Prognostic Value of Non-Obstructive CT Low-Dense Coronary Artery Plaques Detected by Multislice Computed Tomography

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Background  The prognostic value of non-obstructive, CT low-dense plaques (CTLDP) on multislice computed tomography (MSCT) for the prediction of nonfatal acute myocardial infarction (AMI), unstable angina (UA) and cardiac death has not yet been defined.

Methods and Results  In the present study 810 patients who underwent MSCT and had non-obstructive coronary artery disease were followed up for the occurrence of AMI, UA and cardiac death. Non-obstructive CTLDP were defined as plaques with a CT density <68 Hounsfield units, accompanied by mild to moderate coronary artery stenosis (25–75%). Patients were followed-up for 1,062±544 days for the occurrence of (1) acute coronary syndrome (ACS) including nonfatal AMI and UA, and (2) cardiac death. CTLDP were detected in 189 patients (23.3%). The annual event rate of AMI, UA, ACS and cardiac death was 0.91%, 0.91%, 1.82% and 0.36%, respectively, in patients with CTLDP and 0.10%, 0.55%, 0.66% and 0.21%, respectively, in patients without CTLDP. The event rate of ACS was significantly higher in patients with CTLDP than in those without CTLDP (p<0.001). Multivariate Cox proportional regression analysis revealed that previous MI and the presence of CTLDP were independent predictors of ACS.

Conclusion  Non-obstructive CTLDP detected by MSCT yield prognostic information toward the identification of ACS.

Key Words:  Acute coronary syndrome; CT low-dense plaque; Multislice computed tomography

Multislice computed tomography (MSCT) enables visualization of not only coronary artery stenoses and occlusions1–4 but also coronary artery plaque of various textures5–12. Previous studies have repeatedly shown that non-calcified, CT low-dense plaques (CTLDP) on MSCT correspond well to rupture-prone soft plaques on intracoronary ultrasound5,6,9,10,12 and on coronary angiography8. We have shown that patients with acute coronary syndrome (ACS) are likely to have CTLDP and that the CT density of the culprit coronary artery lesion is significantly lower in patients with ACS as compared with that in patients with stable angina8. Furthermore, we have also shown that patients with evolving ACS consistently have CTLDP in their culprit coronary artery lesions7,13. Because ACS is a consequence of coronary artery plaque rupture and subsequent thrombosis14,15, it would be reasonable to speculate that patients who have CTLDP are more likely to have coronary events, including ACS and sudden cardiac death, than patients without plaque. In this study of a large population, we evaluated the prognostic value of non-obstructive

CTLDP in mild to moderate coronary artery stenosis for future cardiac events.

Materials

Methods

Background  The prognostic value of non-obstructive, CT low-dense plaques (CTLDP) on multislice computed tomography (MSCT) for the prediction of nonfatal acute myocardial infarction (AMI), unstable angina (UA) and cardiac death has not yet been defined.

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Conclusion  Non-obstructive CTLDP detected by MSCT yield prognostic information toward the identification of ACS.

Key Words:  Acute coronary syndrome; CT low-dense plaque; Multislice computed tomography

Study Population  We identified 1,179 consecutive patients who underwent MSCT between August 2002 and July 2006, at Nihon University Hospital. The reasons for MSCT were evaluation of typical and atypical chest pain in 715 patients, evaluation of the post-coronary intervention status in 112 patients, and evaluation of coronary artery disease (CAD) in 182 asymptomatic patients with multiple coronary risk factors. A structured interview and clinical history were obtained, and the following cardiac risk factors were assessed prior to the MSCT study: (1) hypertension (defined as blood pressure ≥140/90 mmHg or the use of antihypertensive agents), (2) hyperlipidemia as defined by low-density lipoprotein-cholesterol >140 mg/dl, (3) diabetes mellitus (defined as fasting glucose level >120 mg/dl or the need for insulin or oral antidiabetic medicines), (4) smoking (defined as current or previous smoking), and (5) previous history of acute myocardial infarction (AMI) and unstable angina (UA), and (4). Exclusion criteria for MSCT scans were known allergy to iodine, arrhythmias, impaired renal function (serum creatinine ≥1.3 mg/dl), bronchial asthma and left ventricular failure (left ventricular ejection fraction <30%).

