ORIGINAL

Risk factors associated with soft coronary artery plaques in Japanese, as determined by 16 slice multidetector-row computed tomography

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Abstract : ***Purpose*****: The acute coronary syndrome is often caused by the rupture of plaques and thrombus formation even without significant stenosis, and patients with soft plaques, but without significant stenosis evidenced by coronary angiography(CAG), often develop an acute coronary syndrome. To address this discrepancy, a qualitative diagnosis of coronary plaques using a 16 slice multidetector-row CT was conducted.**
Methods and Results**: Volume rendering and cross-sectional MPR images were obtained. Based on the CT values, plaques on the coronary artery wall were classified as lipid-rich soft plaques(CT value<50 HU) and non-soft plaques (>50 HU).**
A significant correlation was observed between the percent stenosis determined in cross-sectional MPR images and those determined by CAG(r=+0.92, p<0.01). Diffuse plaques with CT values of less than 50 HU often caused stenosis at level of 75% or less, which were not indicated by percutaneous transluminal coronary angioplasty.
Conclusions **: Although diffuse soft plaques with CT values less than 50 HU are not an indication of intervention, a risk of an acute coronary syndrome exists, due to rupture. These soft plaques must be stabilized by treatment even when they do not cause significant stenosis, and MDCT is considered to be useful for their evaluation. J. Med. Invest. 53 : 310-316, August, 2006**

Keywords **:** *acute coronary syndrome, MDCT, soft plaque*

INTRODUCTION

With advances in multidetector-row CT (MDCT), the non-invasive evaluation of coronary artery lesions has become a reality (1-2). These advances have been brought about by shortening the scanning time due to an increase in gantry rotation speed, improvements in the temporal and spatial resolutions along the body axis due to a reduction in slice thickness as a result of an increase in table speed, the development of a new method for reconstructing an image from multiple pulse data, and the consequent improvement in the temporal

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resolution of each image(3). With the advent of 16-slice MDCT in 2002, the diagnosis of coronary stenosis became possible in 88% of patients, and the sensitivity, specificity, and negative predictive value have been reported to be 92%, 93%, and 97%, respectively (1), indicating that the accuracy of the diagnosis of coronary stenosis by MDCT has reached a clinically acceptable level. Moreover, MDCT allows the qualitative diagnosis of plaques according to the CT value, and it has been reported to be effective for the non-invasive diagnosis of lipid-rich soft plaques, which are responsible for the acute coronary syndrome(4-6).

The acute coronary syndrome occurs in many patients due to the rupture of plaques and thrombus formation even without significant stenosis(7). Since patients with no significant stenosis by coronary angiography (CAG) have the risk of the acute coronary syndrome when they have lipid-rich soft plaques, a qualitative assesssment of coronary plaques is an important issue(8). In the present study, the qualitative diagnosis of coronary plaques was attempted using a 16-slice MDCT.

METHODS

1. Subjects

Between January and August, 2004, we examined the coronary arteries of 54 patients (29 men and 25 women, mean age 67.8±10 years) by MDCT at Tokushima University Hospital. Of these patients, 10 had a history of myocardial infarction, 18 had diabetes mellitus, 12 had hyperlipidemia, 24 were hypertensive, and 20 had a history of smoking. The subjects' ECG was monitored during the collection of the MDCT images.

2. MDCT images

MDCT images were obtained using an Advanced Multidetector-row CT Aquilion (Superheart edition, Toshiba, Tokyo, Japan) containing 16 rows of detectors by the ECG-gated reconstruction method. The ECG-gated unit with 40 rows × 896 detectors was operated by 16-row simultaneous sampling (16 DAS) at an X-ray tube rotation speed of 0.4 seconds/rotation, X-ray tube heat capacity of 7.5 MHU, and a slice thickness of 0.5 mm.

The subjects practiced holding their breath prior to the actual examination. They were trained to hold their breath at an inhaled position for about 30 seconds after breathing oxygen at 3L/min using a mask and to keep the thorax and diaphragm stationary during this period. During the training, changes in the heart rate during breath holding were observed, and the optimal values for the scanning parameters were determined.

The subjects were screened for lesions around the heart and in the coronary artery without using a contrast medium, and the scanning area for the study was determined. Cardiac scanning was performed by placing a 20G polyethylene tube in a brachial median superficial vein and infusing 150 mL of a non-ionic iodine contrast medium (300 mgI/ml) in 2 steps (Step 1, 60 ml at 3.0ml/sec; Step 2, 30ml at 1.8ml/sec simultaneously with 30ml of physiologic saline at 1.8 ml/sec to push the contrast medium from behind) using a 2-syringe automatic contrast medium injector.

