Non-Invasive Assessment of Plaque Rupture by 64-Slice Multidetector Computed Tomography
——Comparison With Intravascular Ultrasound——

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Background

Plaque rupture and secondary thrombus formation play key roles in the onset of acute coronary syndrome (ACS). Multidetector computed tomography (MDCT) allows the non-invasive assessment of coronary artery stenosis and plaque properties. In this study, we investigated whether 64-slice MDCT could non-invasively detect a plaque rupture in patients with de novo angina.

Methods and Results

The study population comprised 67 patients with de novo angina. All patients underwent contrast-enhanced 64-slice MDCT and intravascular ultrasound (IVUS). Patients were divided into a plaque rupture group (n=27) and a non-rupture group (n=40) based on the IVUS. The 64-slice MDCT revealed that the prevalence of an ulcer-like enhancement space (37% vs 5%, p<0.01), a ring-like sign (41% vs 18%, p=0.04), in the plaque rupture group was higher than those in the non-rupture group. Maximum plaque thickness (2.1±0.9 mm vs 1.6±1.0 mm, p=0.04), outer vessel area (17.6±4.9 mm² vs 13.4±5.0 mm², p=0.01), percentage plaque area (82.3±9.1% vs 73.4±15.7%, p=0.01), and remodeling index (1.11±0.18 vs 1.01±0.15, p=0.04) of the plaque rupture group were all significantly larger than those of the non-rupture group.

Conclusions

The 64-slice MDCT can identify differences in lesion morphologies between ruptured plaques and non-ruptured plaques. From our results, the 64-slice MDCT might provide a useful tool for the non-invasive detection of plaque rupture. (Circ J 2008; 72: 1276–1281)

Key Words: Computed tomography; Imaging; Intravascular ultrasound; Plaque rupture

Plaque rupture and secondary thrombus formation play key roles in the onset of acute coronary syndrome (ACS). Many post mortem studies have addressed, in cross-section, the morphology of plaque rupture2–10. We have previously reported that pre-intervention intravascular ultrasound (IVUS) can accurately identify lesion morphology, including the features of plaque rupture, in acute myocardial infarction (AMI).11,12 There are, however, no non-invasive modalities that allow the assessment of plaque rupture in vivo.

Multidetector computed tomography (MDCT) allows the non-invasive assessment of coronary artery stenosis13,14. Recent advances in MDCT, especially in 64-slice MDCT, have dramatically improved spatial and temporal resolution15. These advances have brought us not only visualization of the coronary artery lumen, but also assessment of plaque properties, that is, hypodense plaque and plaque remodeling16,17.

In this study, we investigated whether 64-slice MDCT can non-invasively detect a plaque rupture in culprit sites in patients with de novo angina.

Methods

Population

The population used in the present study was drawn from 108 consecutive de novo patients who were admitted to Osaka Ekisaiaiki Hospital from December 2005 to September 2006, to evaluate ischemic heart disease by invasive coronary angiography (CAG). The presence of ischemia was confirmed by the objective evidence obtained from a ²⁰¹Thallium scintigraphy, dobutamine echocardiography, and/or an ECG in all patients. We planned to perform MDCT before invasive angiography and IVUS during invasive angiography.

The definition of ACS (non-ST-segment elevation myocardial infarction (MI), unstable angina) established by a previous multicenter MDCT study was used18. The definition of a non-ST-segment elevation MI was based on new findings of ST-segment depression of more than 0.1 mm, a T-wave inversion of at least 0.4 mm in at least 2 leads or symptoms consistent with AMI and the presentation of elevated serial levels of troponin-I (>0.09 ng/ml) in association with any or all of the previous criteria.

The definition of unstable angina was based on the unstable pattern of chest pain (at rest, new onset, or crescendo angina) coinciding with objective evidence of ²⁰¹Thallium scintigraphy, dobutamine echocardiography, and/or CAG demonstrating a >50% coronary stenosis.
Culprit lesions were identified on the basis of a combination of angiographic findings, ECG changes, defect of scintigraphy, and trans-thoracic echo findings.

