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The relationship between coronary artery calcification detected by non-gated multi-detector CT in patients with suspected ischemic heart disease and myocardial ischemia detected by thallium exercise stress testing

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Objective: To examine whether we could predict myocardial ischemia when coronary artery calcification is detected by non-gated multidetector CT in patients with suspected ischemic heart disease. ***Methods:*** Eighty-three patients suspected of having ischemic heart disease (55 men, 28 women; age range 36–83 years; mean age 68 years) underwent multidetector CT and Tl-201 single photon emission computed tomography. Prediction of myocardial ischemia by coronary arterial calcification detected on CT was evaluated by comparing the coronary artery territories that showed calcification with the area of myocardial ischemia determined by SPECT. The sensitivity, specificity, positive predictive value, and negative predictive value of multidetector CT for predicting myocardial ischemia were calculated. Coronary angiography was also examined and compared with multidetector CT. Risk factors, including hypertension, smoking, hyperlipidemia, diabetes, and family history, were compared for evidence of coronary artery calcification detected by multidetector CT and myocardial ischemia detected by thallium nuclear scans. ***Results:*** For analysis by patients, the sensitivity, specificity, positive predictive value, and negative predictive value of coronary artery calcification for myocardial ischemia detection were 65, 63, 56, and 71%, respectively. Similarly, for analysis by coronary arterial territories, those values were 56, 77, 41 and 86%, respectively. Coronary stenosis on CAG was also related to the ischemia determined by SPECT and calcification on multidetector CT. Ischemia was better influenced by risk factors than was coronary arterial calcification. ***Conclusions:*** For analysis by coronary arterial territories, the specificity and negative predictive value of coronary arterial calcification seen by multidetector CT are relatively high.

Key words: calcification, coronary vessels, ischemic heart disease radionuclide studies, MDCT, risk factors for ischemic heart disease

INTRODUCTION

CORONARY ARTERIAL CALCIFICATION is a well-accepted marker of coronary atherosclerosis since it is not found in its absence.[1,2] Imaging techniques for the detection of coronary calcification include fluoroscopy, sonography, conventional computed tomography (CT) and electron beam computed tomography (EBCT). The standard method for the quantification of coronary artery calcium is EBCT. EBCT combines the high-contrast resolution of CT and eliminates blurring of the image due to cardiac motion by using electrocardiographic triggering and a 100-msec scan time.[3] The reliability and validity of the method is well established.[4–6] The quantity of coronary artery calcium detected by EBCT is a predictor of the incidence of coronary artery events.[7–12] On the other

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Table 1 Patient characteristics

Symptom			
Chest pain	28 (34%)		
Chest oppression	25 (30%)		
ECG abnormality	9 (11%)		
Palpitation	7 (8%)		
Dyspnea on effort	7 (8%)		
Other	7 (8%)		
Final diagnosis			
Angina pectoris	36	Vasospastic angina	6
Arrhythmia	20	Hypertension	7
Pulmonary disease	5	Heart failure	3
Cardiomyopathy	2	Thoracic dissecting aneurysm	
Mitral regurgitation	1		2
Aortic stenosis	1	Aortic regurgitation	1
Esophageal hiatal hernia	1	Tricuspid regurgitation	1
Abnormality on CAG (n = 43)			
1-vessel disease	7 (16%)		
2-vessel disease	12 (23%)		
3-vessel disease	13 (30%)		
Risk factors for ischemic heart disease			
Hypertension	52 (63%)		
Smoking history	51 (61%)		
Hyperlipidemia	48 (58%)		
Diabetes	22 (27%)		
Family history	13 (16%)		

hand, double helix CT, which is an older generation technique of multidetector computed tomography (MDCT), is a useful alternative method of EBCT for the detection and quantification of coronary artery calcification.[13]

