mg, Myocol Spray, Toa Eiyo, Tokyo, Japan) also was administered 5 min prior to the scan. Image acquisition was performed during an inspiratory breath hold preceded by inhalation of oxygen (4.0 L/min). A bolus of 80 ml contrast agent (Optiray 320, Tyco Healthcare, Tokyo, Japan) was injected intravenously at a rate of 3.0 ml/s. As soon as the signal density level in the ascending aorta reached a predefined threshold of 100 Hounsfield units (HU), acquisition of the CT data and the ECG trace were started. The volume data set for coronary artery imaging was acquired in spiral mode, with a collimation of 16×0.5 mm, a gantry rotation of 400 ms, helical pitch of 3.2, tube energy of 120 kV, and an effective tube current of 400 mA. The patient’s ECG was digitized and monitored continuously during image acquisition.

**MSCT Image Reconstruction and Plaque Evaluation**

The raw data from the scans were reconstructed using a half-scan algorithm in all patients. The end of the reconstruction period was set at the peak of the P wave on the monitoring ECG\textsuperscript{11,17} The reconstructed image data from the MSCT angiography were transferred to a computer workstation (M900 quadra, AMIN, Tokyo, Japan) for post processing.

Following visual inspection of the volume-rendered images, which depicted the gross configuration of the coronary artery lumen, the coronary artery plaques were inspected carefully on both the axial and curved multiplanar reconstruction images. Coronary artery lesions in the non-culprit, remote coronary arteries were evaluated on the axial and cross-sectional multiplanar reconstruction images. Coronary artery lesions were identified as non-calcified plaque when they occupied more than 25% of the coronary lumen and were low density. Four randomly selected regions of interest (≥1.0 mm\textsuperscript{2}) were positioned within each plaque, and the lowest CT density was defined as the minimum. The analysis of the plaques was performed for all major coronary arteries with a diameter ≥2.0 mm. When there were multiple non-calcified plaques in the non-culprit coronary artery, the plaque with the lowest CT density was analyzed. Plaques with the lowest CT density (<68 HU) were considered as CT-low-density plaques, based on IVUS observations described later.

We evaluated the images with a window level of 83 HU and a width of 230 HU for non-calcified plaques, and those with 400 HU and 900 HU, respectively, for the identification of calcified plaques. Severely calcified plaques accompanying appreciable artifact were not analyzed.

**Definition of CT-Low-Density Plaque by IVUS**

IVUS of the culprit arteries was performed in another series of 38 lesions (28 patients: 19 with ACS and 9 with non-ACS). All IVUS studies were of the de novo lesions in the culprit arteries as described previously\textsuperscript{18} The CT density of soft plaques on IVUS was determined. Soft plaque was defined as plaque tissue with an echogenicity lower than the adventitia. Hypoechoic plaque was defined as plaque tissue with an echogenicity lower than the adventitia\textsuperscript{12,14,15,19} The lesions visualized by MSCT were identified on IVUS using landmarks such as bifurcations, the distance from the coronary artery ostia and branches. CT-low-density plaque on MSCT was defined as plaque with a density less than the mean density +2 standard deviations (SD).

**Statistics**

Statistical analyses were performed using SPSS software (version 11.0) (SPSS Inc, Chicago, ILL, USA). Continuous variables were described by their means and standard deviations. Analysis of variance followed by Bonferroni/Dunn was used to compare the mean of plaque density, age and high-sensitivity C-reactive protein (hsCRP) between the ACS and non-ACS groups. The percentage of those having

### Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=74)</th>
<th>ACS (n=21)</th>
<th>Non-ACS (n=53)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.7±1.4</td>
<td>60.8±2.3</td>
<td>66.5±1.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>61/13</td>
<td>20/1</td>
<td>41/12</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16 (22)</td>
<td>5 (24)</td>
<td>11 (21)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>50 (68)</td>
<td>11 (52)</td>
<td>39 (74)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>36 (49)</td>
<td>7 (33)</td>
<td>29 (56)</td>
<td>0.12</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>42 (57)</td>
<td>13 (62)</td>
<td>29 (55)</td>
<td>0.61</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>29 (40)</td>
<td>5 (24)</td>
<td>24 (45)</td>
<td>0.11</td>
</tr>
<tr>
<td>hsCRP levels (mg/dl)</td>
<td>0.15±0.21</td>
<td>0.19±0.25</td>
<td>0.13±0.19</td>
<td>0.31</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; hsCRP, high-sensitivity C-reactive protein.
coronary risk factors and CT-low-density plaques were compared between the 2 groups by chi-square analysis. Linear regression analysis was performed to determine interobserver variability in plaque CT density measurements. For the evaluation of image quality, 2 observers judged each coronary artery as assessable or non-assessable for plaque density measurements. Cohen’s kappa was calculated for the interobserver variability. The interobserver variability for the measurement of CT densities within the plaque was evaluated by Pearson’s correlation.

**Results**

The patient characteristics are summarized in Table 1. ACS patients were younger than non-ACS patients, but there were no statistical differences between the 2 groups in the incidence of diabetes mellitus (patients receiving long-term insulin, oral hypoglycemic therapy, or with fasting blood glucose >126 mg/dl), hypertension (patients receiving long-term antihypertensive medication), hypercholesterolemia (patients being treated with a cholesterol-lowering diet or medication, or having a total serum cholesterol level >220 mg/dl) and statin use. The hsCRP value was comparable between groups and there was no statistical difference.

MSCT scans of sufficient quality for plaque evaluation were obtained without complications in all 74 patients (the kappa value was 1.0). The scan was generally completed within 10 min and post-processing and data evaluation required 20–30 min depending on the complexity of the coronary artery. The mean heart rate at the beginning of imaging was 56±7.4 beats/min and increased to 65±7.5 beats/min at the end of the scan.

**Plaque Texture**

Pearson’s analysis revealed that there was an excellent correlation in the evaluation of plaque CT density between the 2 observers (observer A: range 6–137 HU, mean 65.8±34.1 HU; observer B: range 7–143 HU, mean 67.3±35.3 HU, median 59.5 HU, R²=0.85, p<0.0001, Fig 1A). Twenty two of 38 plaques were identified as soft plaques on IVUS. The mean plaque CT density of IVUS-defined soft plaques was 33.7±16.9 HU (range 4–65 HU, Fig 1B). The upper limit of the CT density was 67.5 (mean +2 SD) and plaques were defined as CT-low-density when they had a density <68 HU on MSCT. Non-calcified plaques were detected in 16 of 21 (76%) patients with ACS and in 30 of 53 (57%) patients with non-ACS, although the difference did not reach statistical significance (p=0.18,
Non-calcified plaques of non-culprit coronary arteries were defined as CT-low-density plaques in 13 of 16 (81%) patients with ACS and in 13 of 30 (43%) patients with non-ACS and the incidence of CT-low-density plaques among non-calcified lesions was significantly higher in patients with ACS than in those with non-ACS (p=0.03, Fig 2B). The number and locations of both the non-calcified and CT-low-density plaques in non-culprit coronary arteries is shown in Table 2. In addition, the lowest CT density in the non-culprit lesions was significantly lower in the ACS group compared to the non-ACS group (p=0.001, Fig 3).

### Table 2: Number and Location of Non-Calcified Plaques in Non-Culprit Coronary Arteries

<table>
<thead>
<tr>
<th>Location</th>
<th>ACS group (n=23)</th>
<th>Non-ACS group (n=31)</th>
</tr>
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<tbody>
<tr>
<td>LAD</td>
<td>7 (7)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>LCX</td>
<td>8 (5)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>RCA</td>
<td>8 (3)</td>
<td>11 (6)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. Parentheses indicate the number of computed tomography-low-density plaques.

