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Prevalence of computed tomographic angiography-verified high-risk plaques and significant luminal stenosis in patients with zero coronary calcium score

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ABSTRACT

Background: Some patients were detected with coronary artery disease even if the coronary artery calcium score was (CACS) = 0. We evaluated the prevalence and predictor of significant stenosis and computed tomography (CT) based vulnerable plaque (CTVP) for patients with CACS = 0.
Methods: Subjects were 2160 patients (M/F = 1110/1050, 64.7 ± 11.6 years) who underwent measurement of calcium score and CT coronary angiography. As for CACS = 0 group, age, gender, coronary risk factor (family history (FH), hypertension (HT), hyperlipidemia (HL), diabetes (DM), and smoking), body mass index, history of cerebral infarction, the presence of chest symptom, and abnormal rest ECG findings were investigated as predictors for significant stenosis and CTVP by multivariate analysis using logistic regression analysis.
Results: Out of 2160 patients, 1141 (52.8%, M/F = 655/486, 68.4 ± 9.8 years) were of CACS > 0 and 1019 (47.2%, M/F = 455/564, 60.5 ± 12.0 years) were of CACS = 0. In the CACS = 0 group, 24 patients (2.4%) were found with significant stenosis and 47 (4.6%) with 2FPP. In 104 patients with spotty calcification (10.2%), 10 (9.6%) out of these 104 had significant stenosis and also had CTVP. Multivariate analysis using logistic regression analysis revealed significant predictor for significant stenosis to be only male (Odds ratio (OR): 3.075, 95%CI 1.166–8.109, p = 0.0232) and significant predictor for CTVP to be age (OR: 1.032, 95%CI 1.001–1.063, p = 0.0437) and male (OR: 2.386, 95%CI 1.193–4.775, p = 0.0140).
Conclusions: The present study suggests that the presence of CTVP must be noted, when patients are male and elderly even if CACS = 0 and the presence of spotty calcification increases the prevalence of significant stenosis and CTVP in patients with CACS = 0.

1. Introduction

Coronary artery calcium score (CACS) is closely associated with the presence of coronary atherosclerosis. It has been well established that the greater the CACS, the higher is the likelihood of cardiac events [1]. The absence of coronary calcification has been proposed as the predictor of an uneventful course both in symptomatic and asymptomatic patients [2,3]. In a metanalysis of 18 CACS studies the absence of CACS was associated with a 93% negative predictive value for coronary artery disease (CAD) [2]. In the multicenter CORE64 study, one-fourth of the patients who underwent computed tomography coronary angiography (CTCA) for suspected angina pectoris had CACS of zero (CACS = 0); 19% of the CACS = 0 patients were found to have significant coronary stenosis. Thus, it may be possible that CACS = 0 does not necessarily rule out CAD completely [4].

It has been reported that approximately 60% of coronary lesions that are the underlying cause of acute coronary syndrome (ACS) do not have significant stenosis [5]. Such plaques, however, harbor characteristic morphological features that are distinct from the stable plaques, which include large plaque and necrotic core volumes, thin overlying fibrous caps and intense inflammation by macrophages [6]. Motoyama et al. reported CTA characteristics of the culprit lesions which included following two features; low attenuation plaques (LAP) (suggestive of IVUS-verified necrotic cores) which were more likely to be positively remodeled (PR). These two feature-positive plaques (2FPP) were also associated more frequently with spotty calcification compared to the lesions responsible for stable angina pectoris [7]; such lesions were usually not associated with large

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calcific plates. The presence of 2FPP in the absence of ACS is associated with more than 22% probability of development of ACS over the next 2 years [8]; spotty calcification was two times more prevalent in the 2FPP associated with subsequent development of ACS.

As such, it appears that many of the high-risk lesions may not have calcification. In addition, spotty calcification is not detectable using CACS because Agatston's score uses 3-mm thick slices. Therefore, it might be possible that vulnerable plaque cannot be detected by CACS. In the present CTCA study in the patients with suspected angina pectoris, the prevalence of significant stenosis, spotty calcification and 2FPP were evaluated even though Agaston score revealed CACS = 0.