Recently, many institutions have acquired MDCT devices. An MDCT allows for faster examinations and higher spatial resolution compared with conventional helical CT. In daily practice, incidental detection of coronary artery calcification by non-gated MDCT is encountered as frequently as that by conventional CT, but the detectability must be improved by the new technique. However, the clinical significance of the calcification has not been investigated compared with conventional CT. Therefore, we evaluated the estimation of myocardial ischemia by coronary arterial calcification. Although most studies have investigated the relationship between coronary artery calcification and coronary artery stenosis, only two adopted myocardial perfusion SPECT as an endpoint of coronary artery calcification.[10,14] We believe that myocardial ischemia is a better endpoint for coronary arterial disease than is coronary arterial stenosis, because thallium exercise stress testing shows the microcirculation and perfusion of the myocardium itself. The present study investigated the relationship between coronary artery calcification by non-gated MDCT and myocardial ischemia determined by thallium exercise stress testing.

MATERIALS AND METHODS

Study population

Between October 1999 and May 2005, 7,378 patients who were clinically suspected of having lung disease and cardiovascular disease underwent non-gated MDCT at our hospital. Among them l56 were clinically suspected of having ischemic heart disease and underwent thallium exercise stresss testing within 90 days of MDCT. We included patients with symptoms such as chest pain at rest or effort, chest oppression, palpitation, and/or with ECG abnormalities such as ST depression by master double ECG. Among the 156 patients, 30 were treated by coronary artery bypass grafting (CABG) and 43 by percutaneous coronary intervention (PCI). These 73 patients were excluded because their ischemic disease had been treated before the thallium exercise stress testing. The present analysis included the remaining 83 patients: 55 men and 28 women with a mean age of 68 (range; 36–83 years). The median interval time between the thallium scans and MDCT was 26 days (range; 0–90 days). Forty-three patients underwent coronary angiography (CAG) to confirm their diagnosis. The patient characteristics are shown in Table 1.

Data acquisition

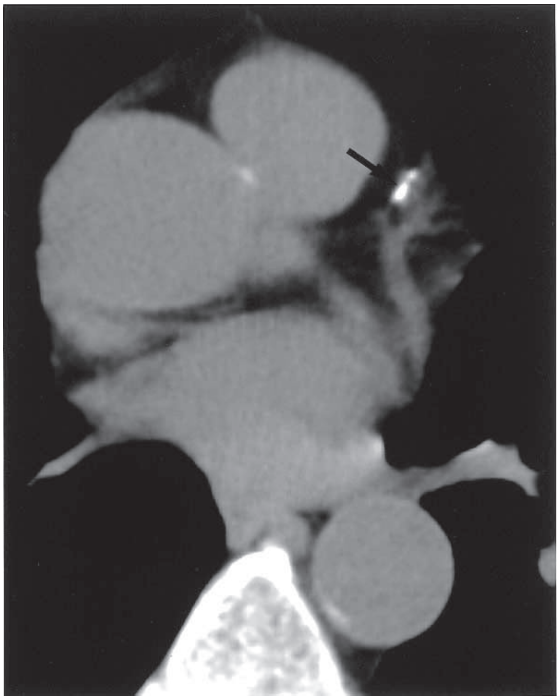
MDCT

CT scans were obtained using a multi-detector CT scanner (Aquilion; TOSHIBA, Japan) without cardiac gating. Scanning was extended from the lung apices to below the costophrenic angles, and no intravenous contrast was administered. The CT scanning parameters were as follows: 120 kVp, 250 mA, 4 × 3 mm collimation, rotation time of 0.5 seconds, pitch of 5.5, reconstruction of 7 mm, four detector rows.

Thallium exercise stress testing

The Bruce treadmill protocol was used to administer the thallium exercise stress tests.[15] For each study, 74 MBq of ^{201}Tl chloride was intravenously injected. The injection was performed at the time of peak exercise achieved using the treadmill, as defined by symptom-limited end points, target heart rate-limited end points, leg fatigue, shortness of breath and ECG abnormality end points.

