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Original Article

Identifying Small Coronary Calcification in Non-Contrast 0.5-mm Slice Reconstruction to Diagnose Coronary Artery Disease in Patients with a Conventional Zero Coronary Artery Calcium Score

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***Aims*: In a new-generation computed tomography (CT) scanner, coronary artery calcium (CAC) scores were measured using 3.0-mm slice reconstruction images originally acquired with 0.5 mm thickness scans in a single beat. This study investigated the usefulness of thin-slice (0.5 mm) reconstruction for identifying small calcifications in coronary arteries and evaluated the association with coronary plaques and stenosis compared to conventional 3.0-mm reconstruction images.**

***Methods*: We evaluated 132 patients with zero CAC scores in conventional 3.0-mm Agatston method using a 320-slice CT. Then, 0.5-mm slice reconstruction was performed to identify small calcifications. The presence of stenosis and coronary plaques was assessed using coronary CT angiography.**

***Results*: In total, 22 small calcifications were identified in 18 patients. There were 28 (21%) patients with any (≥ 25%) stenosis (34 lesions). Forty-seven coronary plaques were found in 33 patients (25%), including 7 calcified plaques in 7 patients (5%), 34 noncalcified plaques in 27 patients (20%), and 6 partially calcified plaques in 5 patients (4%). Patients with small calcifications had a significantly higher prevalence of noncalcified or partially calcified plaques (83% vs 14%; $p<0.001$) and obstructive stenosis (33% vs 5.2%; $p<0.001$) compared to those without small calcifications. The addition of small calcifications to the coronary risk factors when diagnosing stenosis significantly improved the diagnostic value.**

***Conclusion*: Small calcifications detected by thin-slice 0.5-mm reconstruction are useful for distinguishing coronary atherosclerotic lesions in patients with zero CAC scores from conventional CT reconstruction.**

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Key words: Coronary CT angiography, Small calcification, Coronary artery calcium, Coronary plaque

Introduction

The coronary artery calcium (CAC) score as detected using computed tomography (CT) correlates with the presence of coronary artery disease (CAD)[1-3], mortality, and coronary morbidity[3-6] and has recently been reported to be related to left ventricular diastolic function[7]. The absence of CAC is associated with a very low risk of coronary mortality and morbidity, particularly in asymptomatic individuals. The CAC score has prognostic value in symptomatic patients, with significantly more events occurring in patients with higher CAC scores[8, 9]. However, several multicenter studies have demonstrated that zero CAC scores did not completely eliminate the possibility of CAD in some patients[10-12].

Conventional scans for CAC measurement are usually performed with 2.5 to 3.0-mm slices[1, 2]. However, in the new-generation, 320-slice CT, 3.0-mm

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slice images are reconstructed from 0.5-mm slice, whole-heart data, and then 0.5-mm slice reconstruction images are available without additional radiation exposure[13]. The study found that small amounts of coronary calcium could be distinguished more sensitively with thin 0.5-mm slice reconstruction than with standard 3.0-mm reconstruction, resulting in a positive calcium score in 21% of patients who had zero calcium scores in standard reconstruction[14]. However, it is unclear whether these small calcifications have a clinical significance in identifying obstructive or non-obstructive lesions with the potential to rupture or erose.

Aim

We sought to investigate the usefulness of thin-slice, 0.5-mm reconstructions to identify small calcifications in the coronary artery wall, and to evaluate their importance in addition to conventional risk factors in CAD diagnosis among patients with zero CAC scores from conventional 3.0-mm slice reconstructions.

Methods

Study Population

From April 2012 to June 2013, we identified 153 consecutive participants with a CAC score of zero who underwent coronary CT angiography (CCTA). Exclusion criteria included poor CCTA images because of motion artifacts, poor coronary contrast concentration, and missing information, such as traditional coronary risk factors or laboratory data ($n=10$). In total, 132 patients were included in the study. Indications for CCTA based on chest symptoms (chest pain, palpitation, or dyspnea) were as follows: typical type chest pain ($n=9$), atypical or non-anginal type ($n=102$), no symptom with ischemic findings ($n=11$), and no symptom with high-risks ($n=10$; 2 vascular diseases, 1 prior cerebral infarction, 2 familial hypercholesterolemia, 2 treated diabetes mellitus, and 3 multiple coronary risk factors). Furthermore, 43 patients underwent CCTA before catheter ablation for atrial fibrillation.