Patients who presented with ST segment elevation MI (n=18), congestive heart failure (n=7), non-adequate MDCT imaging due to heavily calcified lesions (n=6), non-adequate IVUS images (n=3), arrhythmia (n=4), or chronic renal failure on artificial dialysis (n=2) were excluded from the present study. Patients whose culprit site could not be identified on angiography (n=3) were also excluded.

This study complies with the Declaration of Helsinki. The protocol for the study was approved by the Ethics Committee of Osaka Ekisaikai Hospital. Written informed consent was obtained from all participants prior to initial CAG.

Scan Protocol of 64-Slice MDCT

The 64-slice MDCT data were acquired using a SOMATOM Sensation 64 cardiac (Siemens Medical Solutions, Forchheim, Germany). All patients with a heart rate >70 beats/min received a ß-blocker (50–100 mg oral metoprolol) before the CT scan. A bolus of 65 ml of contrast (Omnipaque350, Daiichi Pharmaceutical Co, Ltd, Tokyo, Japan) was injected intravenously at a flow rate of 3.5–4.5 ml/s followed by a 30 ml saline injection at the same flow rate.

Scans were obtained with a collimation of 0.66 mm with dual focus spots per detector row, a table feed of 6.0 mm/rotation, a tube current of 750–850 mA depending on patient body weight, a tube voltage of 120 kV, and a gantry rotation speed of 330 ms. An estimated mean effective radiation dose was approximately 13–16 mSv.

Image Analysis of the Coronary Arteries by a 64-Slice MDCT

The analysis of 64-slice MDCT image data was performed by 2 experienced readers (KS, KY) blinded to the IVUS findings. Quantitative measurements were performed under concordance of 2 observers.

Overlapping transaxial images were reconstructed using a medium sharp convolution kernel (B30f) with an image matrix of 512×512 pixels, slice thickness of 0.6 mm, and an increment of 0.4 mm using an ECG-gated 1-segment scan algorithm with a resulting temporal resolution of 330 ms in the center of rotation. Images were initially reconstructed at 65% of the cardiac cycles. All main coronary arteries and large (>2 mm) side branches were evaluated irrespective of image quality. Maximum intensity projections were used to identify coronary lesions, and multi-planar reconstructions in 2 orthogonal longitudinal axes across the coronary lumen were utilized to classify lesions as significant stenosis, which was defined as a diameter reduction of >50%.

The outer vessel area and arterial remodeling index were assessed by cross-sectional images. The arterial remodeling index was defined as the ratio between the outer vessel area at the site of maximal luminal narrowing and the mean of the proximal and distal reference sites. Calcium depositions were classified as long (>3 mm), short (≤3 mm), or none.

The setting to evaluate coronary plaques is obtained, on average, at a width representing 200% of the mean intensity within the lumen and at a level representing 65% of the lumen intensity.

Ulcer-Like Enhancement Space

An ulcer-like enhancement space was defined as: (1) the contrast pooling space existing in the coronary plaque and/or in the caved-in space from the coronary lumen toward the plaque; (2) an ulcer-like space possessing continuities from the coronary lumen; and (3) having a ratio of computed tomography (CT) attenuation between the ulcer-like space and those in the coronary lumen between 0.70 and 1.0. A representative case of an ulcer-like enhancement space is shown in Fig 1.
Ring-Like Sign  A ring-like sign was defined as: (1) the presence of a ring of high attenuation around certain coronary artery plaques; and (2) the CT attenuation of a ring presenting higher than those of the adjacent plaque and no greater than 130 HU. A representative case of a ring-like sign is shown in Fig 2.

Invasive CAG
In all patients, CAG was performed using a 6F Judkins-type catheter from a femoral or radial approach. All patients received an intravenous bolus injection of 3,000 IU of heparin and intracoronary isosorbide dinitrate (2 mg) before angiography.