Exercise was continued for an additional 60 seconds to allow for adequate circulation of the tracer. Five minutes after injection, stress SPECT images were acquired using a three-head gamma camera (IRIX; Picker, USA) with a 360° arc. The projections were acquired over 360° using a 64 × 64 matrix and a zoom of 1.42. The slice thicknesses for the SPECT were 6.6 mm and the voxel dimensions were 6.6 mm × 6.6 mm × 6.6 mm. Three hours after the stress study, resting imaging was initiated using the same acquisition protocol. Since a strict caffeine restraint was not maintained, thallium drug stress testing was excluded.



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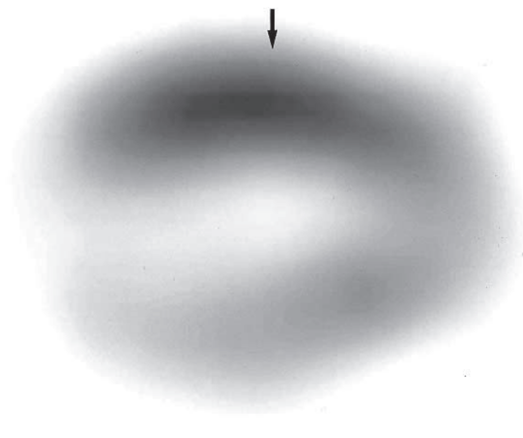

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Fig. 1 A 74-year-old man with chest pain (true positive case). a) MDCT scan of the patient showed calcification of the LAD coronary artery (*black arrow*). b) ^{201}Tl myocardial perfusion SPECT during stress showed hypoperfusion of the anterior wall (*black arrow*). c) ^{201}Tl myocardial perfusion SPECT during rest showed fill-in of the anterior wall (*black arrow*) indicating ischemia of the LAD territory. CAG of this patient also showed 60% stenosis of the LAD.

Determination of myocardial ischemia

Myocardial ischemia was determined by stress-rest myocardial perfusion SPECT. An abnormal area in early images with complete or partial redistribution in delayed images was considered to be an indicator of myocardial ischemia. Perfusion defects that remained unchanged in the delayed images were also considered to be a myocardial ischemia indicator. Abnormalities by SPECT were independently interpreted by two radiologists who did not know the results of calcification by MDCT (Fig. 1).

Definition of coronary calcification

The presence of calcium was evaluated for the three main coronary vessels: the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). Major coronary arteries were identified by their anatomic location. Coronary artery calcification was defined as the presence of a visible calcific lesion of area more than 1 mm^2 with a maximal CT number of greater than 130 HU. This criterion for coronary artery calcification could be used to discriminate a single pixel with a CT number of 130 HU that might result from noise.[16] All MDCT scans were interpreted by a radiologist who did not know the results of the thallium nuclear scans (Fig. 2).

Risk factors

Risk factors such as hypertension, smoking, hyperlipidemia, diabetes, and family history were compared for evidence of coronary artery calcification detected by multidetector CT and myocardial ischemia detected by thallium nuclear scans.

Statistical method

Using the chi-square test with Yate's correction, groups with and without calcification by MDCT were compared for evidence of ischemia upon thallium exercise stress testing by patients and by major coronary arterial branches. A p-value of <0.05 was considered to be statistically

