Total Coronary Artery Plaque Burden Measured by Cardiac Computed Tomography is Associated with Metabolic Syndrome

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Aim: Increased coronary plaque burden, which could be involved in the pathogenesis of atherothrombotic events, is difficult to evaluate in the three major coronary arteries. The purpose of this study was to quantify coronary plaque volume using 64-slice computed tomography (CT).

Methods: We measured coronary plaque volume with our new protocol in 23 consecutive patients (48% men; 66 ± 11 years old) who underwent cardiac CT for suspicion of coronary artery disease and had noncalcified plaques. We counted the total pixel volume of noncalcified plaques in the three major coronary arteries.

Results: The coronary plaque volume was 1.29 ± 0.56 cm³ in the right coronary artery, 1.29 ± 0.42 cm³ in the left main coronary artery and left anterior descending artery, and 0.88 ± 0.32 cm³ in the left circumflex artery. The total coronary plaque burden (TCPB) was 3.45 ± 1.02 cm³/patient and had a positive correlation with waist circumference (r=0.44, p<0.05) and insulin resistance (r=0.46, p<0.05). TCPB was significantly greater in men (3.89 ± 1.07 cm³ vs. 3.06 ± 0.82 cm³ in women, p<0.05), patients with diabetes or impaired glucose tolerance (3.77 ± 0.94 cm³ vs. 2.86 ± 0.92 cm³ in non-diabetics, p<0.05), and patients with metabolic syndrome (3.91 ± 0.95 cm³ vs. 3.03 ± 0.91 cm³ in patients without metabolic syndrome, p<0.05).

Conclusions: Cardiac CT can provide a noninvasive assessment of TCPB, which was significantly associated with metabolic syndrome and its components. Measuring TCPB by CT could be an important strategy for identifying high-risk patients with suspected coronary artery disease.


Key words: Computed tomography, Plaque, Metabolic syndrome

Introduction

Coronary plaque disruption often evolves from vessels with mild to moderate stenosis and noncalcified plaque. Patients with acute coronary syndromes (ACS) often have plaques on uninvolved vessels, which may cause recurrent symptoms of ACS.
Hence, noninvasive evaluation of such plaques in the three major coronary arteries may improve clinical outcome.

Total coronary artery plaque burden (TCPB) can be quantitatively assessed using a coronary artery calcium scan and an intravascular ultrasound (IVUS). A coronary artery calcium scan provides ample evidence of prognosis but cannot be applied to early stage and noncalcified plaques. While IVUS can also quantify the local coronary plaque burden, predict adverse cardiovascular events, and be used as a surrogate endpoint in large clinical trials, it is a technically complex, invasive, and time-consuming procedure, and it cannot be practically applied to the three major coronary arteries in routine coronary angiography. IVUS examinations are usually performed at the time of coronary intervention in patients with advanced CAD. There is little information about TCPB in the early stage of CAD. Sixty-four-slice computed tomography (CT) can noninvasively provide important information about TCPB in the early stage of CAD. This study aimed to quantify the TCPB using cardiac CT and to evaluate the association between TCPB and metabolic syndrome.

Methods

Study Sample

Patients with suspected CAD and without a history of thoracic surgery, percutaneous coronary intervention, or arrhythmias were enrolled from September 2006 to October 2008. They underwent coronary CT angiography and were eligible for inclusion if they had noncalcified plaque. Thus, 23 consecutive patients were included in the present study. The study was approved by the ethics review committee at our institution, and signed informed consent was obtained from each patient before participation. This study was registered in the UMIN protocol registration system with the identification number UMIN000001581.

Multislice CT Scan Protocol

Sixty-four-slice CT (Brilliance-64; Phillips Medical Systems, Cleveland, OH) was used with the following parameters: detector collimation 64x0.625 mm, table feed 19.7 mm/sec, 0.2 helical pitch (beam pitch), rotation time 420 msec, tube current 900 mAs, and voltage 120 kVp. Depending on cardiac dimensions, the scanning time varied from 6 to 8 sec. Eleven reconstruction sets at 75% and 10% intervals ranging from 0% to 90% of the cardiac cycle were reconstructed from the raw data file. The optimal phase showing the least amount of motion was selected for coronary CT angiography. The contrast material (Omnipaque-350; Daiichi Pharmaceutical, Tokyo, Japan) was administered using a mechanical power injector (Dual Shot; Nemoto-Kyorindo, Tokyo) through a 20-gauge cannula inserted into an antecubital vein. To minimize variations in arterial enhancement among patients, we used a contrast dose based on body weight (0.7 mL/kg) and a fixed injection duration (9 sec). A test bolus of 10 mL contrast was administered intravenously, and dynamic monitoring scans were acquired at the level of the ascending aorta to generate a patient-specific enhancement curve. For angiographic scanning, we selected a delay of 3 sec after peak enhancement, which was determined by the enhancement curve. This resulted in relatively small variation (375 ± 57 HU in aortic root). An oral β-blocker (metoprolol, 20 mg) was administrated one hour prior, and nitroglycerin (0.3 mg) was given just prior to CT imaging. The reconstructed image of the CT was transferred to a workstation for postprocessing (ZIO M900; Amin/ZIO, Tokyo).