Coronary angiograms were reviewed separately by an independent observer (SJ), who was unaware of the 64-slice MDCT and IVUS findings.

An angiographic lesion was considered complex when irregular borders and/or intraluminal lucencies suggestive of an ulcer were present.

Quantitative angiography was performed offline using a CMS-QCA system (CMS-MEDIS; Medical Imaging Systems, Leiden, The Netherlands).

IVUS Imaging Protocol
After completion of diagnostic CAG and before any intervention, all patients were evaluated with IVUS. The IVUS catheter (2.9 F Atlantis, 40 MHz, Boston Scientific Corporation/SCIMED, Maple Grove, MN, USA) was carefully advanced distal to the lesion under fluoroscopic guidance. It was then pulled back automatically from the distal portion at 0.5 mm/s, facilitating observation of the lesion. IVUS images were recorded on S-VHS video for offline analysis.

The images were digitized and analyzed with commercially available software for longitudinal reconstructive IVUS image analysis (Netra IVUS, ScImage Inc, Los Altos, CA, USA). While pulling back the catheter, we manually infused a contrast medium suitable for IVUS imaging to carefully observing the lesion.

IVUS Image Analysis
IVUS images were interpreted by 2 independent experienced observers (AT, HT), who were unfamiliar with the 64-slice MDCT data. Evaluation of 2-D lesion morphology and other measurements during IVUS was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). We defined IVUS plaque rupture lesions as follows: (1) lesions with fissure/dissection; or (2) lesions without fissure/dissection but in which injection of saline or contrast medium confirmed a communication between the plaque and the coronary artery lumen.

Patients were divided into plaque rupture and non-rupture groups on the basis of the presence of plaque rupture at the culprit site, as detected by IVUS, to compare the MDCT findings. The anatomical cross correlation between MDCT and IVUS was achieved using the nearest bifurcation points in CAG as reference markers and by measuring the distance from bifurcation point in MDCT images and IVUS images.

Statistical Analysis
Statistical analysis was performed using StatView 5.0J (Abacus Concept, Inc, Berkeley, CA, USA). Results are expressed as mean±SD for continuous variables. Qualitative data are presented as numbers (%). Continuous variables have been compared using the ANOVA test, and categorical data have been compared using the chi-square test with Fisher’s exact test. A p value <0.05 was considered statistically significant.

Results
Patient Characteristics
Both IVUS and MDCT were performed in 67 patients without any serious complications. All patients successfully underwent percutaneous coronary intervention.

There were 31 (46%) patients with ACS, and IVUS identified plaque rupture in 27 (40%) patients. Patient characteristics are summarized in Table 1. There were 5 patients...
who presented with clinically stable symptoms but showed plaque rupture at the culprit site. Prevalence of ACS and history of smoking was significantly higher in the plaque rupture group as compared to the non-rupture group.

**Invasive Angiographic Results**

Invasive angiographic results are summarized in Table 2. There were no differences in QCA data of invasive angiography between the plaque rupture group and non-rupture group. Complex lesions were more often associated with culprit sites in the plaque rupture group.

**Plaque Rupture Detected by IVUS and MDCT Findings**

The mean time between MDCT and IVUS was 1.4 days (range 1–3 days).

No patient received any additional medication between when MDCT and IVUS were conducted.

MDCT findings for both groups are summarized in Table 3. Ulcer-like enhancement space, ring-like sign, maximum plaque thickness, outer vessel area, percentage plaque area, and remodeling index of the plaque rupture group were significantly larger than those of the non-rupture group. The CT attenuation values of culprit plaques in the plaque rupture group were lower than those in the non-rupture group (46.8±30.0 HU vs 73.4±50.0 HU, p=0.02).