Risk Factor Assessment and Laboratory Examinations

Hypertensive patients were defined as those with a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or who were receiving antihypertensive therapy. Dyslipidemia was defined as having a serum low-density lipoprotein cholesterol level ≥ 140 mg/dl on direct measurement, a serum triglyceride level ≥ 150 mg/dl, or currently receiving lipid-lowering medication. Diabetes mellitus was defined as a hemoglobin A1c level ≥ 6.5% and/or current use of hypoglycemic agents. Current smokers were defined as subjects who smoked regularly or had quit in the 30 days prior to CCTA[15]. For each participant, the Framingham risk score was calculated and a 10 year risk was estimated[16]. Estimated glomerular filtration rate (eGFR) was calculated based on the four-variable Modification of Diet in Renal Disease study equation[17]. The serum C-reacting protein level was measured.

Coronary CT Scan Protocol

Coronary CT examinations were performed using a 320-slice CT scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan). If the patient's resting heart rate was >65 beats per minute, a β-blocker (metoprolol 20–40 mg) was administered orally 60 minutes before the CT scan to avoid motion artifacts. All patients received 0.3 mg nitroglycerin immediately before the CT scan.

Prior to the contrast-enhanced scan, a non-contrast CT scan was performed to detect coronary artery calcifications. The scanning parameters were as follows: tube potential 120 kV; gantry rotation time 0.35 s; z-coverage 120–160 mm; and tube current between 200 mA and 540 mA according to body weight. Full cardiac non-contrast coronary artery imaging was performed in a single gantry rotation during breath-hold and inspiration in a single cardiac phase (75% of the R-R interval).

The contrast-enhanced coronary CT scan was performed by prospective ECG-triggered CCTA, with the center of the imaging window corresponding to 75% of the R-R interval ($n=80$), or retrospective ECG-gated CTA ($n=52$) with dose modulation (the window of full tube current limited to 65%–85% of the R-R interval) in 1–3 beats (depending on heart rate) during an inspiratory breath-hold. A patient's body weight-adjusted volume of nonionic contrast material (iodine 245 mg/kg) was injected into the antecubital vein over a fixed duration of 10 seconds, followed by 20 mL of 0.9% saline solution chaser at the same flow rate[15, 18].

CAC Score and Identification of Small Coronary Calcifications

Non-contrast CT images were reconstructed with either standard 3.0 or 0.5-mm axial slices from the same data. CAC scores were calculated by the conventional Agatston method with 3.0-mm slice reconstruction using Smartscore version 4.0 software (GE Healthcare, Little Chalfont, Buckinghamshire, UK). A small calcification was defined as a calcium deposit

visually identified in a 0.5-mm slice in non-enhanced axial data by two independent, blinded observers. Both readers (Y.U. and H.T.) were cardiologists who had more than 5 years' experience of assessing coronary CT images, and both agreed on the identification for all small calcifications.

Evaluation of CCTA

CCTA images were assessed by the same two observers according to the Society of Cardiovascular Computed Tomography–recommended 18-segment mode[19]. All coronary segments >2 mm in diameter were evaluated with curved multiplanar reformation and cross-sectional images in a direction perpendicular to the vessel center line. Obstructive stenosis was defined as luminal stenosis ≥ 50% and any stenosis as vessels with ≥ 25% stenosis.

Based on our previous report[15], the observers determined the presence of calcified plaque (CP), non-calcified plaque (NCP), and partially calcified plaque (PCP). CP was defined as any structure with a CT density ≥ 130 HU which could be visualized separately from the contrast-enhanced coronary lumen. NCP was defined as any distinguishable region with a low-density (<130 HU) area >1 mm^2 in size. PCP was defined as having both calcified and non-calcified components.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as numbers (proportion). Student's *t*-test or the Wilcoxon test were used to compare continuous variables. The chi-square test was used to compare categorical variables. The presence of small calcifications was assessed as a binary outcome. Receiver-operating characteristic (ROC) curves were constructed to compare the accuracy of predictions of the presence of NCP and/or PCP (NCP/PCP), any stenosis, and obstructive stenosis. Any incremental improvement in the accuracy of prediction was determined after adding the presence of small calcifications to coronary risk factors, including age, sex, hypertension, dyslipidemia, diabetes mellitus, and current smoking, and calculating the c-statistics with 95% confidence interval (CI). p values of <0.05 were considered statistically significant. All statistical analyses were performed with JMP 10 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

