Characteristics of Patients With a Significant Stenosis in a Conventional Coronary Angiogram With a Normal Multi-Detector Computed Tomographic Coronary Angiogram

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SUMMARY

Multi-detector computed tomography (MDCT) has high diagnostic value for detecting or excluding coronary artery stenosis. However, conventional coronary angiograms (CCA) are occasionally required in patients having persistent chest pain with normal MDCT.

We retrospectively analyzed 90 patients who underwent CCA due to persistent chest pain with normal MDCT. The patients were classified into patients having more than 50% diameter stenosis in CCA (false negative, group I: $n = 14$, 62.6 ± 7.5 years, 7 males) and those having less than 50% diameter stenosis (true negative, group II: $n = 76$, 52.1 ± 12.0 years, 42 males). Significant stenosis was observed in 9 patients at the left anterior descending artery, 4 at the right coronary artery, and 1 at the left circumflex artery in group I. Group I patients were older than group II patients (63 ± 8 versus 52 ± 12 years, $P < 0.001$). There were more patients with hypertension and smoking in group I (64.3% versus 7.9%, 35.7% versus 3.9%, $P < 0.001$, $P < 0.001$, respectively). The levels of uric acid and homocysteine were higher in group I than in group II (5.7 ± 1.5 versus 4.6 ± 1.2 mg/dL, 9.6 ± 3.1 versus 7.4 ± 2.5 mol/L, $P = 0.008$, $P = 0.010$, respectively). There were more ST or T changes in the electrocardiograms in group I (35.7% versus 1.3%) ($P < 0.001$). In multivariate analysis, a history of hypertension, uric acid levels, and ischemic evidence in the electrocardiogram were independent factors for a false negative of MDCT (odds ratio 11.11, 4.76, 1.81, 95% confidence interval 4.67 to 10.00, 1.41 to 1.61, 1.05 to 3.33, $P = 0.009$, $P = 0.012$, $P = 0.046$, respectively).

In certain situations, the findings of coronary stenosis by MDCT do not always correlate with that of CCA. (Int Heart J 2009; 50: 13-22)

Key words: Coronary artery disease, CT angiogram, Conventional coronary angiogram

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CORONARY artery disease represents a leading cause of death and health care expenditure in industrialized countries.^{1,2)} Establishing its anatomic diagnosis requires conventional coronary angiography (CCA), a procedure that is costly and carries risks and discomfort.^{3,4)} Contrast-enhanced multi-detector-row computed tomography (MDCT) is now capable of providing high-quality noninvasive views of cardiac anatomy and 'instant' noninvasive coronary angiography. With current generation 64-slice scanners, MDCT can be performed in most patients with minimal patient discomfort and high diagnostic accuracy.^{5,6)} MDCT may obviate the need for invasive diagnostic CCA in patients with borderline symptoms or equivocal noninvasive testing.

Single-center studies have reported sensitivities between 85% and 100%, specificities between 50% and 95%, positive predictive values between 75% and 93%, and negative predictive values between 75% and 99% for the detection of obstructive coronary lesions using 16-row MDCT scanners.^{7,8)} However, MDCT has disadvantages too. Calcified vessels are still difficult to assess, as is the accurate evaluation of implanted coronary stents. The volume of contrast material required for proper opacification limits the use of MDCT in patients with renal dysfunction.⁹⁾ Finally, CCA is occasionally required in patients having persistent chest pain with normal MDCT findings. The purpose of this study was to elucidate the characteristics of patients with a significant stenosis in CCA using normal MDCT coronary angiography.

METHODS

Study population and study design: Between January 2006 and July 2007, 5,207 patients with atypical chest pain underwent cardiac MDCT at Chonnam National University Hospital. Among these patients, 492 patients with abnormal MDCT findings underwent CCA and percutaneous coronary intervention (PCI). The other 90 patients with a normal MDCT coronary angiogram (defined as a total calcium score of zero and the absence of critical stenosis in both coronary arteries) complained of recurrent chest pain. These patients underwent diagnostic CCA to determine the cause of the chest pain. All patients underwent a CT angiogram and CCA within a relatively short interval (mean, 13 ± 6 days). Fourteen patients had significant stenosis and 76 patients had no significant stenosis in the CCA. The CCA was interpreted by a board-certified cardiologist. Diameter stenosis was assessed by quantitative coronary angiography (QCA). Diameter narrowing of more than 50% was considered to be significant. Lesion type was determined according to the criteria of the American College of Cardiology/American Heart Association (ACC/AHA). Patients with significant stenosis in CCA were assigned to group I (14 patients, 63 ± 8 years, 7 males)

while those with no significant stenosis were assigned to group II (76 patients, 52 ± 12 years, 42 males). Age, sex, body mass index, risk factors for coronary artery disease (hypertension, diabetes, smoking, hyperlipidemia, family history of ischemic heart disease), clinical impression of patients, past medication [aspirin, clopidogrel, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins], blood chemistry (lipid profiles, inflammatory markers, cardiac enzymes, N-terminal pro-B-type natriuretic peptide (NT-proBNP)), electrocardiographic (ECG), echocardiographic, and CCA findings were analyzed.