**Discussion**

**MDCT for Plaque Rupture**

In this study, it was demonstrated that the morphologies present in ruptured plaques and non-ruptured plaques as detected by 64-slice MDCT were quite different. It is widely believed that ACS is mainly caused by plaque rupture and secondary thrombus formation. Previous postmortem studies have suggested that plaque rupture occurs most frequently at the point where the fibrous cap is thinnest and most heavily infiltrated by macrophage foam-cells, a point most often found in the shoulder of eccentric plaque. Therefore, the proposed morphological features of vulnerable plaque are a thin fibrous cap with a large lipid core; a fissured/injured plaque; and a plaque presenting positive remodeling. We considered that ulcer-like enhancement space might correspond to the cavity of a ruptured plaque. All patients who presented ulcer-like enhancement space had plaque rupture at the culprit site in IVUS. A previous invasive angiography and an IVUS study reported that a complex lesion in an invasive angiography suggestive of an ulcer was considered to be a ruptured plaque. In our study, the complex lesion in invasive angiography was also more frequently observed in the plaque rupture group. The ulcer-like enhancement space might directly indicate the presence of plaque rupture on MDCT.

It is unclear what status the a ring-like sign reflects. Interestingly, some patients with stable symptoms presented with a ring-like sign. We consider a ring-like sign to be an indicator not for an already ruptured plaque but for a rupture-prone plaque. A recent study suggested that the proliferation of vasa vasorum is part of the “response to injury” phenomenon in the process of plaque formation. Fleiner et al showed that there were strong correlations between neovessel formation and macrophage infiltration in atherosclerotic plaque, suggesting vasa vasorum density as a surrogate marker of plaque vulnerability. We speculate that a ring-like enhancement sign reflects this highly active neo-

**Table 1 Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Plaque rupture</th>
<th>Non-rupture</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>27</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60±11</td>
<td>64±9.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Men</td>
<td>23 (85)</td>
<td>27 (68)</td>
<td>0.10</td>
</tr>
<tr>
<td>ACS</td>
<td>22 (81)</td>
<td>9 (23)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>18 (67)</td>
<td>20 (50)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (52)</td>
<td>17 (42)</td>
<td>0.45</td>
</tr>
<tr>
<td>Smoking</td>
<td>16 (59)</td>
<td>13 (33)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (37)</td>
<td>24 (60)</td>
<td>0.07</td>
</tr>
<tr>
<td>Obesity (BMI &gt;25)</td>
<td>4 (15)</td>
<td>6 (15)</td>
<td>0.99</td>
</tr>
<tr>
<td>hs-CRP (ng/L)</td>
<td>3.9±6.5</td>
<td>2.7±5.2</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Data presented are mean ± SD or numbers (%). ACS, acute coronary syndrome; BMI, body mass index; hs-CRP, high-sensitive C-reactive protein.

**Table 2 Invasive Angiographic Findings**

<table>
<thead>
<tr>
<th></th>
<th>Plaque rupture (n=27)</th>
<th>Non-rupture (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culprit site</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Left descending artery</td>
<td>18 (67)</td>
<td>25 (63)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>1 (4)</td>
<td>5 (13)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>8 (30)</td>
<td>10 (25)</td>
<td></td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>16 (59)</td>
<td>28 (70)</td>
<td>0.17</td>
</tr>
<tr>
<td>Complex lesion</td>
<td>14 (52)</td>
<td>11 (28)</td>
<td>0.04</td>
</tr>
<tr>
<td>QCA data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal lumen diameter (mm)</td>
<td>0.6±0.7</td>
<td>0.7±0.7</td>
<td>0.55</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.1±0.6</td>
<td>2.9±0.8</td>
<td>0.38</td>
</tr>
<tr>
<td>% diameter stenosis</td>
<td>79.6±21.8</td>
<td>74.9±22.9</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data presented are number (%) or mean ± SD.