The mean age of the 132 patients was 57.3 ± 11.7 years, and 61% were men. **Table 1** compares the clinical characteristics of patients with and without small calcifications. The proportions of men (89% vs 57%; $p=0.0099$), hypertension (83% vs 46%; $p=0.0029$), and current smoking (33% vs 13%; $p=0.030$) in patients with small calcifications were significantly higher than in patients without small calcifications. The mean Framingham risk score was significantly higher in the small calcifications group than in the group without small calcifications (9.1 ± 5.3 vs 6.0 ± 5.7; $p=0.0072$).

Small Calcifications and CCTA Findings

Of a total of 2,052 segments from 132 patients, small calcifications were detected in 22 lesions from 18 patients (14%). Among all subjects, obstructive stenosis was found in 15 lesions from 12 patients (9%), and any stenosis in 34 lesions from 28 patients (21%). Any type of coronary plaque was visualized in 47 lesions of 33 patients (25%). CPs were observed in 7 lesions from 7 patients (5%); NCPs in 34 lesions from 27 patients (20%); and PCPs in 6 lesions from 5 patients (4%). A total of 40 NCP/PCPs were found in 30 patients (23%) (**Table 2**). **Fig. 1** presents a representative case of a patient with small calcifications who had significant stenosis in the proximal left anterior descending artery.

CCTA findings were compared between groups with ($n=18$) and without ($n=114$) small calcifications (**Fig. 2**). All patients in the small calcification group had at least one plaque of any type, compared to 13% in the no small calcification group ($p<0.001$). The prevalence of NCP/PCPs was significantly higher in the small calcification group than in the no small calcification group (83% vs 14%; $p<0.001$). In addition, there was a significantly higher proportion of patients in the small calcification group than in the no small calcification group with any stenosis (83% vs 11%; $p<0.001$) or obstructive stenosis (33% vs 5.2%; $p<0.001$)

Incremental Diagnostic Values of Small Calcifications with Coronary Risk Factors to Detect Plaques and Stenosis

ROC analyses demonstrated that the c-statistics for coronary risk factors, including age, sex, hypertension, dyslipidemia, diabetes mellitus, and current smoking, for the presence of NCP/PCPs, any stenosis, and obstructive stenosis were 0.81 (95% CI, 0.72–0.87), 0.82 (95% CI, 0.73–0.88) and 0.89 (95% CI, 0.81–0.94), respectively. The c-statistics for the presence of NCP/PCPs and any stenosis were significantly increased after the addition of the presence of small calcifications to 0.89 (95% CI, 0.82–0.94; $p=0.0037$)

Table 1. Clinical characteristics compared between presence and absence of small calcifications