MSCT Protocol  MSCT was performed using either a SOMATOM Volume...
Prognostic Value of CT Low-Dense Plaques

Zoom (4-detector-row, Siemens, Germany), which provides spatial resolution of 0.6 mm on the horizontal axis and 1.0 mm on the vertical axis (835 patients) or an Aquilion 16 (Toshiba Medical, Tokyo, Japan), which provides spatial resolution of 0.5 mm on both horizontal and vertical axes (341 patients). Our MSCT scan and ECG-gated image reconstruction methods have been described previously. In brief, metoprolol (20–60 mg) or atenolol (50 mg) was given 90–120 min prior to the MSCT study to reduce the heart rate in order to perform the single-phase algorithm (reconstructing 1 image from a single cardiac cycle). Sublingual glycerin (0.3 mg) was also administered 5 min prior to the scan. After imaging at the level of the carina and positioning the region of interest (ROI) in the center of the ascending aorta, a bolus of 20 ml of the contrast medium (Iomeron 300: 100 ml syringe; Eisai, Tokyo, Japan) was injected intravenously at 3.3 ml/s via a 20-gauge catheter placed in the cubital vein, and the time interval between contrast agent injection and the maximum enhancement within the ROI was measured. The remainder of the contrast medium (80 ml) was then injected and the scan was started with a delay according to the previously determined contrast transit time. The volume data set for coronary imaging were acquired in the spiral mode, with simultaneous acquisition of 4 parallel slices (slice thickness 1.0 mm, table feed 3.2 mm/rotation, 140 kV, 400 mA and the gantry rotation time 500 ms) for the SOMATOM Volume Zoom and acquisition of 16 parallel slices (slice thickness 0.5 mm, table feed 3.2 mm/rotation, 140 kV, 400 mA and the gantry rotation time 400 ms). The raw data of the scans were reconstructed using a single-phase algorithm in all the patients as described previously. We used an ECG-gated, retrospective image reconstruction technique developed in our laboratory, which has been shown to substantially reduce cardiac motion artifacts occurring during the ventricular rapid filling and atrial contraction periods. Reconstruction was performed using a half reconstruction technique in all patients. The reconstruction window (250 ms for the SOMATOM Volume Zoom and 200 ms for the Aquilion 16) was positioned so that the end of the reconstruction period was set at the peak of the P wave on monitor ECG. The reconstructed image data of CT angiography were transferred to a computer workstation (3D Virtuoso, Siemens, Germany for the SOMATOM Volume Zoom and M900 Quadra for the Aquilion 16) for post-processing. The estimated radiation dose was 5–12 mSV.

Written informed consent was given by all patients for MSCT scanning and the study was approved by the hospital’s ethics committee.

**MSCT Image Analysis**

Following visual inspection of the volume-rendering images, which depicted the gross coronary artery luminal configuration, the coronary artery plaques were carefully inspected on axial images, curved multiplanar reformatted (MPR) images, and cross-sectional MPR images (Fig 1). Coronary artery lesions were identified as atherosclerotic plaques when the coronary lumen was occluded more than 25%, but less than 75%, in diameter and had a CT-low-density appearance. Coronary artery segments with heavy calcification (calcium deposits of CT densities ≥300 Hounsfeld units (HU)) occupying more than 50% of the coronary artery lumen were not analyzed. On the axial or cross-sectional MPR images, a ROI greater than 1.0 mm² was placed on at least 4 randomly selected points within each plaque and the lowest CT density was defined as the minimum plaque density. The analysis was performed for 8 coronary artery segments: the left main coronary artery, proximal portions of the left anterior descending artery (segments #6 and #7), the left circumflex artery (segments #11 and #13) and the right coronary artery (segments #1, #2 and #3). Coronary artery segments with a diameter <2.0 mm were not analyzed. CTLDPs were defined if the plaque had a minimum CT density <68 HU, which has been reported from our laboratory.