Multislice CT Image Analysis

Both the cross-sections and longitudinal reconstructed images were manually inspected to define coronary atherosclerotic plaques. Structures clearly assignable to the vessel wall with densities less than the lumen contrast were classified as noncalcified plaque components. Calcified tissue were represented by areas with a density of > 220 HU inside the vessel wall. For each patient, we defined a range of CT density that represented the patient's largest plaque by visual inspection (Fig. 1A and B). Then, we counted the pixels of the patient's plaque density in three coronary arteries (left main coronary artery plus left anterior descending artery, left circumflex artery, and right coronary artery) and defined this value as the total coronary plaque burden (TCPB).

To determine the interobserver variability in measuring TCPB, 10 images were randomly selected and read by another reader that was blinded to the previous results. Interobserver variability in determining TCPB was 7.6%, which were calculated by a formula reported previously [(volume observer 1 − volume observer 2)/[(0.5×volume observer 1) + (0.5× volume observer 2)]. The average variability was determined by averaging the values obtained from each individual patient.

Assessment of Risk Factors and Covariates

Blood was drawn after an overnight fast. Diabetes mellitus was diagnosed based on the criteria set by the World Health Organization or the use of hypoglyc-
Impaired glucose tolerance was defined as 2-hour plasma glucose between 140 and 200 mg/dL after a 75 g oral glucose tolerance test. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive treatment. We used homeostasis model assessment of insulin resistance [HOMA-IR, (insulin (U/mL)) × (fasting glucose (mg/dL))/405] to calculate insulin resistance. The estimated glomerular filtration rate (eGFR) was calculated by a modified formula of the Modification of Diet in Renal Disease study equation, which was proposed by the Japanese Society of Nephrology\textsuperscript{10}. Metabolic syndrome was diagnosed by having three or more metabolic abnormalities according to the modified Adult Treatment Panel III criteria, which include a waist circumference cut-off of 85 cm for Japanese males and 90 cm for Japanese females.

Fig. 1. Representative CT image of a 55-year-old male patient. (A) Volume-rendered image of his aortic root, lumen of coronary arteries (left), and extracted plaque on left anterior descending artery (right) observed from a left anterior cranial view. (B) Cross-sectional (left) and axial (right) image of his largest plaque (arrow in (A)). The area of 40-240 HU was defined as plaque in this patient and is shown as a red area (below).
Statistical Analysis

Data are expressed as the mean ± standard deviation (SD). Pearson's correlation between TCPB and metabolic risk factors were calculated. The difference of TCPB between men and women, patients with and without metabolic syndrome, and patients with and without diabetes were analyzed by the unpaired Student's t-test. A p value of <0.05 denoted statistical significance, and all tests were two-tailed. Variables were log-transformed if they showed skewed distribution. All analyses were performed using SPSS 17.0J for Windows (SPSS Inc., Tokyo).

Results

Table 1 shows the characteristics of participating patients.

The values of coronary plaque volume were 1.29 ±0.56 cm³ in the right coronary artery, 1.29 ±0.42 cm³ in the left main coronary artery plus left anterior descending coronary artery, and 0.88 ±0.32 cm³ in the left circumflex artery. TCPB was 3.45 ±1.02 cm³/patient in a total length of 39.0 ±6.4 cm. Mean plaque volume was 88.3 ±20.2 mm³ in a 10-mm segment. TCPB had a positive correlation with waist circumference (r=0.44, p<0.05; Fig. 2A), HOMA-IR (r=0.46, p<0.05; Fig. 2A), and body mass index (r=0.43, p<0.05). TCPB had a negative correlation with age (r=-0.45, p<0.05) and no significant correlation with low-density lipoprotein cholesterol (r=-0.41, p=0.06), high-density lipoprotein cholesterol (r=-0.10, p=0.66), triglycerides (r=-0.01, p=0.98), hemoglobin A1c (r=0.28, p=0.19), high-sensitivity C-reactive protein (r=-0.04, p=0.87), fasting plasma glucose (r=0.18, p=0.42), and eGFR (r=0.26, p=0.23). TCPB was significantly greater in men (3.89 ±1.07 cm³ vs. 3.06 ±0.82 cm³ in women, p<0.05), patients with diabetes or impaired glucose tolerance (3.77 ±0.94 cm³ vs. 2.86 ±0.92 cm³ in non-diabetics, p<0.05; Fig. 2B), and patients with metabolic syndrome (3.91 ±0.95 cm³ vs. 3.03 ±0.91 cm³ in patients without metabolic syndrome, p<0.05; Fig. 2B). TCPB was comparable in patients with hypertension (3.64 ±0.99 cm³ vs. 2.58 ±0.66 cm³, in patients without hypertension, p=0.06), dyslipidemia defined as serum low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol ≥40 mg/dL, triglyceride ≥150 mg/dL or use of lipid-lowering agents (3.44 ±1.02 cm³; 15 patients vs. 3.49 ±1.08 cm³, in 8 patients without dyslipidemia, p=0.90), and significant coronary stenosis (3.41 ±1.09 cm³ vs. 3.48 ±1.00 cm³, in patients without stenosis, p=0.87).