Characteristics	Small calcification present ($n=18$)	Small calcification absent ($n=114$)	p value
Age (year)	59.7 ± 13.5	56.9 ± 11.5	0.29
Male *n* (%)	16 (89%)	65 (57%)	0.0099
Body mass index (kg/m^2)	23.2 ± 3.6	23.7 ± 4.7	0.62
Hypertension *n* (%)	15 (8%3)	52 (46%)	0.0029
Dyslipidemia *n* (%)	12 (67%)	65 (57%)	0.44
Diabetes mellitus *n* (%)	4 (22%)	12 (11%)	0.16
Current smoker *n* (%)	6 (33%)	15 (13%)	0.030
Framingham-risk score (10 years risk %)	9.1 ± 5.3	6.0 ± 5.7	0.0072
Indication for CCTA			0.12
Evaluation for typical chest symptom *n* (%)	2 (11%)	7 (6%)	
Atypical or non-cardiac chest symptom *n* (%)	10 (56%)	92 (81%)	
No symptom with ischemic findings,	3 (17%)	8 (7%)	
No symptom, high-risk *n* (%)	3 (17%)	7 (6%)	
Catheter ablation for transient AF *n* (%)	5 (28%)	38 (33%)	0.79
Blood examination			
HDL cholesterol (mg/dl)	57.1 ± 16.1	66.4 ± 21.4	0.052
LDL cholesterol (mg/dl)	110.3 ± 30.7	123.6 ± 35.7	0.15
Triglycerides (mg/dl)	158.7 ± 120.5	132.5 ± 97.1	0.37
Hemoglobin A1c (%)	5.7 ± 1.0	5.4 ± 1.0	0.35
eGFR (ml/min/1.73 km^2)	74.2 ± 17.3	74.2 ± 20.0	0.97
C-reacting protein (mg/dl)	0.11 ± 0.15	0.15 ± 0.21	0.55
Medication			
Aspirin use *n* (%)	2 (11)	5 (4)	0.24
Statin use *n* (%)	4 (22)	14 (12)	0.25
RAS inhibitor use *n* (%)	8 (44)	24 (21)	0.031
Hypoglycemic drugs *n* (%)	3 (17)	7 (6)	0.12

Data expressed as number (percent) or mean ± standard deviation.
AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin angiotensin system inhibitor.

Table 2. Small calcification and coronary computed tomography angiography finding

Variables	Number of patients (132 patients)	Number of segments (2052 segments)
Small calcification	18 (14%)	22 (1.1%)
Any plaque	33 (25%)	47 (2.3%)
Calcified plaque	7 (5%)	7 (0.3%)
NCP	27 (20%)	34 (1.7%)
PCP	5 (4%)	6 (0.3%)
NCP and/or PCP	30 (23%)	40 (1.9%)
Any stenosis (≥ 25%)	28 (21%)	34 (1.7%)
Obstructive stenosis (≥ 50%)	12 (9%)	15 (0.7%)

Data were expressed as number (percent). NCP, noncalcified plaque; PCP, partially calcified plaque

and 0.89 (95% CI, 0.81–0.94; $p=0.013$), respectively. However, the presence of small calcifications did not significantly increase the diagnostic value for the presence of obstructive stenosis ($p=0.50$) (**Fig. 3**).

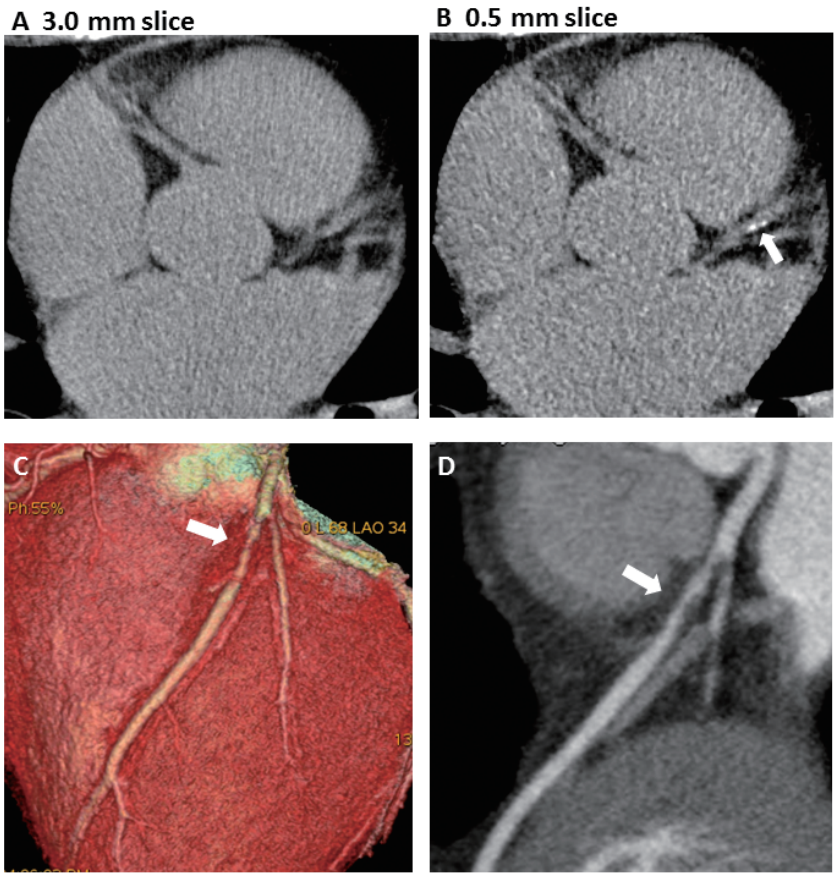

Fig. 1.