Patients were then designated to the following 2 groups based on the presence or absence of CTLDP: Group 1 consisted of 189 patients who had at least 1 CTLDP and Group 2 consisted of 621 patients who had no CTLDP.

**Patient Follow-up**

Patient follow-up was performed by checking the medical records or by mail interview by person unaware of the patients’ MSCT results. Events were defined as follows: (1) ACS: AMI as evidenced by an elevation of creatine kinase and creatine kinase-MB more than 2-fold the normal values, and UA defined as Braunwald severity class II and III (acute and subacute angina at rest), and the clinical circumstance...
B (primary UA) angina, and (2) cardiac death as noted and confirmed by review of hospital charts or physician’s records. All patients were followed for at least 4 weeks and the mean follow-up interval was 1,062±544 days.

Statistical Analysis

Continuous variables are expressed as the means ± standard deviation. A p-value <0.05 was considered as statistically significant. The Cox proportional regression analysis (Dr SPSSII version 11, Chicago, IL, USA) was used in a stepwise fashion to define models with ACS (nonfatal AMI and UA) as separate endpoints. The threshold for entry of variables into all models was p<0.05. The Kaplan-Meier method was used to calculate the ACS-free survival in both groups of patients that were divided on the basis of the presence or absence of CTLDP. Statistical difference was determined by the log-rank test.

Results

Patients’ Characteristics

Of 1,179 consecutive patients undergoing MSCT, 8 were excluded from the analysis because of poor image quality related to cardiac motion artifact (n=7) and respiratory motion artifact (n=1); 164 patients declined to participate in the study and 77 patients with coronary artery stenosis >75% (n=60) or heavy coronary calcification that hampered the assessment of coronary luminal narrowing (n=17) were also excluded. Therefore, 930 patients were enrolled and replies were obtained from 829 patients (follow-up rate = 89.1%). Of these, 19 were also excluded because they had revascularization treatment within 2 months after the MSCT study, so the prognostic analysis was performed in a total of 810 patients.

The clinical characteristics of the patients with (Group 1) or without CTLDP (Group 2) are described in Table 1. Group 1 had a larger male population than Group 2. Diabetes mellitus, hyperlipidemia and smoking were more frequently present in Group 1 than in Group 2, while the incidence of hypertension and previous myocardial infarction (MI) was similar between 2 groups.

Outcome Events

Of the 810 patients included in this study, 22 cases of ACS (2.71%), consisting of 7 nonfatal AMIs (0.86%), 15 UA (1.85%) and 6 cardiac deaths (0.74%), occurred during the follow-up period (total event rate 3.45%). The annual event rate of ACS was 0.93% (0.29% for AMI and 0.63% for UA), and that of cardiac death was 0.25%. During the follow-up period, 10 of 189 (5.29%) patients in Group 1 had ACS (5 nonfatal AMIs, 2.64%, and 5 UA, 2.64%) and 2 cases (1.05%) of cardiac death. The annual rate of nonfatal AMI, UA, ACS (nonfatal AMI+UA) and cardiac death in Group 1 was 0.91%, 0.91%, 1.82%, and 0.36%, respectively, while in Group 2 there were 12 cases of ACS (1.93%) consisting of 2 AMI (0.32%) and 10 UA (1.61%). Four cardiac deaths (0.64%) occurred in Group 2. The annual rate of nonfatal AMI, UA, ACS (nonfatal AMI+UA) and cardiac death was 0.10%, 0.55%, 0.66% and 0.21%, respectively. The annual event rate of ACS was

![Table 1 Patients’ Characteristics](image)

<table>
<thead>
<tr>
<th></th>
<th>Total (n=810)</th>
<th>Group 1 (n=189)</th>
<th>Group 2 (n=621)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.3±13.2</td>
<td>61.3±13.2</td>
<td>61.3±13.2</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>298 (36.7%)</td>
<td>81 (42.8%)</td>
<td>217 (34.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>154 (19.0%)</td>
<td>48 (25.3%)</td>
<td>106 (17.0%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>322 (39.7%)</td>
<td>92 (48.6%)</td>
<td>230 (36.9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>135 (16.6%)</td>
<td>43 (22.7%)</td>
<td>92 (14.7%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Previous MI</td>
<td>57 (7.0%)</td>
<td>17 (8.99%)</td>
<td>40 (6.44%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant; MI, myocardial infarction.