Scanning was started by the bolous tracking technique. Using real time observation of the influx of the contrast medium into the ascending aorta, scanning was started manually and advanced from the cephalic to the caudal direction. The scanning area was from the level of the trunk of the pulmonary artery to about 1 cm caudally from the lower margin of the heart. The scanning time was about 30 seconds for all subjects. After scanning, the absence of any abnormality was confirmed in each subject, and the needle was removed.

3. Reconstruction of coronary CT images

A cardiac cycle was divided into 20 phases, all phases were compared, and the image of each coronary artery in the phase with the smallest cardiac movement and the best resolution was selected visually. Using the coronary artery imaging software (ZIOSOFT M900 QUADRA), volume rendering images, curved MPR images, and cross-sectional MPR images were prepared.

4. Evaluation of coronary artery percent stenosis and wall properties

An experienced radiologist and an experienced cardiologist evaluated coronary CT and CAG images by agreement. Plaques on the coronary artery wall were detected in curved MPR images, and their cross-sectional MPR images were obtained. All of them were compared with CAG. To measure percent stenosis by MDCT, reference points were determined proximally and distally to the area of the stenosis similarly to CAG. CT values of them were measured by using circular ROIs on the cross-sectional MPR images. Based on the CT values, the plaques were differentiated into soft plaques (CT value<50 HU) and non-soft plaques (>50 HU).

In the subjects with soft plaques, the relative risks of coronary risk factors (age, blood pressure, body mass index, fasting blood sugar level, glycohemoglobin level, total-cholesterol level, triglyceride (TG) level, LDL-cholesterol level, HDL-cholesterol level, and smoking) and inflammatory cytokines (high-sensitivity CRP, interleukin-6) were calculated.

Statistical analyses

Statistical analyses were performed using Stat View 5.0 (SAS Institute Inc., USA). The percent stenosis determined by MDCT and that determined by CAG were compared by a simple regression analysis. The relative risk of soft plaques was evaluated by calculating the 95% confidence interval by a multivariate analysis using a logistic regression model. P<0.05 was regarded as significant.

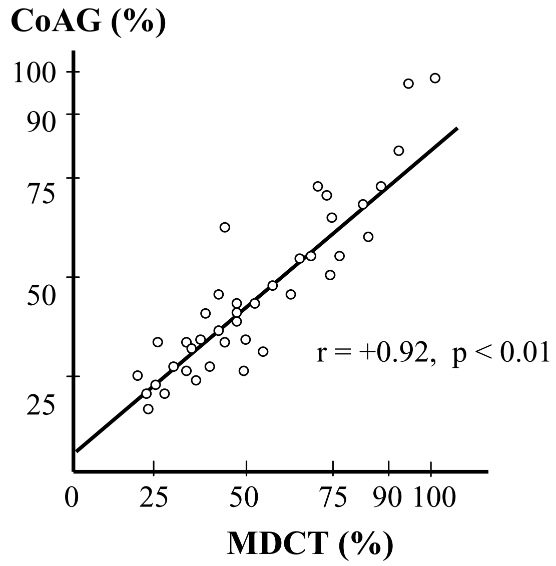

Fig. 1 Correlation between the percent stenosis determined by MDCT and that determined by CAG.

RESULTS

1. Comparison of percent stenosis between MDCT and CAG

Images of 54 subjects were evaluated. Of these, the images of 6 subjects were excluded, because we could not evaluate them due to poor breath holding or body movements. The mean heart rate during the scanning period was 67.6±15.3/min. Among 48 subjects 40 plaques including 13 soft plaques were detected by MDCT, and all of them were compared with CAG. Fig. 1 shows the correlation between the percent stenosis determined by MDCT and that determined by CAG. The percent stenosis determined by MDCT was significantly correlated with that determined by CAG (r=+0.92, p<0.01).

2. Properties and relative risks of plaques on the coronary artery wall

Fig. 2 shows the relative risks of coronary risk factors (age, blood pressure, body mass index, fasting blood sugar level, glycohemoglobin level, total-cholesterol level, triglyceride level, LDL-cholesterol level, HDL-cholesterol level, and smoking) and inflammatory cytokines (hs- CRP, IL-6) in patients with soft plaques. The glycohemoglobin level (relative risk=0.65, p=0.031), total-cholesterol level (relative risk=0.55, p=0.023), LDL-cholesterol level (relative risk=0.45, p=0.019), HDL-cholesterol level (relative risk=1.61, p=0.043), and high-sensitivity CRP level (relative risk=0.70, p=0.038) were independent risk factors of coronary soft plaques. However, the age (relative risk=1.28, p=0.082), blood pressure (relative risk=0.81, p=0.094), body mass index (relative risk= 0.78, p=0.079), fasting blood sugar level (relative risk=0.88, p=0.092), triglyceride level (relative risk =0.75, p=0.102), and interleukin-6 (relative risk= 0.74, p=0.068) did not reach the level of statistical significance.