Cardiac MDCT angiography: In the absence of contraindications [contraindication to intravenous contrast agents (contrast allergy) or elevated serum creatinine (> 1.3 mg/dL) or atrial fibrillation or frequent ventricular ectopy (> 10 extra systoles per minute), or a heart rate > 90 bpm], all patients with a resting heart rate of > 70 bpm received 50-100 mg of metoprolol orally 1-2 hours before the

Figure 1. Example of mismatch of stenosis between multi-detector computed tomogram (MDCT) and conventional coronary angiogram (CCA) in a 58 year-old male patient. There was no significant stenosis of either coronary artery on 3-dimensional reconstruction by MDCT (A, B, C). Close-up multiplanar reformation image of the right coronary artery (RCA) revealed no significant stenosis (D).

scan. Blood pressure and pulse were rechecked immediately prior to performing the procedure. CT examinations were performed with a two-phase, contrast-enhanced, ECG-gated, MDCT scanner (Sensation Cardiac 64, Siemens, Forchheim, Germany) set at a 0.75-mm section thickness with a gantry rotation time of 330 msec and a kernel value of B25f. The tube current was 800 mAs at 120 kVP. The pitch, defined as the ratio of the table feed in one rotation over the detector coverage in the transverse direction, was determined as 0.2. The scan delay was determined using the bolus tracking technique: when a threshold of 120 Hounsfield Units (HU) was reached in the ascending aorta at the level of the origin of the coronary arteries, a delay of 5 seconds was applied before the scan was initiated. Serial CT scanning in the axial plane, together with an ECG triggered examination, was performed from the level of the left ventricular apex after a

Figure 2. Significant stenosis of the mid-RCA was seen on CCA (A). Intravascular ultrasonogram (IVUS) revealed significant mixed plaque in the mid-RCA (B). IVUS-guided stenting (3.0 × 23 mm Cypher) was performed for this lesion. The final coronary angiogram showed good distal flow without residual stenosis (C). IVUS findings after stent implantation (D).

bolus injection of 60 mL of nonionic contrast media (Ultravist 370[®], Schering) followed by a 60 mL saline bolus injection, and both were injected at a flow rate of 4 mL/second. All CT images were analyzed by a radiologist who had 5 years experience with coronary CTA imaging. The axial images were reconstructed at multiple phases that covered the cardiac cycle in increments of 10% of the RR interval between 5% and 95%. Multiphase reconstruction was performed using short axis slices from the base to the apex of the heart using commercially available software (Argus[®], Siemens) (Figure 1).

Conventional coronary angiography: CCA was performed using a digital flat panel fluoroscope (Phillips) via a femoral approach applying nonionic contrast material (Ultravist[®] 370, Schering, Berlin, Germany). A minimum of 4 orthogonal views were obtained (Figure 2).

Statistical analysis: Continuous variables with normal distributions are expressed as the mean $\pm$ SD and were compared using an unpaired Student's *t*-test. Categorical variables were compared using the chi-square test, where appropriate. Relative risks were calculated by dividing the Kaplan-Meier estimated rate of factors in the false negative group by that in the true negative group. The 95 percent confidence interval for the relative risk was calculated using the standard errors from the Kaplan-Meier curve. The predictive factors for significant stenosis were calculated by multiple logistic regression analysis. A *P* value less than 0.05 was deemed as being significant. Statistical analyses were performed with Statistical Package for Social Sciences software (SPSS 15.0 for Windows).

RESULTS

Clinical characteristics: The mean age was higher in group I than in group II (63 ± 6 versus 52 ± 12 years, $P < 0.001$). Sex and body mass index were not significantly different between the groups. There were higher incidences of a history of hypertension (64.3% versus 7.9%, $P < 0.001$) and current smoking (35.7% versus 3.9%, $P < 0.001$) in group I. There were no significant differences in the incidences of diabetes and hyperlipidemia between the groups. Past pharmacological therapy was similar between the groups; 28.6% of group I and 17.1% of group II had taken aspirin, 14.3% and 7.9% clopidogrel, 21.4% and 18.4% beta-blockers, 14.3% and 7.9% angiotensin converting enzyme inhibitors, 14.3% and 11.8% angiotensin receptor blockers, and 14.3% and 14.5% statins (Table I).