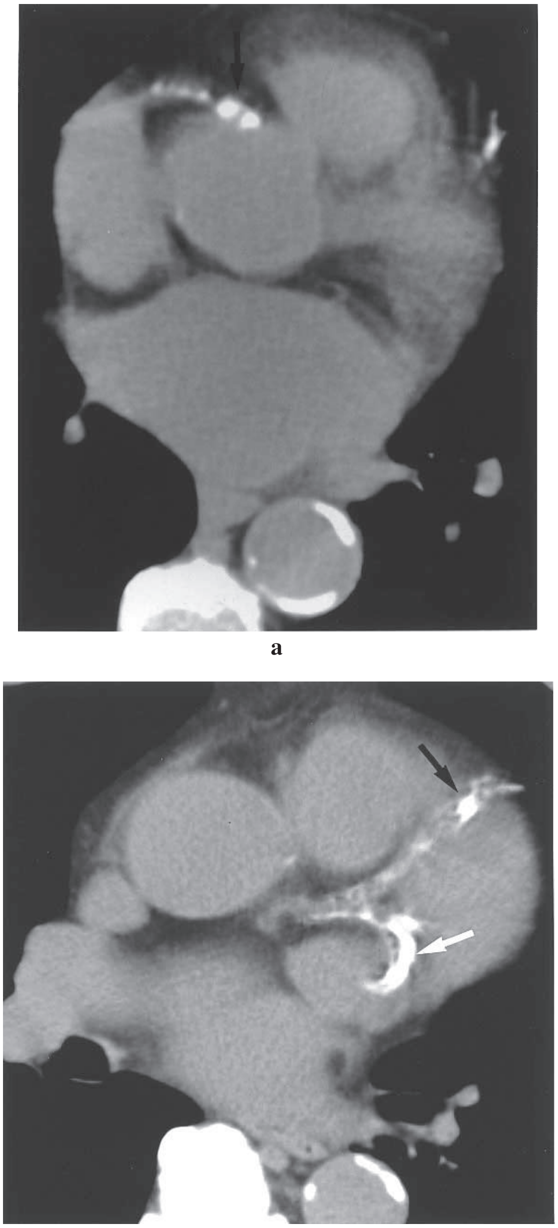

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Fig. 2 A 54-year-old man with dyspnea during effort. a) Transvers CT scanning showed coarse calcification of the RCA (*black arrow*). b) Transvers CT scanning showed coarse calcification of the LAD coronary artery (*black arrow*) and the LCX coronary artery (*white arrow*). CAG of this patient also showed 75% stenosis of the LAD and 50% stenosis of the LCX.

significant. The sensitivity, specificity, and positive (PPV) and negative predictive value (NPV) of MDCT for detecting myocardial ischemia upon thallium exercise stress testing were calculated.

Similarly, the detectability of ischemia by CAG was examined. Significant stenosis of the coronary artery was defined as more than 70% stenosis of the coronary artery on coronary angiography. The relationship between CAG

Table 2 The relationship between calcification of the coronary arteries found by MDCT and ischemic changes found by thallium exercise stress testing

	Thallium exercise stress testing	
	Ischemia (n = 35)	No ischemia (n = 48)
Calcification on MDCT (n = 41)	23 (66%)	18 (38%)
No calcification (n = 42)	12 (34%)	30 (62%)

Chi-square test: $p < 0.02$
(Yate's correction: 5.367)
Note: Coronary artery calcification was defined as the presence of a visible calcific lesion area of more than 1 mm with maximal CT number greater than 130 HU. An abnormal area in the early image with complete or partial redistribution in the delayed images was considered to be an indicator of ischemia. P-values were derived using the chi-square test. MDCT = multidetector computed tomography.

Table 3 The relationship between calcification of the coronary arteries found by MDCT and ischemic changes found by thallium exercise stress testing for coronary arterial territories

	Thallium exercise stress testing	
	Ischemia (n = 54)	No ischemia (n = 195)
Calcification on MDCT (n = 74)	30 (56%)	44 (23%)
No calcification (n = 175)	24 (44%)	151 (77%)

Chi-square test: $p < 0.001$
(Yate's correction: 20.486)
Note: Coronary artery calcification was defined as the presence of a visible calcific lesion area of more than 1 mm with maximal CT number greater than 130 HU. An abnormal area in the early image with complete or partial redistribution in the delayed images was considered to be an indicator of ischemia. P-values were derived using the chi-square test. MDCT = multidetector computed tomography.

and calcification was also calculated by the same methods.

