Clinical Significance of the Coronary Calcification Score by Multidetector Row Computed Tomography for the Evaluation of Coronary Stenosis in Japanese Patients

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Background  The coronary artery calcification (CAC) score measured by multidetector row computed tomography (MDCT) has emerged as a marker for predicting coronary artery disease (CAD). To evaluate the clinical significance of the CAC score, coronary artery stenosis as assessed by coronary angiography (CAG) was compared with the CAC score determined by MDCT, risk factors and medications.

Methods and Results  Subjects included 374 consecutive patients who underwent ECG-gate CT angiography using MDCT. The accuracy in patients with a CAC score ≥400 was 84%, and significantly lower than that in patients with a CAC score =0. In addition 92 patients (68 males, 24 females; mean age, 63±11 years) who underwent both MDCT and CAG within a 1-month period were selected for further investigation. Patients with significant coronary stenosis had a significantly higher CAC score than those without stenosis. In addition, a higher number of stenosed vessels was associated with a higher CAC score. The subjects were divided into 3 groups according to the CAC score: low (0–12), intermediate (13–444) and high (≥445). The CAC score was significantly associated with age, and plasma levels of total cholesterol and hemoglobinA1c, and logistic regression analysis revealed that significant coronary stenosis as assessed by CAG was most closely correlated with the CAC score (p=0.03).

Conclusions  The CAC score determined by MDCT can predict CAD independent of other factors, such as age, metabolic diseases and medications, when coronary stenosis can not be diagnosed because of severe calcification. (Circ J 2006; 70: 1122–1127)

Key Words:  Coronary angiography; Coronary artery calcification score; Multidetector row computed tomography; Risk factors

Coronary artery disease (CAD) is the most important cause of death in the industrialized world1,2 and an efficient noninvasive method of detection is needed. Techniques for measuring coronary artery calcification (CAC) as a marker of atherosclerosis using electron-beam computed tomography (EBCT) have been developed3,4. Calcification as assessed by EBCT is associated with atherosclerosis at autopsy and the results of coronary angiography (CAG)5. Multidetector row computed tomography (MDCT) has become more widely available in many general hospitals, and it is becoming increasingly likely that high-risk patients will undergo CAC scoring by MDCT as well as EBCT, because MDCT enables accurate assessment of coronary artery luminal narrowing6,7 and several studies have shown a high correlation between CAC scores as assessed by MDCT and those determined by EBCT8,9. In addition, MDCT has emerged as a potential noninvasive method for imaging the coronary arteries and is a sensitive modality for the diagnosis of coronary artery stenosis. It can be very difficult to detect coronary artery stenosis if there is advanced calcification, although the CAC score has been shown to be a marker for predicting CAD. The presence of CAC can be assessed noninvasively using either EBCT or MDCT. Although several studies have revealed a correlation between CAC and angiographic stenosis10,11 and several studies have used MDCT and it is unknown whether the CAC score is the most important predictor of significant coronary stenosis as assessed by CAG independent of other factors, such as age, body mass index and medication. To evaluate the clinical significance of the CAC score determined by MDCT, we compared coronary artery stenosis as assessed by CAG with the CAC score, coronary risk factors and medications. In addition, when it was difficult to assess the coronary artery lumen on MDCT because of severely calcified lesions, we analyzed whether a higher CAC score might be a helpful indicator of the need to perform CAG.
Methods

Subjects
The study group comprised 374 consecutive patients without symptoms or with at least 1 cardiac risk factor or chest pain. Patients who had atrial fibrillation, renal insufficiency (creatinine >1.5 mg/dl), or heart failure (ejection fraction <40%) or who were unable to hold their breath for 30 s were excluded. They underwent ECG-gate CT angiography 16-MDCT between April 2004 and August 2005. In total, 92 patients underwent both MDCT and CAG within a 1-month period, and we used their data for further investigation. The ethics committee of Fukuoka University Hospital approved the study and informed consent was given by each patient.