Representative case of a 58-year-old man who had a zero coronary artery calcium score but also had a small calcification; non-contrast scan of the proximal left anterior descending artery (LAD) with a conventional 3.0-mm slice (A) and a 0.5-mm slice (B). Volume rendering (C) and curved multiplanar construction (D) images in coronary computed tomography angiography showed obstructive stenosis in the proximal LAD (arrow).

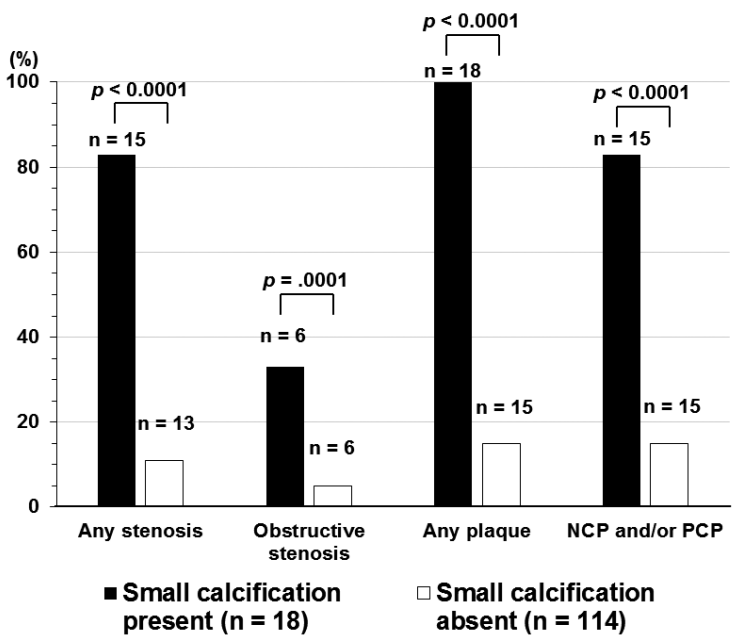

Fig. 2.

Prevalence of stenosis or plaques in coronary computed tomography angiography according to the presence (solid bar) or absence (open bar) of small calcifications.