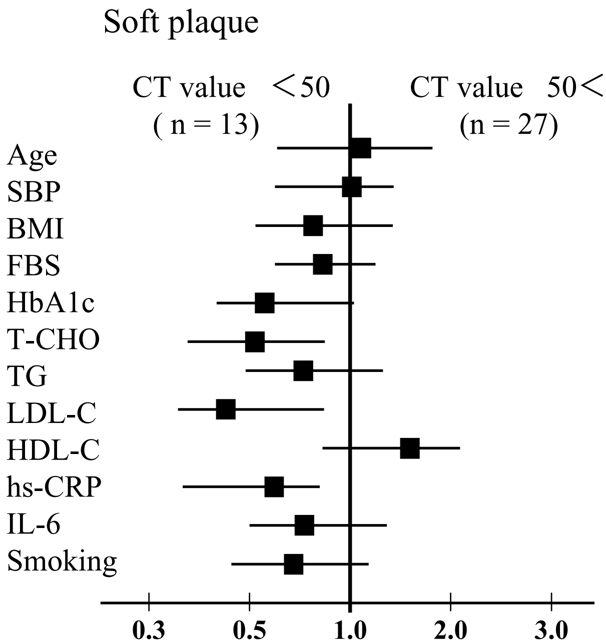

Fig. 2 Relative risks of coronary risk factors and inflammatory cytokines in patients with soft plaques.

3. Patients

a) Case 1

Fig. 3 shows volume rendering (A), curved MPR (B), cross-sectional MPR (C), and CAG images (D) of a 75-year-old women. The volume rendering image showed stenosis in the anterior descending branch. The curved MPR image showed calcified lesions in the left main trunk and stenotic lesions, in which low-signal areas and areas of calcification were mixed, in the middle part of the anterior descending branch. The cross-sectional MPR image of the low-signal area of the coronary artery showed a low-signal lesion that filled the lumen. The CT value in this low-signal area was 112 HU. The curved MPR image also showed diffuse low-signal lesions in the proximal part of the anterior descending branch, where the CT value was 38.5 HU, indicating soft plaques. This patient's CAG showed complete occlusion of the anterior descending branch and collateral blood flows from the right coronary artery, in agreement with MDCT findings. However, no significant stenosis was detected in the proximal part of the anterior descending branch on CAG.

b) Case 2

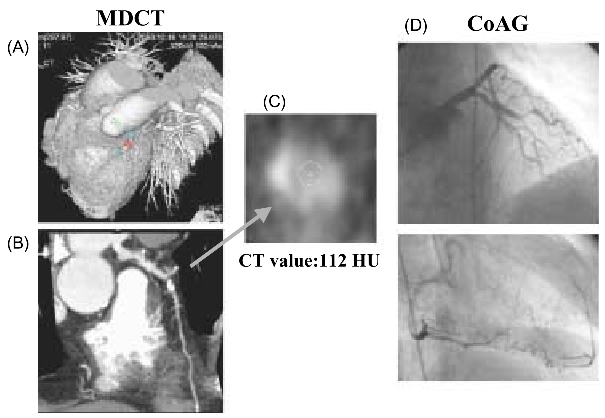

Fig. 3 Volume rendering (A), curved MPR (B), cross-sectional MPR (C), and coronary angiograhy (D) images. (75-year-old women)

Fig.4 shows a transverse CT (A), curved MPR (B), cross-sectional MPR (C), and CAG images (D) of a 74-year-old men. The transverse CT image showed a high-signal area in the anterior descending branch, and the curved MPR image showed high-signal areas considered to be calcification in the proximal part of the anterior descending branch and in the circumflex branch. The cross-sectional MPR image of the high-signal area of the coronary artery showed diffuse high-signal lesions of 25-50% stenosis. The CT value of this high-signal area was 412 HU. On CAG, no significant stenosis was noted, but diffuse calcification was noted in the anterior descending branch, in agreement with the MDCT findings. In this patient, the body mass index (BMI) was 20.3, glycohemoglobin (HbA1c) 5.4%, total cholesterol (T-CHO) 188 mg/dl, triglyceride (TG) 74 mg/dl, low density lipoprotein cholesterol (LDL-C) 84 mg/dl, high density lipoprotein cholesterol (HDL-C) 45 mg/dl, high sensitivity C-reactive protein (hs-CRP) 0.012 mg/dl, and interleukin 6 (IL-6) 0.263 pg/ml.