2. Methods

2.1. Study population

2380 consecutive patients underwent coronary 64 or 320-slice multi-detector CT (MDCT) angiography and measurement of CACS from 9/30/2008 to 5/26/2010 for suspected coronary artery disease. The CCTA was performed due to symptoms of chest pain, to exclude coronary disease in patients carrying one or more risk factors or electrocardiographic abnormality, or as a part of preoperative evaluation. Of the 2380 patients, 45 patients with previous myocardial infarction, 44 with percutaneous interventions or CABG and 131 patients with unacceptable CCTA image quality were excluded, allowing enrollment of the remaining 2160 patients (M/F = 1110/1050, 64.7 ± 11.6 years) who underwent 64 (N = 1191) or 320-slice (N = 969) MDCT in this study.

All 2160 patients were divided into CACS = 0 and CACS > 0 group. Age, gender, coronary risk factor (family history (FH), hypertension (HTN), hyperlipidemia (HL), diabetes (DM), smoking, and body mass index (BMI)), the history of cerebrovascular event, presence of chest pain or abnormal rest ECG findings were recorded for all patients. Analysis of CCTA was undertaken to identify significant stenotic lesions, 2FPP and the presence of spotty calcification in the CACS = 0 and >0 groups. Multivariate analysis using logistic regression analysis was performed to identify the clinical features and risk factors predictive of CCTA features in CACS = 0 group. Risk factors were defined as follows.

2.2. Definition of risk factors

Hypertension was defined as systemic blood pressure ≥ 140/90 mm Hg or the use of antihypertensive treatment. Diabetes mellitus was defined as fasting blood sugar ≥ 126 mg/dl, postprandial blood sugar ≥ 200 mg/dl, hemoglobin A1c ≥ 6.5% or the use of treatment. Dyslipidemia was defined as total cholesterol ≥ 220 mg/dl, low-density lipoprotein cholesterol ≥ 140 mg/dl, fasting triglycerides ≥ 150 mg/dl, high density cholesterol < 40 mg/dl or the use of lipid-lowering treatment. Smokers were defined as someone who smoked within 1 year at the time of MDCT imaging.

2.3. 64-slice MDCT protocol

Scanning was performed using an MDCT scanner (Aquilion 64, Toshiba Medical Systems Corporation), an ECG monitor (BSM-2401, Nihon Kohden), and an injector (Stellant Dual Flow, Nihon Medrad K.K.). A 3D workstation (Zio M900, Ziosoft) was used for CACS and to generate 3-D (volume rendering) and curved planar reconstruction (CPR) images. The contrast medium injection time was fixed and the injection rate and injection volume were determined according to the patient's weight. The Stellant Dual Flow was employed for injection via an antecubital vein using a three-phase injection method: contrast medium, a 50:50 mixture of contrast medium and saline solution. In the MDCT scanner, the plane for the bolus-tracking method was set to the 4-chamber view level, and injection was then started. After 8 s, bolus tracking was performed and scanning was started when arrival of the contrast medium in the left ventricle was visually confirmed. At the same time, a voice message instructing the patient to hold his or her breath was played back (for 3 s), a delay time of 5 s after the voice message (total 8 s) was provided to permit the variation in HR to decrease, and MDCT cardiac scanning was then performed from the feet to the head. The volume of contrast medium administered was 60 to 80 ml. Scanning was performed at a tube voltage of 120 kV (for patients with <70 kg), a tube current of 400 to 600 mA, a guntry rotation speed of 0.35, 0.375, 0.4, or 0.45 s/rot., a helical pitch of 8.0 to 11.2 (BP: 0.125 to 0.175), a scan slice thickness of 0.5 mm × 64 rows, an image slice thickness of 0.5 mm, and a reconstructed interval of 0.3 mm. For patients with a HR ≥ 60 bpm, 25 mg of atenolol was administered orally on the night before the examination unless contraindications were present. Alternatively, 2 to 10 mg of propranolol was injected intravenously immediately before scanning to obtain low HR.