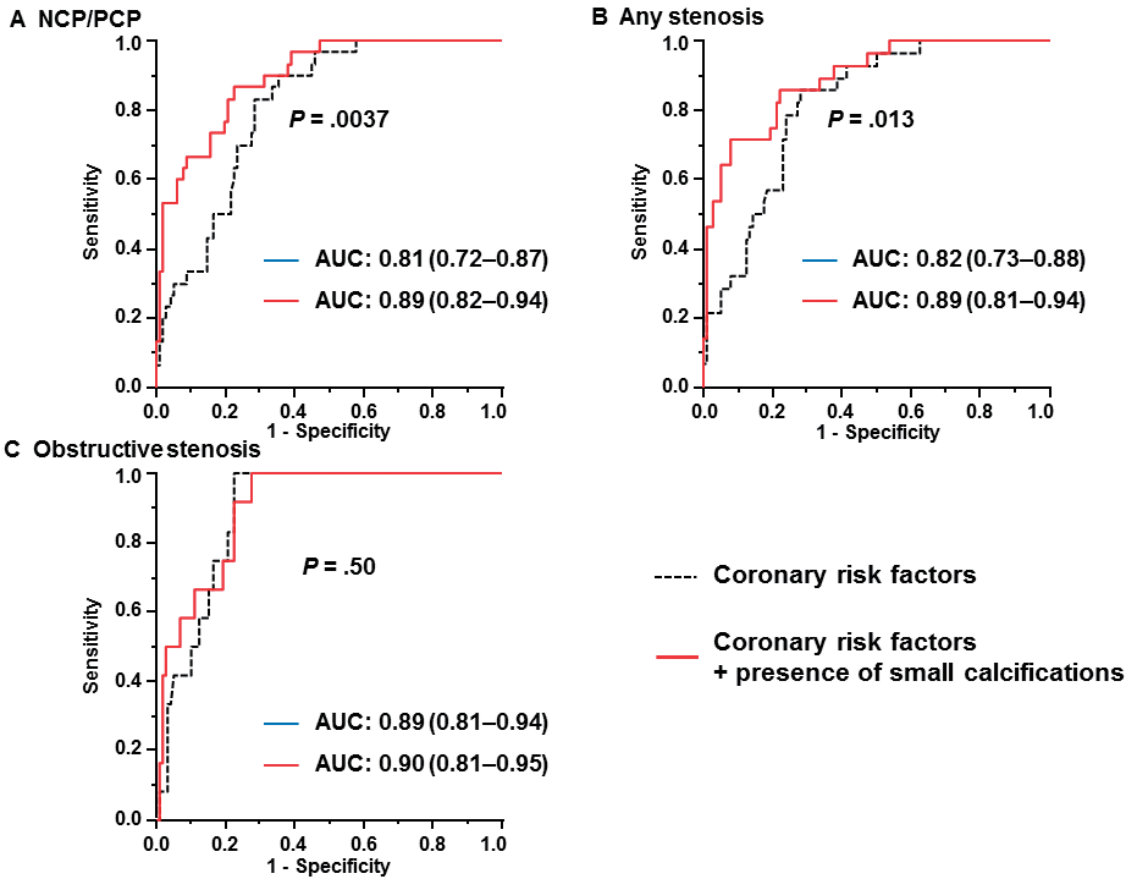

Fig. 3.

Incremental diagnostic values of small calcifications in addition to coronary risk factors for identifying patients with (A) non-calcified plaques (NCPs) and/or partially calcified plaques (PCPs), (B) any stenosis (≥ 25%), or (C) obstructive stenosis (≥ 50%). Coronary risk factors included age, sex, hypertension, dyslipidemia, diabetes mellitus, and current smoking.

Discussion

Small calcifications detected in 0.5-mm slice reconstructions increased the possibility of obstructive and non-obstructive CAD in patients with a conventional zero CAC score. Patients with small calcifications had a higher prevalence of multiple coronary risk factors compared to patients without small calcifications. Furthermore, small calcifications in addition to traditional coronary risk factors had incremental diagnostic values when predicting any coronary stenosis. Consequently, we believe that the identification of small calcifications is a convenient and efficient method for stratifying the risk of CAD.

Prevalence of Coronary Plaques and Stenosis in Patients with Zero CAC Scores

The identification of small calcifications using thin-slice reconstruction can help identify subjects with zero CAC scores from conventional reconstructions who are at higher risk for CAD. Although the prevalence of CAD is very low in subjects with a zero CAC score, the presence of CAD cannot be completely dismissed. The present study showed that 23% of patients had NCP/PCPs, 21% had any stenosis, and 9% had obstructive stenosis on CCTA. Previous studies identified a 13%–39% prevalence for coronary plaques in patients with a zero CAC score[20, 21]. The CoRE-64 study found that 19% of patients with zero CAC scores had obstructive CAD[9]. Our previous study with a 64-slice CT found NCP/PCPs in 29% and obstructive stenosis in 4% of suspected CAD patients with zero CAC scores[22]. In the present study, the prevalence of obstructive CAD in the conventional zero CAC group decreased from 9% to 5.2% with the use of 0.5-mm thin-slice reconstructions.

The predictive values of zero CAC scores in excluding CAD were different for asymptomatic and symptomatic patients. However, 10 patients with CAC scores of zero in the present study, even with no

chest symptoms, were considered to be equivalent to symptomatic patients, because most of them had complications such as extra-coronary vascular disease, diabetes, or familial hypercholesterolemia. On the other hand, 32% of cases in our data had transient atrial fibrillation scheduled for catheter ablation. The usefulness of CAC scores and CCTA for these cases are still controversial.