MDCT Scan and Image Reconstruction Protocol
Patients were scanned with 16-MDCT (Aquilion 16, TOSHIBA, Tokyo, Japan) within 1 month of conventional diagnostic CAG. Patients with a heart rate of >65 beats/min received 20–60 mg metoprolol orally 1 h before the MDCT scan. Angiographic scan parameters were as follows: 0.5 mm collimation width, a gantry rotation speed of 0.4 s/rotation, 135 kV, and 360 mA. Calcification scoring parameters were 2 mm collimation width, a gantry rotation speed of 0.4 s/rotation, 120 kV, and 360 mA, which was used to determine the location of the heart. A 65-ml bolus of contrast agent (300–370 mgI/ml according to body weight) at a flow rate of 3.6 ml/s followed by 30 ml of contrast agent and 30 ml of saline solution, each at a flow rate of 1.8 ml/s, was injected with a dual injector. To monitor the arrival of contrast agent, axial scans were obtained at the level of the left ventricle after the start of contrast injection. The scan was manually started when the contrast agent reached the left ventricle. Data sets were reconstructed in the cardiac cycle (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% of the R-R interval), and those with the fewest motion artifacts were used for further evaluation of the coronary artery.

Calcification was quantified on a workstation (M900 Quadra, ZIO SOFT) with scoring software (Fig 1). CAC was defined on CT images as the presence of more than 2 contiguous pixels with greater than 130 Hounsfield units (HU). The regions of interest in the coronary artery were marked at the workstation by an experienced cardiologist. Lesion areas were measured and the maximal CT number in each lesion was counted automatically. The CAC score in each lesion was then computed by the Agatston method. The Agatston score represents the area score multiplied by an attenuation factor, which is based on the peak CT number of the lesion as follows: factor 1 = 130–199 HU, factor 2 = 200–299 HU, factor 3 = 300–399 HU, factor 4 = 400 or greater.

All scans were analyzed by 2 independent cardiologists who were unaware of the results of conventional CAG. The MDCT data sets were evaluated for the presence of significant coronary artery stenosis within 10 segments (1–3, 5–7, 9, 11, 13, 15) of the modified 16-segment model of the American Heart Association (AHA). Any narrowing of the normal contrast-enhanced lumen to <50% that could be identified in multiplanar reconstructions or cross-sectional images was defined as significant coronary stenosis.

CAG
Coronary angiograms were recorded and divided into 15 segments according to the classification of the AHA.
Grading Committee. The presence of stenosis was determined using a computer-assisted CAG analysis system (Philips-H3000CCD, the Netherlands) after the direct intracoronary injection of isosorbide dinitrate. Arterial stenosis that produced more than 50% luminal narrowing was considered significant. Angiograms were evaluated visually by an independent cardiologist who was unaware of the results of the MDCT examination.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MDCT for all segments and CAC = 0 groups (Table 1) were calculated on a per-segment basis in 92 patients. The CAC score in patients with significant stenosis in at least 1 coronary segment was compared with that in patients without significant stenosis as determined by CAG. In addition, the CAC scores in 0-vessel disease (VD), 1VD, 2VD, and 3VD, as determined by CAG, were compared.

**Determination of Serum Biochemical Parameters**

Blood was drawn in the morning of the imaging after an overnight fast. Serum total cholesterol (TC), triglyceride and high-density lipoprotein cholesterol were determined enzymatically. Serum uric acid and hemoglobin (Hb) A1c concentrations were also determined.

**Statistical Analysis**

Statistical analysis was performed using the SAS software package (version 6.12, SAS Institute Inc, Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Data are shown as the mean ± standard deviation. Categorical and continuous variables were compared between the groups by chi-square analysis and analysis of variance, respectively. A value of p < 0.05 was considered significant. Multivariable analysis was performed by logistic regression analysis for independent variables that were related to the CAC score.

**Results**

Data obtained for 92 patients (68 males, 24 females; mean age, 63 ± 11 years; body mass index, 24.4 ± 3 kg/m²) were analyzed. Of the total of 920 segments (92 patients × 10 segments), we excluded 101 because of motion artifacts (n=14), small vessels (<2 mm, n=48), calcification (n=33) and stenting (n=6). The sensitivity for all segments was 75%. Specificity, PPV, NPV and accuracy were 92%, 56%, 96% and 90%, respectively (Table 1). Because a CAC score over 400 has been shown to reflect at least 1 significantly stenosed lesion, we divided the samples into 3 groups: CAC score = 0, 0 < CAC score < 400 and CAC score ≥ 400.
The specificity, NPV and accuracy significantly decreased when the CAC score increased, suggesting that the group with severe coronary calcification showed lower accuracy.

Next, the 92 patients were divided into 2 groups according to the presence (+, n=60) or absence (−, n=32) of significant coronary stenosis as assessed by CAG. The baseline characteristics are shown in Table 2. There were no differences in age, sex, systolic or diastolic blood pressure, lipid profile, etc. Only the CAC score in patients with significant coronary stenosis was significantly higher than that in the stenosis (−) group. In addition, a higher number of stenosed vessels was associated with a higher CAC score (Fig 2). The CAC score in 3VD was significantly higher than in the other groups (0, 1VD and 2VD).