Table 1. Characteristics of 23 patients

<table>
<thead>
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<tr>
<td>Number</td>
<td>23</td>
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<tr>
<td>Age, years</td>
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<tr>
<td>Male gender, %</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Waist circumferences, cm</td>
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<td>Hypertension, %</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
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<tr>
<td>LDL cholesterol, mg/dL</td>
<td>113 (34)</td>
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<tr>
<td>HDL cholesterol, mg/dL</td>
<td>56 (17)</td>
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<tr>
<td>Triglycerides, mg/dL</td>
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<td>Fasting plasma glucose, mg/dL</td>
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<tr>
<td>HOMA-IR</td>
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<td>Hemoglobin A1c, %</td>
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<td>Diabetes mellitus, %</td>
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<tr>
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<td>Current smoker, %</td>
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<tr>
<td>eGFR, mL/min/1.73 m²</td>
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<td>Coronary angiography, %</td>
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<td>Significant stenosis, %</td>
<td>43</td>
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</table>

Data are the mean (standard deviation) or number (percentage). *

Discussion

We found that 64-slice CT can provide a noninvasive assessment of TCPB. TCPB was significantly associated with metabolic syndrome and its components.

The efficacy of assessing subclinical atherosclerotic plaque to predict future vascular events has already been demonstrated by studies of the carotid intima-media thickness using ultrasound[11]. Carotid intima-media thickness, however, was less useful in predicting cardiovascular events than cerebrovascular events[11]. Assessing subclinical coronary atherosclerosis may have more predictive value for future cardiovascular events, but there is no established marker of early coronary atherosclerosis. We proposed TCPB as a novel quantitative marker that can be measured in
every coronary artery starting in the early stage of atherosclerosis. In fact, TCPB was significantly associated with metabolic syndrome and its components. Arai et al. measured coronary plaque volume by CT\(^{12}\), but they assessed only ostial lesions in the three coronary arteries.

The present study is a preliminary study; therefore, a larger cohort is needed to confirm our findings. In larger studies, the risk factors associated with early, noncalcified coronary atherosclerosis, which have never been studied, will be revealed. If TCPB contributes to the incidence of cardiovascular events in prospective studies, measuring TCPB could be an important diagnostic strategy in identifying high-risk patients with suspected CAD. TCPB could also serve as a surrogate endpoint in large clinical trials.

This study had three major limitations. First, TCPB assessment was limited to noncalcified plaques; therefore, new comprehensive parameters, including TCPB and CAC score, need to be invented to better risk stratify patients, including those who have calcified plaques. For example, in case of mildly calcified

![Graph A](image1)

**Fig. 2.** (A) Correlation between total coronary plaque burden, waist circumference, and homeostasis model assessment of insulin resistance. Total coronary plaque burden had a positive correlation with waist circumference \((r=0.44, p<0.05)\) and homeostasis model assessment of insulin resistance \((r=0.46, p<0.05)\). HOMA-IR: homeostasis model assessment of insulin resistance. (B) Total coronary plaque burden in patients with and without diabetes and metabolic syndrome. Data are the mean ± SD. IGT: impaired glucose tolerance.
plaque, a parameter simply consisting of the sum of calcified plaque volume and noncalcified plaque volume may be reasonable. Second, the error in quantifying TCPB by CT is not negligible. The mean plaque volume in our study was 88.3 ± 20.2 mm³ in a 10-mm segment. This value is higher than that assessed by IVUS in large studies (55-66 mm³ in the most diseased 10-mm segments). CT may overestimate plaque volume because it cannot distinguish media from adventitia, whereas IVUS measures plaque only inside the external elastic membrane. Another possible explanation is that CT has insufficient spatial/temporal resolution and uneven contrast enhancement. Although interobserver variability in measuring TCPB was reasonable (7.6%), the reliability of plaque volume values in the distal part of coronary arteries (with vessel diameter < 1 or 2 mm) could not be confirmed according to the spatial resolution of cardiac 64-slice CT. To reduce this error, it is necessary to trace the coronary tree manually to some extent and it requires 30 to 60 minutes to assess TCPB for 1 patient. When we consider the clinical utility of the method, it should be less time-consuming and a new program to measure TCPB automatically is desirable.

Third, there was a relatively small study population because we completely excluded patients with any calcified plaques. Although TCPB was comparable between patients with and without hypertension with a statistically marginal p-value of 0.06, the very small number of patients without hypertension (4 patients) might cause the lack of statistically significant difference in this analysis. There is a possible association of TCPB with concomitant hypertension.

**Conclusions**

Sixty-four-slice CT can provide a noninvasive assessment of TCPB. TCPB was significantly associated with metabolic syndrome and its components. TCPB assessment by 64-slice CT could be an important clinical diagnostic strategy in identifying high-risk patients with suspected CAD.

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**Disclosures**

None.

**References**

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