c) Case 3

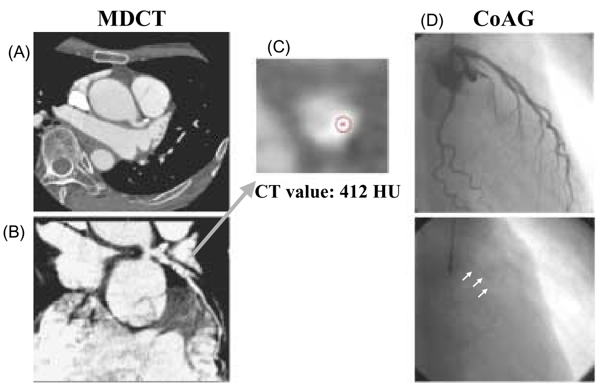

Fig. 4 Transverse CT (A), curved MPR (B), cross-sectional MPR (C), and CAG (D) images. (74-year-old men)

Fig. 5 shows volume rendering(A), curved MPR (B), cross-sectional MPR (C), and CAG (D) images of a 65-year-old woman. The volume rendering image showed stenosis in the anterior descending branch, and the curved MPR image showed a diffuse low-signal area in the proximal part of the anterior descending branch. The cross-sectional MPR image of the low-signal area of the coronary artery showed diffuse low-signal lesions with about 50% stenosis. The CT value of this low-signal area was 43.2 HU. On CAG, diffuse 25-50% stenosis was noted, and no significant stenosis was noted, in agreement with the MDCT findings. In this patient, the BMI was 25.5, HbA1c 8.4%, T-CHO 258 mg/dl, TG 176 mg/dl, LDL-C 168 mg/dl, HDL-C 35 mg/dl, hs-CRP 0.215 mg/dl, and IL-6 1.20 pg/ml.

Fig. 6 shows right coronary angiography (A), cross-sectional MPR (B), and curved MPR (C) images for this patient. No significant stenosis was noted on CAG, and the curved MPR image showed no significant change, but the cross-sectional MPR image showed a circumferential thickening of the vascular wall, indicating advanced atherosclerosis.

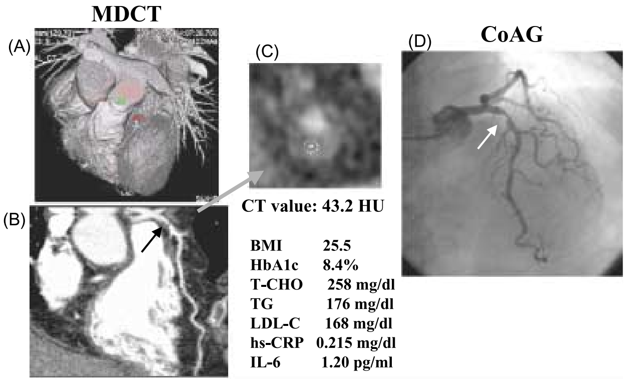

Fig. 5 Volume rendering(A), curved MPR (B), cross-sectional MPR (C), and CAG (D) images (65-year-old woman)

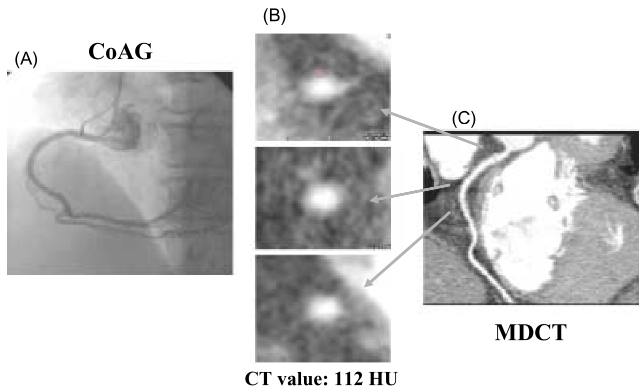

Fig. 6 Right coronary angiography (A), cross-sectional MPR (B), and curved MPR (C) images. (patient of Fig.3)

DISCUSSION

An advantage of MDCT in the diagnosis of coronary artery diseases is that the coronary artery wall as well as stenotic lesions can be evaluated non-invasively(9-12). Clinically, plaques of coronary arteries are evaluated by intravascular ultrasound (IVUS), performed by cardiac catheterization, but IVUS is invasive and cannot be performed repeatedly. MDCT may provide more information concerning coronary arteries than coronary angiography, and its clinical utility has been evaluated.