Because the CAC score was associated with significant coronary stenosis, we determined the factors that were related to the CAC score. To analyze the relationship between the CAC score and other factors, the patients were equally divided according to the CAC score and those with a higher CAC score were further equally divided (L, low CAC score group, score =0–12, n=44; M, intermediate...
The major findings of the present study are (1) using 16-MDCT, coronary artery stenosis could be detected with high accuracy (sensitivity, 84%; specificity, 94%) in patients without coronary calcification, (2) the CAC score in the 3VD group was significantly higher than in the other groups, and (3) significant coronary stenosis as assessed by CAG was most closely associated with the CAC score. Finally, because coronary stenosis was significantly associated with CAC score, we analyzed contributors to coronary stenosis. The results of logistic regression analysis showed that the CAC score most strongly contributed to coronary stenosis (p=0.03) (Table 4).

**Discussion**

The major findings of the present study are (1) using 16-MDCT, coronary artery stenosis could be detected with high accuracy (sensitivity, 84%; specificity, 94%) in patients without coronary calcification, (2) the CAC score in the 3VD group was significantly higher than in the other groups, and (3) significant coronary stenosis as assessed by CAG was most closely associated with the CAC score.

With regard to the CAC score, Runberger et al showed that a score of 0–10 is associated with a very low probability of significant CAD; 11–100 indicates that mild disease is likely; 101–400 is associated with a high likelihood of non-obstructive disease; and over 400 indicates a high likelihood of at least 1 significantly stenosed lesion. Our study results are consistent with a previous study that showed that patients in group H may have at least 1 significantly stenosed lesion. On the other hand, Bormann et al reported that CAC scores did not predict significant stenosis at the calcification site and suggested that the extent and site of calcification are not associated with site-specific stenosis. Because a patient-based analysis might be more sensitive than a vessel analysis, further investigation is needed to determine the association with site-specific stenosis.

In patients with none to intermediate coronary calcium burden, MDCT of the coronary arteries is a suitable technique for diagnosing coronary artery stenosis. Severe coronary calcifications may still have affected the diagnostic accuracy of 16-MDCT CAG in this study and others. In severe calcification, 16-MDCT, consistent with the detection and quantification of CAC by EBCT, may be useful for detecting atherosclerosis and may play an important role in risk assessment. In this study using MDCT, the CAC score predicted significant coronary stenosis independent of other factors, such as standard cardiovascular risk factors and medication.

Of the 92 patients with suspected CAD who underwent both MDCT and CAG within a 1-month period, 75 underwent MDCT before CAG. The MDCT results were significant coronary stenosis (n=44), no diagnosis because of severe calcification (n=18) and normal (n=13). The 13 patients with a normal study, still underwent CAG and an ergometrine provocation test because their symptoms might be due to vasospasm angina and 4 of them were positive for the latter test. Seventeen patients underwent CAG before MDCT and 15 had significant coronary stenosis by CAG (2 were normal). Informed consent was given by all 17 patients and we performed MDCT. The reduced specificity in the CAC score >400 group has been ascribed to a lower rate of detection because of severe calcification and a post-test referral bias, in that patients with an abnormal CT study are preferentially referred for CAG. This selection process would reduce the number of true-negative results because most subjects with a normal CT study would not undergo CAG.

### Table 4 Contributors to Coronary Stenosis as Assessed by Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
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<tbody>
<tr>
<td>CAC group</td>
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</tr>
<tr>
<td>Statin</td>
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</tr>
<tr>
<td>Total cholesterol</td>
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<tr>
<td>Age</td>
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<tr>
<td>HemoglobinA1c</td>
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Abbreviation see in Table 1.
**Study Limitations**

This study has 2 important limitations. First, the sample size is relatively small, which limited our ability to determine significance. Most of the subjects in the present study were male patients with CAD. Second, our study was observational only. We simply examined the association of coronary stenosis with the CAC score and standard risk factors. A large prospective trial using patients with or without CAD is warranted to evaluate the potential benefits of the CAC score. Despite these limitations, our data suggest that the CAC score is quite effective for selecting patients who need to undergo coronary catheterization.

In conclusion, CAG is required for a definite diagnosis of CAD, regardless of the presence of coronary risk factors and medication when coronary stenosis cannot be evaluated by CT angiography because of severe calcification.

**References**