The patients were stratified by the number of risk factors, and the probability of calcification and ischemia was calculated for each group. The relationship between the number of risk factors and coronary artery calcification or ischemia was examined using the Mann-Whitney U test.

RESULTS

In total, 249 coronary areas of the 83 patients were analyzed by MDCT and thallium exercise stress testing (Tables 2, 3). Myocardial ischemia was found in 54 coronary areas (22%) of 35 patients (42%) by thallium

Table 4 The relationship between calcification of coronary arteries found by MDCT and stenosis by CAG for coronary arterial territories

	CAG	
	Significant stenosis (n = 68)	No significant stenosis (n = 61)
Calcification on MDCT (n = 52)	38 (56%)	14 (23%)
No calcification (n = 77)	30 (45%)	47 (77%)

Chi-square test: $p < 0.001$
(Yate's correction: 13.157)
Note: Coronary artery calcification was defined as the presence of a visible calcific lesion area of more than 1 mm with maximal CT number greater than 130 HU. Significant stenosis of the coronary was defined for >70% coronary angiography. P-values were derived using the chi-square test. MDCT = multidetector computed tomography. CAG = coronary angiography.

Table 5 The relationship between ischemia changes found by thallium exercise stress testing and stenosis by CAG for coronary arterial territories

	Ischemia (n = 51)	No ischemia (n = 78)
Significant stenosis (n = 68)	42 (82%)	26 (33%)
No significant stenosis (n = 61)	9 (18%)	52 (67%)

Chi-square test: $p < 0.001$
(Yate's correction: 27.793)
Note: Coronary artery calcification was defined as the presence of a visible calcific lesion area of more than 1 mm with maximal CT number greater than 130 HU. Significant stenosis of the coronary was defined for >70% coronary angiography. P-values were derived using the chi-square test. MDCT = multidetector computed tomography. CAG = coronary angiography.

nuclear scans, while the remaining 195 coronary areas (78%) and 48 patients (58%) were normal.

Of the 83 patients, coronary artery calcification was detected by MDCT in 74 major coronary branches (30%) of 41 patients (49%). Except for one patient with calcification of the RCA, 40 patients had calcification of the LAD. Eighteen of the patients had calcification of the RCA and LAD, and 4 patients had calcification on the LCX and LAD. Eleven patients had calcification of all three major coronary branches.

The frequency of coronary artery calcification with/without myocardial ischema is summarized by patient group in Table 2 and by coronary artery territories in Table 3. By patients, the sensitivity, specificity, PPV and NPV of coronary artery calcification seen using MDCT for detection of myocardial ischemia were 65, 63, 56, and 71%, respectively.

Table 6 The relationship between calcification of coronary arteries found by MDCT, ischemic changes found by thallium exercise stress testing and risk factors for ischemic heart disease

	Calcification		Ischemia	
	+ (n = 41)	− (n = 42)	+ (n = 35)	− (n = 48)
Hypertension (n = 52)	27	25	24	28
Smoking (n = 51)	28	23	25	26
Hyperlipidemia (n = 48)	24	24	21	27
Diabetes (n = 22)	12	10	14	8
Family history (n = 13)	6	7	8	5

Table 7 The relationship between calcification of coronary arteries found by MDCT, ischemic changes found by thallium exercise stress testing and risk factors for ischemic heart disease

Number of risk factor (*1)	Calcification (*2)	Ischemia (*3)
0 (n = 2)	2 (100%)	1 (50%)
1 (n = 18)	4 (22%)	3 (17%)
2 (n = 30)	16 (53%)	12 (40%)
3 (n = 20)	12 (60%)	9 (45%)
4 (n = 12)	6 (50%)	9 (75%)
5 (n = 1)	1 (100%)	1 (100%)

Correlation between *1 and *2: $p = 0.405$
Correlation between *1 and *3: $p = 0.038$ (Mann-Whitney U test)

When calcification was evaluated by coronary artery territories, the sensitivity, specificity, PPV and NPV were 55, 77, 41, and 86%, respectively.