Clinical Significance of Small Calcifications in Patients with Conventional Zero CAC Scores

The present study indicated that the detection of small calcifications in earlier stages of coronary atherosclerosis was important in identifying coronary plaques or stenosis in patients with conventional zero CAC scores. A recent multicenter study demonstrated that patients with coronary stenosis detected by CCTA, regardless of obstruction, had a poorer prognoses than those without[23]. We found small calcifications in 14% of patients with zero CAC scores from conventional 3.0-mm reconstructions. The proportion was similar or lower than that in previous reports, and several articles demonstrated that the conventional CAC method misclassified 21%–23% of patients[13, 14, 24]. In addition, Van der Biji et al. reported that in thin-slice reconstruction, the Agatston score was overestimated because the peak CT attenuation number in each voxel was counted[14]. However, in fact, our study demonstrated that small calcifications in thin-slice images were associated with coronary atherosclerotic lesions. Taken together, we propose that assessment of visually detecting small calcifications may allow identification of patients with CAD and rupture-prone coronary atherosclerotic lesions in subjects with conventional zero CAC scores.

Generally, vascular calcifications have been associated with advanced stages of atherosclerosis[25]. However, some studies have reported that micro-calcification was occasionally observed in the early stage of atherosclerosis[26, 27]. In addition, spotty calcifications detected by intravascular ultrasound were reported to be associated with coronary plaque vulnerability[28]. Therefore, this new method is expected to be a useful indicator for examination by CCTA, and for therapeutic interventions.

Limitations

First, our study was retrospective and had a small number of patients with CAC scores of zero, and did not evaluate patients with positive (>0) CAC scores. It is unclear whether the identification of small calcifications in 0.5-mm slice images is more useful for detecting coronary plaques and stenosis as detected by CCTA than stratification by conventional CAC score in patients with positive CAC scores. This study did not examine the prevalence of stenosis with invasive coronary angiography. Second, because of the low incidence of small calcification, we could not compare predictive powers in sub-group analyses such as scheduled catheter ablations for transient atrial fibrillation. Third, our data indicated that small calcifications had incremental diagnostic values when used with with coronary risk factors to predict coronary plaques and any stenosis, but not to predict obstructive stenosis. We believe that the identification of small calcifications was useful for detecting early stages of coronary atherosclerosis which have the potential to progress to obstructive lesions or culprit lesions in acute coronary syndrome. Furthermore, CT-derived vulnerable characteristic analyses were not performed because of the small numbers of NCP and/or PCP (40 segments in 30 patients). Finally, small calcifications detected by thin-slice scans may be misidentified because the signal-to-noise ratio in the thin-slice images is higher than that in conventional-slice images. However, recent developments in CT, such as using iterative reconstruction to decrease the signal-to-noise ratio, should overcome this problem[29, 30].

Conclusions

The identification of small calcifications using 0.5-mm thin-slice reconstruction is useful for detecting coronary plaques and coronary stenosis in patients with zero CAC scores from conventional 3.0-mm slice reconstructions. In contrast, because the incidence of coronary lesions in patients without CAC in a thin-slice reconstruction was lower compared to conventional zero CAC, the need for contrast-enhanced CCTA may be eliminated in such patients.

Disclosures

None of the authors have any conflicts of interest to disclose.

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Supplemental data

Comparison between AF ablation patients and no AF ablation patients

parameter	AF ($n = 43$)	no AF ($n = 89$)	P value
Age (yrs)	56.6 ± 11.4	57.7 ± 12.0	0.63
Male, %	79	53	0.004
Hypertension, %	44	54	0.35
Dyslipidemia, %	40	67	0.003
Diabetes mellitus, %	5	15	0.089
Smoking, %	14	17	0.8
FRS	5.9 ± 3.8	6.7 ± 6.4	0.62
CCTA results			
Small calcification, %	11	15	0.79
obstructive stenosis, %	2	8	0.27
any stenosis, %	12	26	0.07
Plaque, %	16	29	0.13

Predictive values of small calcification

parameter	AF ($n = 43$) SC+, SC−	no AF ($n = 89$) SC+, SC−
any stenosis, Odds ratio (p value)	3/5 (60%), 2/38 (5%) 24 ($p = 0.0075$)	12/13 (15%), 11/76 (92%) 70 ($p < 0.0001$)