Laboratory findings: The lipid profiles were not significantly different between the groups (Table II). The levels of uric acid and homocysteine were higher in group I than in group II ($P = 0.008$, $P = 0.010$, respectively). The levels of fibrinogen and high sensitivity C-reactive protein (hs-CRP) were not significantly different between the groups. The levels of NT-proBNP and cardiac enzymes

Table I. Baseline Clinical Characteristics

	Group I (n = 14)	Group II (n = 76)	P
Age (years)	62.6 ± 7.5	52.1 ± 12.0	< 0.001
Male (%)	7 (50.0)	42 (55.3)	0.735
Body mass index (kg/m ²)	24.9 ± 12.7	24.6 ± 7.5	0.744
Risk factor (%)			
Hypertension	9 (64.3)	6 (7.9)	< 0.001
Diabetes mellitus	0 (0.0)	2 (2.6)	0.539
Smoking	5 (35.7)	3 (3.9)	< 0.001
Hyperlipidemia	2 (14.3)	2 (2.6)	0.052
Family history	2 (14.3)	6 (7.9)	0.298
Past medication (%)			
Aspirin	4 (28.6)	13 (17.1)	0.314
Clopidogrel	2 (14.3)	6 (7.9)	0.440
Beta-blocker	3 (21.4)	14 (18.4)	0.792
Angiotensin converting enzyme inhibitor	2 (14.3)	6 (7.9)	0.440
Angiotensin receptor blocker	2 (14.3)	9 (11.8)	0.798
Statin	2 (14.3)	11 (14.5)	0.985

Table II. Laboratory Findings

	Group I (n = 14)	Group II (n = 76)	P
Lipid profiles			
Total cholesterol	182.5 ± 50.3	172.1 ± 41.3	0.589
Low density lipoprotein	130.6 ± 43.0	111.1 ± 36.8	0.287
High density lipoprotein	61.8 ± 25.3	50.4 ± 15.1	0.080
Triglycerides	130.3 ± 41.1	106.8 ± 83.0	0.203
Apolipoprotein A	153.7 ± 39.6	140.6 ± 26.0	0.121
Apolipoprotein B1	98.1 ± 31.8	103.0 ± 93.5	0.732
Lipoprotein(a)	24.4 ± 16.0	31.4 ± 25.1	0.192
Inflammatory markers			
Uric acid	5.7 ± 1.5	4.6 ± 1.2	0.008
Homocysteine	9.6 ± 3.1	7.4 ± 2.5	0.010
Fibrinogen	256.7 ± 48.6	271.4 ± 67.3	0.568
Highly sensitive C-reactive protein	0.4 ± 1.2	0.3 ± 0.2	0.708
Cardiac enzymes			
Creatine kinase	93.1 ± 46.7	89.5 ± 40.2	0.824
Creatine kinase-MB	5.2 ± 3.4	5.6 ± 3.1	0.729
Troponin I	0.02 ± 0.02	0.04 ± 0.08	0.306
Troponin T	0.01 ± 0.01	0.01 ± 0.0	0.370

[creatin kinase (CK), CK-MB, troponin T and I] were not significantly different between the groups.

Electrocardiographic and echocardiographic findings: ST segment depression or T-wave inversion was observed on the ECG in 5 patients in group I and in 1 patient in group II (35.7% versus 1.3%, $P < 0.001$). The ejection fraction was 69.1% in group I and 66.6% in group II (Table III).

CCA findings in group I: In 14 patients, the vessel involved was the left anterior

Table III. Electrocardiogram and Echocardiogram Findings

	Group I (n = 14)	Group II (n = 76)	P
Electrocardiogram findings			< 0.001
Within normal limits	9 (64.3)	75 (98.7)	
ST segment depression or T inversion	5 (35.7)	1 (1.3)	
Echocardiogram findings			
Ejection fraction	69.1 ± 7.5	66.6 ± 5.7	0.174

Table IV. Conventional Coronary Angiographic Findings

	Group I (n = 14)
Artery of stenosis (%)	
Left main	0 (0.0)
Left anterior descending artery	9 (64.3)
Left circumflex artery	1 (7.1)
Right coronary artery	4 (28.6)
Lesion type* (%)	
A	0 (0.0)
B1	4 (28.6)
B2	7 (50.0)
C	3 (21.4)
Diameter stenosis (%)	86.7 ± 14.2
TIMI flow (%)	
0 or 1	1 (7.1)
2	5 (35.6)
3	8 (57.3)
Percutaneous coronary intervention	
Success rate (%)	14 (100.0)
Bare metal stent (%)	1 (7.1)
Sirolimus-eluting stent (%)	5 (35.6)
Paclitaxel-eluting stent (%)	9 (64.3)
Stent diameter (mm)	3.6 ± 1.4
Stent length (mm)	25.7 ± 7.9