In the present study, the percent stenosis of the proximal parts of the coronary arteries determined in MPR images of MDCT was significantly correlated with those determined by CAG, indicating the utility of MDCT for the evaluation of coronary stenosis. In patients with plaques, a qualitative diagnosis of soft plaques was also possible according to the CT values determined by an analysis of cross-sectional MPR images. In patients with soft plaques, HbA1c, T-CHO, LDL-C, HDL-C, and hs-CRP levels were found to be independent risk factors of coronary artery soft plaques. Evaluation of coronary artery lesions by MDCT is considered to be effective for the primary and secondary prevention of ischemic heart disease and its clinical evaluation.

With the recent trend toward increasing the number of detectors in MDCT, it has now become possible to obtain high-resolution images more quickly in the field of coronary CT angiography. The conventional single-detector CT had various problems including restrictions in the scanning area, slice thickness during breath holding, and artifacts due to pulses. With MDCT having 4 rows of detectors, these problems are overcome, high-speed scanning, scanning of a wide area, and collection of high-resolution volume data became possible, the clarity of 3-dimensional images is improved, and the clinical utility of CT is now markedly enhanced (3, 13, 14). Moreover, with the advent of a 16-slice MDCT system, the scanning speed is further increased. The scanning time was almost 40 seconds with the 4-slice MDCT at a slice thickness of 1 mm, but this time is shortened to 15-20 seconds at a slice thickness of 0. 5 mm with a 16-slice MDCT, making scanning the entire heart in 1 breath holding possible (1, 15). The sensitivity, specificity, and negative predictive value of diagnoses of coronary stenosis with a 16-slice MDCT were also reported to be 92%, 93%, and 97%, respectively, further confirming the clinical usefulness of the examination (1).

Moreover, as shown in Fig. 4, the external development of coronary artery plaques by leaving the luminal cross-sectional area intact until plaques occupy about 40% of the area (a condition called positive remodeling) can be readily observed on CT.

Patients who suffered acute myocardial infarction or sudden death but had shown no clear stenosis on coronary angiography before the event have been frequently reported. In 1992, Fuster *et al*. named this condition the acute coronary syndrome and suggested that the rupture of unstable plaques was involved (7). Since these data suggest that soft plaques are present more often in patients with myocardial infarction than in those with stable angina pectoris, soft plaques are considered to be a likely cause of myocardial infarction when ruptured.

In these circumstances, the non-invasive qualitative diagnosis of plaques by CT has attracted considerable attention. According to a report in which the CT value determined by analysis of cross-sectional MPR images of MDCT with that determined by IVUS was compared, the CT value of lipid-rich soft plaques was less than 50 HU, while that of fibrous plaques was 50-120 HU, and that of calcified plaques was higher than 120 HU(16). Recent results of 16-slice MDCT also showed significant correlations with those using IVUS(5,16) and MRI(4,17).

In the present study, HbA1c, T-CHO, LDL-C, HDL-C, and hs-CRP levels were identified as independent risk factors of coronary artery soft plaques. LDL-C and oxidative stress have been reported to be important condition for the formation of soft plaques(18). Diabetic patients, who have high oxidative stress and a simultaneous high LDL-C level, are considered to have soft plaques and to be a high-risk group for the acute coronary syndrome. In the present study using MDCT, the HbA1c and LDL-C levels were also found to be predictive factors of soft plaque formation.

Therefore, in such patients with many coronary risk factors, it may be important to perform MDCT to detect soft plaques even if they show no symptoms of angina pectoris. If soft plaques are detected, strict lipid-lowering therapy is indicated. MDCT appears to be useful also for the determination of the therapeutic approach. On the other hand, we need to consider some side effects of contrast media and radiation dose for the patients.

64 multi-slice CT systems have recently been introduced clinically, and as the breath holding time was reduced less than 10 seconds, it has become possible to perform CT in elderly patients and patients with heart failure(19). In addition, motion artifacts due to movements of the diaphragm are also reduced with the new system, and a more accurate evaluation of coronary artery lesions has become possible. With further hardware and software improvements, the number of rows of detectors is expected to increase, and MDCT to replace coronary angiography in the near future.

CONCLUSIONS

16-slice MDCT allowed the detection of soft plaques, which cause the acute coronary syndrome, as well as stenosis in the proximal parts of the coronary arteries. Since patients with soft plaques showed high HbA1c, LDL-C, and hs-CRP levels, they are considered to need more strict lipid-lowering therapy, and MDCT appears to be important for the diagnosis and determination of therapeutic approaches in such patients.

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