Similarly, the frequency of coronary artery stenosis in arterial territories with/without myocardial ischemia and calcification are shown in Tables 4 and 5, respectively.

The numbers of patients with risk factors are shown with or without calcification and ischemia in Table 6. Individual risk factors did not show strong relationships with calcification or ischemia. However, the number of risk factors showed a greater correlation with ischemia than with calcification in Table 7.

DISCUSSION

Since the examination time for MDCT is decreasing, the number of screening studies of chest CT on patients with suspected chest disease is increasing. Coronary artery calcification is often incidentally noted in these patients. In the present study, the clinical significance of such incidental discovery of coronary artery calcification by non-gated MDCT was evaluated in relation to myocardial ischemia found by thallium exercise stress testing. The sensitivity, specificity, PPV and NPV reported by an AHA report that compared the calcium detected by EBCT and angiographic stenosis were 100–85, 76–41, 84–55, and 70–100%, respectively.[2,17–22]

Although the sensitivity and PPV of coronary arterial calcification by non-gated MDCT were low, specificity by patients, and specificity and NPV by coronary arterial territories were relatively high in comparison with those other reports adopted by the American Heart Association (AHA) consensus report.

Temporal resolution of EBCT should be better than that of MDCT without the ECG-gated image reconstruction technique, and minute calcification might be overlooked by MDCT. Although an ECG-gated technique would improve the visibility of arterial calcification, we focused on routine CT in the present study because standard CT is widely applicable and performed. If ischemia could be predicted by routine CT, it would have greater clinical impact than that predicted by high-performance and time-consuming examination.

The endpoint was also different between the present study and the AHA consensus report.[2] In the AHA consensus report, significant stenosis of the coronary artery was defined as more than 70% stenosis of the coronary artery on coronary angiography, while in the present study thallium exercise stress testing was used as an indicator of myocardial ischemia. Myocardial ischemia occurs when the requirement for oxygen by either ventricle exceeds its supply.[23] Thallium nuclear testing is more suitable for screeing for ischemic heart disease because it shows the microcirculation and perfusion of the myocardium itself.

In the present study, the mean patient age was 68 years, which was higher than that of the AHA consensus report.[2] The difference may be attributed to the late onset of atherosclerosis in Japanese people compared to the North American population.[9]

According to a statement for health professionals from the AHA, the absence of calcified deposits found by EBCT implies the absence of significant angiographic coronary narrowing. However, it does not imply the absence of atherosclerosis, including unstable plaques because they do not calcify. Therefore the presence of atherosclerotic plaques including unstable plaques can not be ruled out if no coronary arterial calcification is noted by EBCT, but it implies a very low likelihood of significant luminal obstruction.[2]

The probability of myocardial ischemia was low for the coronary arterial territories without coronary arterial calcification examined by non-gated MDCT, and the predictive values were comparable to those by CAG. We did not perform CAG on all of the patients in this study, because it was not clinically practical to perform CAG when ischemic diseases were not suspected. Although we could not directly compare the detectability of ischemia between calcification and CAG, the relationship between CAG and ischemia was shown in the analysis by coronary arterial territories applying the non-ischemic territories as true negative.

On the other hand, among patients with coronary arterial calcification observed by non-gated MIDCT, 66% had ischemic heart disease. Therefore, for patients with an incidental finding of coronary arterial calcifcation by non-gated MDCT, further cardiac study including thallium nuclear testing is recommended.

In conclusion, the risk for myocardial ischemia of the coronary arterial territories is relatively low for patients with suspected ischemic heart disease without calcification of the coronary arterial territories observed by non-gated MDCT. If coronary artery calcification is detected by a non-gated multidetector CT, the patients should be asked whether they have any symptoms of ischemic heart disease. In addition thallium exercise stress testing should be recommended, if the patient reports any such symptoms.

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