*Lesion type according to ACC/AHA

descending artery in 9 patients, the right coronary artery in 4 patients, and the left circumflex artery in 1 patient. Lesion type according to the ACC/AHA criteria was type B1 in 4 patients, B2 in 7, and type C in 3. Mean diameter stenosis was $86.7 \pm 14.2\%$. Pre-PCI thrombolysis in myocardial infarction (TIMI) flow was 1 in one patient, 2 in 5 patients, and 3 in 3 patients.

All patients underwent PCI with stent implantation. A bare metal stent was used in 1 patient, sirolimus-eluting stents in 5 patients, and paclitaxel-eluting stents in 9 patients. Mean stent diameter was 3.6 ± 1.4 mm and mean stent length was 25.7 ± 7.8 mm (Table IV).

Predictors for significant stenosis in CCA with normal MDCT: A past history of hypertension, high uric acid levels, and ST segment depression or T wave inver-

Table V. Multivariate Analysis of Significant Coronary Artery Stenosis in Conventional Coronary Angiogram

	Odd ratio	95% confidence interval		<i>P</i>
		Lower	Upper	
Hypertension	11.11	4.67	10.00	0.009
High level of uric acid	4.76	1.41	1.61	0.012
ST segment depression or T inversion in electrocardiogram	1.81	1.05	3.33	0.046
Old age	1.10	0.09	6.22	0.097
High level of homocysteine	1.26	0.92	1.73	0.161
High body mass index	1.49	0.69	3.25	0.314
Statin treatment	0.42	0.16	1.09	0.601
High level of hs-CRP	1.03	0.68	2.05	0.678
Ejection fraction	0.97	0.79	1.17	0.738
High level of NT-pro BNP	1.10	0.77	1.85	0.789
Diabetes	1.10	0.88	1.74	0.881

hs-CRP indicates high sensitivity C-reactive protein; and NT-pro BNP, N-terminal pro brain natriuretic peptide.

sion in ECG are independent predictive factors for significant stenosis in CCA ($P = 0.009$, $P = 0.012$, $P = 0.046$, respectively) in patients having normal MDCT findings (Table V).

DISCUSSION

To the best of our knowledge, this is the first study to show that the findings of coronary stenosis by MDCT do not always correlate with that of CCA in certain situations.

It is known that anatomical coronary artery disease, such as that assessed by CCA, does not always correlate with the functional severity of the disease.⁹⁻¹²⁾

A recent study has demonstrated how much the latest improvement in MDCT technology with a faster gantry rotation time and submillimeter slices acquired with 64-slice CT scanners has led to an increase in segments of the coronary tree being evaluable for the detection of coronary artery stenosis. MDCT has been shown to be a reliable diagnostic technique for the evaluation of coronary artery stenoses.¹⁰⁻¹³⁾ However, coronary calcification influences image quality, and blurring due to severe calcification can cause an image to be uninterpretable.¹⁴⁻¹⁸⁾ Furthermore, MDCT tends to overestimate the degree of stenosis compared with that of CCA.^{10,11)}

Until now, Medline searches have not identified any reports that analyzed the characteristics of patients with false negatives using MDCT.

This study has several limitations. First, the study population was very small. Only 14 patients were enrolled in the false negative group. As mentioned

above, because of the high negative predictive value of MDCT, whose maximum is 99%, the frequency of discordance between MDCT and CCA is very low. Multicenter trials are necessary to overcome this limitation. Second, assessment of diameter stenosis was only performed by QCA. Intravascular ultrasonography (IVUS) has advantages for the evaluation of coronary atherosclerotic burden and disease progression.¹⁹⁻²³⁾ Third, our study was a retrospective and cross-sectional study, and not a randomized and controlled prospective study. Finally, all patients with normal MDCT findings did not undergo CCA. The sensitivity, specificity, positive predictive value, and negative predictive value could not be calculated in our study.

CCA may be necessary in patients who complain of persistent chest pain with hypertension, high levels of uric acid, and ischemic evidence in electrocardiograms, although having normal findings in MDCT. Although MDCT appears to be useful as a screening tool for patients with suspected coronary artery disease, it does not yet seem to have a complementary role in clinical decision-making for revascularization strategies.

Prospective studies involving many patients are warranted to define the characteristics of patients with a false negative in MDCT in clinical practice.

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