ACS, acute coronary syndrome; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. Parentheses indicate the number of computed tomography-low-density plaques.
group than in the non-ACS group (44.1±22.9 and 77.3±33.7 HU, respectively, p=0.001, Fig 3).

Representative MSCT images in a patient with ACS and one with non-ACS are shown in Figs 4 and 5, respectively.

Discussion

Our study showed that patients with ACS more frequently had CT-low-density plaques in their non-culprit coronary arteries than patients with non-ACS. We also showed that the minimum CT density within the plaque was significantly lower in ACS patients than in those with non-ACS. These findings are consistent with previous studies using IVUS, which showed that the majority of patients with ACS had multiple plaque ruptures in the non-culprit coronary artery. The presence of rupture-prone, vulnerable plaques in non-culprit coronary arteries has also been observed by coronary angioscopy. Taken together, these findings, including those from the present study, suggest that ACS is a consequence of simultaneous development of vulnerable plaques in the whole coronary artery system. Recent observations have suggested that ACS is frequently associated with inflammation, as documented by the increase in hsCRP levels and circulating cytokines and with the increased fibrinolysis status. In fact, Hong et al. and Tanaka et al. found an association between elevated hsCRP levels and the presence of plaque rupture in their IVUS studies, although our study did not show statistical difference in hsCRP levels between patients with and without ACS.

Study Implications

Although a culprit lesion is clinically important in the early phase of ACS and is usually treated by catheter intervention, a certain number of patients develop plaque ruptures in sites remote from the culprit coronary artery. Thus, detection of rupture-prone, vulnerable coronary artery plaques in the whole coronary artery system is essential for therapeutic decision making. For example, aggressive lipid-lowering therapy by statins should be considered if there are not only culprit lesions but also additional atherosclerotic lesions in remote sites. Although IVUS is the gold-standard for detecting and characterizing plaques, it is limited by its invasive nature and cannot be performed for non-culprit coronary arteries in the routine clinical setting. Our study suggests that coronary MSCT angiography is an appropriate substitute of IVUS for such purposes.

Study Limitations

First, the spatial resolution (0.5 mm) of our MSCT equipment limited the fine morphological assessment of plaque texture, such as thickness of the fibrous caps and the volume of the lipid core. Thus, accurate assessment of vulnerable plaque is not possible with this technique. Second, the frequent observation of thrombus associated with ruptured plaques in non-culprit arteries in patients with ACS might have resulted in erroneous CT measurements. At present, there are no data concerning the ability of MSCT to distinguish thrombi from non-calcified plaques. We excluded heavily calcified plaques from the analysis because the partial volume effect from calcification might have led to erroneous CT density measurements. However, a recent observation suggests that rupture occurs frequently in patients with acute myocardial infarction and plaques with spotty calcification. Exclusion of calcified plaques might have resulted in underestimation of the total plaque burden in ACS patients. Third, our definition of CT-low-density plaques (<68 HU) was based on a small number of lesions (n=22) detected on IVUS. However, no direct comparison has been made between the plaque CT density obtained by 16-detector-row CT, which provides slice thickness of 0.5 mm, and plaque morphology on IVUS. CT density may vary depending on the slice thickness and density of the contrast-enhanced arterial lumen, and on the complexity of plaque composition. More detailed observations are definitely needed to define the morphological features of MSCT-detected plaque in comparison with other imaging modalities used to assess plaque vulnerability, such as coronary angiography and optical coherent tomography.

These limitations aside, our study demonstrated the feasibility of using MSCT to evaluate plaque texture. Because ACS appears to be a consequence of plaque development within the total coronary system, a long-term, prospective study is definitely needed to assess the incidence of future coronary events in ACS patients who have CT-low-density plaques in the non-culprit coronary arteries.

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References

Coronary Artery Plaque in Non-Culprit Arteries