2.4. 320-slice MDCT protocol

Scanning was performed using an MDCT scanner (Aquilion ONE V4.51, Toshiba Medical Systems Corporation), an ECG monitor (BSM-2401, Nihon Kohden), and an injector (Stellant Dual Flow, Nihon Medrad K.K.). In addition, a 3D workstation (Ziostation, Ziosoft) was used for CACS and to generate 3-D volume rendered and curved planar reconstruction (CPR) images. The contrast medium injection time was fixed and the injection rate was determined as the patient's weight × 0.06 ml/s. The Stellant Dual Flow was employed for injection via an antecubital vein using a two-phase injection method: contrast medium for 10 s and saline solution for 8 s. In the MDCT scanner, the plane for the bolus-tracking method was set to the 4-chamber view level, and injection was then started. After 7 s, bolus tracking was performed and scanning was started when arrival of the contrast medium in the left ventricle was visually confirmed. At the same time, a voice message instructing the patient to hold his or her breath was played back (for 3 s), a delay time of 4 s after the voice message (total 7 s) was provided to permit the variation in HR to decrease, and MDCT cardiac scanning was then performed. Scanning was performed at a tube voltage of 120 kV, a guntry rotation speed of 0.35, 0.375, or 0.4 s/rot, a scan slice thickness of 0.5 mm, an image slice thickness of 0.5 mm, and a reconstructed interval of 0.25 mm. As for tube current, in ECG asynchronous volume scan plan, the mean tube current numbers were calculated using standard deviation 19 using automatic exposure control function at the range of 40 mm in the cephalic direction from the inferior border of the periphery of the right coronary artery. The imaging range was set up at the minimal range choosing from 200 raw, 240 raw, 256 raw, 280 raw and 320 raw by referring to non-enhanced CT images for calcium score measurement. For patients with a HR ≥ 60 bpm, 25 mg of atenolol was administered orally on the night before the examination unless contraindications were present. Alternatively, 2 to 10 mg of propranolol was injected intravenously immediately before scanning to obtain low HR. We always considered reduction of radiation dose using prospective ECG gated scan as possible.

2.5. Image reconstruction

Half image reconstruction or segmental image reconstruction was performed in the slow filling phase and end-systolic phase using the "R + absolute time" method to generate images, and images with the lowest level of motion artifacts were selected on the 4-chamber cardiac cine CT.

2.6. CTCA interpretation

For plaque detection, both cross-sectional and longitudinal curved multiplanar reformation images were analyzed. Coronary arteries were divided into 17 segments based on the recommendations of the modified American Heart Association [9]. Coronary artery segments with a diameter of >2 mm were evaluated for the presence of plaques. All plaques were characterized for the presence of significant stenosis, the presence of vessel remodeling (positive, negative, and none), plaque consistency (low or intermediate attenuation) and disposition of coronary calcification (spotty, moderate, and severe). Three observers were involved in the interpretation of data.

2.7. CACS scoring

All data were evaluated on a workstation software (Zio M900 or ZioStation, Ziosoft). A calcified lesion was defined as ≥ 3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units (HU). The total CACS was calculated per recommendations of Agatston et al. [10].

2.8. Definition of CT plaque characteristics

2.8.1. Degree of stenosis

Visual assessment of the stenotic lesion was undertaken based on the modified AHA classification. The percentage ratio of the stenotic lumen to the original vessel diameter of the lesion analogized by a presumed-to-be-healthy site distal and proximal to the stenosis was obtained and the degree of stenosis was expressed by subtracting this from 100. Out of end-diastolic still images taken from multiple projections, measurements were taken in the angle showing the greatest degree of stenosis to classify the lesion into 6 stages: 25% for stenosis of 0%–25%, 50% for 26%–50%, 75% for 51%–75%, 90% for 76%–90%, 99% for 91%–99%, and 100% for total occlusions. Lesions with stenosis of 75% or more were defined to be significant stenotic lesions.

2.8.2. Vessel remodeling

Coronary arterial remodeling was defined as a change in the vessel diameter at the plaque site in comparison to the reference segment set proximal to the lesion in a normal-appearing vessel segment (reference diameter). Manual inspection, in both cross-section and longitudinal reconstruction, was used for defining the remodeling index (lesion diameter/reference diameter). The remodeling index was reported as positive remodeling when the diameter at the plaque site was at least 10% larger than the reference segment.