![Fig 2. Annual event rates of nonfatal acute myocardial infarction (AMI), unstable angina (UA), acute coronary syndrome (ACS, AMI+UA) and cardiac death (CD) in Group 1 and Group 2.](image)

![Fig 3. ACS-free survival curves for patients with (Group 1) or without (Group 2) CT low-dense plaques. ACS, acute coronary syndrome.](image)
significantly higher in Group 1 patients than in Group 2 patients (p<0.001), whereas the rate of cardiac death was similar between groups (Fig 2).

Kaplan-Meier analysis showed that Group 1 had a poorer prognosis than Group 2 (Fig 3).

**Prediction of Cardiac Events**

Univariate Cox proportional regression analysis of age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking, previous MI and the presence of CTLDP showed that diabetes mellitus (Wald 4.69; p<0.05), previous MI (Wald 14.9; p<0.001) and the presence of CTLDP (Wald 6.14; p<0.05) were predictors of ACS (Table 2). Multivariate Cox proportional regression analysis revealed that previous MI (Wald 12.4; p<0.001) and the presence of CTLDP (Wald 4.60; p<0.05) were independent predictors of ACS (Table 3).

**Discussion**

Classification of patients into various risk groups for cardiac events, including fatal or nonfatal AMI, UA and sudden cardiac death, provides valuable information in the management of patients with CAD. For instance, patients at high risk of cardiac events benefit from revascularization, whereas patients at low, but substantial risk, might rather benefit from medical therapy. At present, myocardial perfusion single-photon emission computed tomography (SPECT) is the most reliable diagnostic modality to estimate a patient’s prognosis and improves stratification of patients into different levels of risk. Its major shortcoming is the identification of patients who are likely to have ACS because this imaging technique basically evaluates the severity of coronary artery stenosis, but does not enable detection of rupture-prone, vulnerable plaques.

MSCT is the most reliable method for detecting and evaluating coronary artery plaques, and several studies have demonstrated a good agreement between MSCT-derived plaque texture and that determined by intravascular ultrasound. In the present study, we have clearly shown that MSCT provides independent prognostic information for predicting cardiac events. Patients with non-obstructive CTLDP are more likely to have ACS than patients without CTLDP. This is the first study to demonstrate in a large patient population the prognostic value of CTLDP for predicting a patient’s long-term prognosis. In a small number of patients (n=100), Pundziute et al demonstrated that patients with non-obstructive coronary artery plaques of various CT densities (n=32) had a cardiac event rate (AMI, UA, cardiac death and revascularization) of 8% during a mean follow-up period of 16 months, whereas patients without plaques (n=20) had no events. Their result implies that non-obstructive coronary artery plaques are still a significant risk of hard coronary events, although patients with obstructive coronary artery lesions have a much higher risk (annual event rate 60%). In our study the annual event rate of non-obstructive CTLDP was 2.18%, which was lower than that in the study by Pundziute et al (annual event rate 8%). The discrepancy may result from the inclusion of revascularization as an endpoint in their study whereas we did not include patients undergoing revascularization treatment during the follow-up period.