**Table 3 Comparison Between IVUS and 64-Slice MDCT**

<table>
<thead>
<tr>
<th></th>
<th>Plaque rupture (n=27)</th>
<th>Non-rupture (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer-like enhancement space</td>
<td>10 (37)</td>
<td>2 (5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ring-like sign</td>
<td>11 (41)</td>
<td>11 (28)</td>
<td>0.04</td>
</tr>
<tr>
<td>Calcium deposition</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long (&gt;3 mm)</td>
<td>2 (7)</td>
<td>11 (28)</td>
<td></td>
</tr>
<tr>
<td>Short (≤3 mm)</td>
<td>7 (26)</td>
<td>5 (13)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>18 (67)</td>
<td>24 (60)</td>
<td></td>
</tr>
<tr>
<td>Maximum plaque thickness (mm)</td>
<td>2.1±0.9</td>
<td>1.6±1.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Outer vessel area (mm²)</td>
<td>17.6±4.9</td>
<td>13.4±5.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Luminal area (mm²)</td>
<td>3.0±1.3</td>
<td>3.3±1.7</td>
<td>0.41</td>
</tr>
<tr>
<td>% plaque area</td>
<td>82.3±9.1</td>
<td>73.4±15.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Remodeling Index</td>
<td>1.1±0.18</td>
<td>1.0±0.15</td>
<td>0.04</td>
</tr>
<tr>
<td>CT attenuation values (HU)</td>
<td>46.8±30.0</td>
<td>73.4±50.0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data presented are numbers (%) or mean ± SD.

IVUS, intravascular ultrasound; MDCT, multidetector computed tomography; CT, computed tomography.

vascularization in vasa vasorum in vulnerable plaque.

Hoffmann et al, Imazeki et al and Inoue et al have reported that the remodeling index and plaque area of an ACS lesion were larger than those of non-ACS lesions as investigated by MDCT. In this study, we also confirmed that the remodeling index and plaque area of the plaque rupture group was higher than that of the non-plaque rupture group. Recently, Leber et al and Motoyama et al have reported that a 64-slice MDCT non-invasively detects different types of coronary plaques, including lipid pool, which is located in the proximal coronary system. These
findings from MDCT might correspond to a large necrotic core in pathological analysis. Hoffmann et al further reported that the prevalence of non-calcified plaque was 100%, 62% and 77% in culprit lesions of patients with ACS, stable lesions of patients with ACS and in stable angina, respectively. In this study, non-calcified plaque at the culprit site was observed in 70% of patients with plaque rupture.

Clinical Implication

Non-invasive detection of plaque rupture/vulnerable plaque is a great dream for cardiologists everywhere. The available data indicate that 64-slice MDCT can detect the morphological features of ruptured plaque. Therefore, we assume extensive clinical implications.

A 3 vessel IVUS study revealed that ruptured plaque exists not only at the culprit site, but also in the whole coronary tree and patients with multiple plaque rupture showed poor prognosis after onset of ACS. Therefore, it is very important to search for additional plaque ruptures in remote sites in ACS patients. MDCT can assess the whole coronary artery system non-invasively.

We previously reported that a lesion with plaque rupture is associated with stent restenosis. MDCT can detect both coronary artery stenosis and coronary plaque characteristics including plaque rupture. MDCT can contribute to the build-up of strategy for percutaneous coronary intervention before invasive angiography.

Study Limitations

It can be said that there are a number of limitations associated with the present study. We excluded many patients from the original population. Therefore, the study population was relatively small. Lesions containing small-ruptured plaques might have been misread as non-ruptured plaques by IVUS. Also, a sub-occluded artery is devoid of pressure and undergoes elastic recoil with a marked reduction in all volumetric measurements, and so positive remodeling and its assessment can be substantially influenced by either the presence or absence of physiological pressure in the artery. Additionally, thrombus exists at the culprit site in the acute phase of ACS, and it is difficult for either IVUS or MDCT to distinguish thrombus from plaques. There is a possibility that the plaque volumes reported in this study have misrepresented actual plaque volumes. Calcium deposits deeply affected the reading of MDCT images. There is also a possibility that tandem plaque might be misread as ulcer-like enhancement space. Although a 64-slice MDCT can identify differences in lesion morphologies between ruptured plaques and non-ruptured plaques, further studies to identify rupture-prone plaques are needed to aid in the prevention of ACS events.

References

8. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994; 89: 36 – 44.