The relatively high rate of cardiac events in patients with non-obstructive CAD is not surprising. Previous studies support the notion that plaque composition is the major determinant of the future occurrence of ACS, rather than the severity of coronary stenosis or the plaque size. Pathologic characteristics of rupture-prone, vulnerable plaques include large lipid core and minimal thickness of the fibrous cap. Therefore, vulnerable plaques may occur in a wide spectrum of coronary artery lesions, irrespective of the grade of stenosis. In fact, pooled data from previous angiographic studies show that 68% of AMI are attributable to angiographic stenosis <50%, whereas only 14% was assigned to a severe stenotic lesion >70%. In line with these investigations, multivariate Cox regression analysis of the possible predictors of cardiac events in our study showed that non-obstructive CTLDP was indeed an independent predictor of future cardiac events.

**Table 2 Predictors of ACS by Univariate Cox Proportional Hazards Regression Analysis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald</th>
<th>p value</th>
<th>95% CI</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.14</td>
<td>0.70</td>
<td>0.97–1.04</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>0.57</td>
<td>0.44</td>
<td>0.54–3.98</td>
<td>1.47</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.68</td>
<td>0.19</td>
<td>0.75–4.00</td>
<td>1.73</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.69</td>
<td>&lt;0.05</td>
<td>1.09–6.23</td>
<td>2.61</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.00</td>
<td>0.93</td>
<td>0.44–2.42</td>
<td>1.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.05</td>
<td>0.81</td>
<td>0.38–3.37</td>
<td>1.13</td>
</tr>
<tr>
<td>Previous MI</td>
<td>14.9</td>
<td>&lt;0.001</td>
<td>2.52–16.9</td>
<td>6.58</td>
</tr>
<tr>
<td>CTLDP</td>
<td>6.14</td>
<td>&lt;0.05</td>
<td>1.24–6.73</td>
<td>2.90</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CI, confidence interval; OR, odds ratio; CTLDP, CT low-dense plaque. Other abbreviation see in Table 1.

**Table 3 Predictors of ACS by Multivariate Cox Proportional Hazards Regression Analysis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald</th>
<th>p value</th>
<th>95% CI</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>12.4</td>
<td>&lt;0.001</td>
<td>2.15–14.7</td>
<td>5.63</td>
</tr>
<tr>
<td>CTLDP</td>
<td>4.60</td>
<td>&lt;0.05</td>
<td>1.08–5.92</td>
<td>2.53</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1, 2.
Study Limitations

We did not evaluate heavily calcified plaques because the partial volume effect of calcification hampers the accurate estimation of coronary artery luminal narrowing. However, previous studies using electron-beam computed tomography have consistently indicated that the total amount of coronary calcification correlates well with future cardiac events. Pathological studies have indicated a strong correlation between the extent of coronary calcification and the total plaque burden, including non-calcified, vulnerable components. Thus we should have evaluated the possible risk in patients with calcified plaques. Future improvement in spatial resolution will decrease the partial volume effect and will allow accurate characterization and risk stratification of calcified plaques.

Although MI, UA and cardiac death are related in many patients, it is practically impossible to accurately determine the cause of cardiac death in each patient. Also, because the diagnosis of UA was made by the patients’ referring physician in more than half of cases, non-ST-elevation AMI might have been included as separation of both conditions is practically difficult and it was impossible to obtain ECG and laboratory data for each patient. In addition, it was also impossible to determine whether or not ACS occurred in cases of CTLDP detected by MSCT.

Finally, the CT density of plaque may vary in the following situations, in addition to the differences in the slice thickness obtained with 4- and 16-row detector equipment (1.0 mm and 0.5 mm, respectively): (1) the CT density of the enhanced coronary artery lumen, (2) partial volume effect from adjacent calcified lesions (which is also related to the slice thickness), (3) the type of kernel used for image reconstruction and (4) the tube voltage. These are insurmountable limitations when assessing the CT density of the coronary artery plaque.

These limitations aside, our data indicate that the presence of non-obstructive CTLDP is prognostic information about ACS. Although MSCT is not a totally noninvasive diagnostic modality, because of the significant radiation exposure and requirement for contrast medium, it may become a routine diagnostic modality for the assessment of rupture-prone, vulnerable plaques in patients with suspected CAD and individuals with coronary risk factors.

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References


