Prognosis of vulnerable plaque on computed tomographic coronary angiography with normal myocardial perfusion image

Kenichiro Otsuka1, Shota Fukuda2*, Atsushi Tanaka3, Koki Nakanishi1, Haruyuki Taguchi2, Minoru Yoshiyama1, Kenei Shimada1, and Junichi Yoshikawa4

1Department of Internal Medicine and Cardiology, Osaka City University Graduate School of Medicine, Osaka, Japan; 2Department of Medicine, Osaka Ekisaikai Hospital, 2-1-10 Honden, Nishi-Ku, Osaka 550-0022, Japan; 3Department of Cardiovascular Medicine, Social Insurance Kinan Hospital, Tanabe, Japan; and 4Nishinomiya Watanabe Cardiovascular Center, Nishinomiya, Japan

Received 8 August 2013; revised 6 October 2013; accepted after revision 11 October 2013; online publish-ahead-of-print 7 November 2013

Aims
Increasing clinical evidence has emphasized the importance of coronary plaque characteristics, rather than the severity of luminal narrowing on acute coronary syndrome (ACS) outcome. Computed tomographic coronary angiography (CTCA) is a unique, non-invasive approach for assessing plaque characteristics. This study was prospectively designed to investigate the prognostic value of physiologically non-obstructive but a vulnerable coronary plaque on CTCA for predicting future ACS events.

Methods and results
This study consisted of 543 patients who had undergone CTCA and had normal findings on exercise-stress myocardial perfusion single-photon emission computed tomography. CTCA analysis included the presence of >50% luminal stenosis and vulnerable features including positive remodelling (PR), low-attenuation plaque, and ring-like sign. The primary endpoint was ACS events including cardiac death, non-fatal myocardial infarction, and unstable angina. The mean follow-up period was 3.4 ± 0.8 years. The 3-year cumulative event rate was 1.2% per year, and 87% of ACS events occurred in plaques with at least one of vulnerable features. In patient-based multivariate analysis, the presence of plaque with vulnerable features on CTCA was a significant predictor for future ACS events (P = 0.001). Patients with vulnerable plaque had worse ACS outcomes compared with those without vulnerable plaques (3-year cumulative event rate: 3.2 per year vs. 0.8%, P < 0.001).

Conclusion
This study demonstrated that physiologically non-obstructive but vulnerable coronary plaques were associated with future ACS events. We should pay more attention to currently non-obstructive plaque but showing vulnerable morphologies on CTCA.

Keywords
acute coronary syndrome • computed tomographic angiography • prognosis

Introduction
Myocardial perfusion on exercise-stress single-photon emission computed tomography (SPECT) is an established gold standard technique for physiological assessment of luminal narrowing. Because normal findings on myocardial perfusion SPECT are associated with benign outcomes, plaque showing a normal myocardial perfusion image has been disregarded in terms of predicting future acute coronary syndrome (ACS) events.

Computed tomographic coronary angiography (CTCA) has emerged as an accurate and non-invasive imaging modality that can identify plaque composition as well as the severity of coronary artery lumen narrowing. Recent CTCA studies have shown that certain plaque morphologies on CTCA, including positive remodelling (PR), low-attenuation plaque (LAP), and ring-like sign, are closely associated with future ACS events. A recent intravascular ultrasound study suggested the importance of assessing plaque characteristics for predicting ACS events, irrespective of coronary artery luminal narrowing. However,
discussion still remains whether plaques that do not cause physiological obstruction but have vulnerable characteristics have any clinical significance for predicting future ACS events. This prospective study aimed to investigate the prognostic importance of CTCA-featured plaque characteristics on the occurrence of future ACS events in patients with normal findings on exercise-stress myocardial perfusion SPECT.

Methods

Study population

During the period from April 2007 to March 2011, consecutive 1956 patients who prospectively underwent CTCA for chest pain (n = 1212) or multiple coronary artery disease (CAD) risk factors (n = 744) were screened for participation in the present study. Patients gave written informed consent before the CTCA examinations, and patients with coronary plaques on CTCA who had normal SPECT results were followed. The exclusion criteria were (i) previous history of coronary artery bypass grafting, (ii) previous history of myocardial infarction, and (iii) valvular heart disease of more than moderate severity. Based on the findings of CTCA, patients with normal coronary arteries (no plaque) (n = 390) and patients who required coronary angiography and/or revascularization (n = 406) were excluded. Also, patients were excluded when at least one major coronary artery segment was uninterpretable due to motion artefacts or heavy calcification (n = 19). Following the protocol, 762 patients were referred for exercise stress SPECT within 4 weeks after CTCA examination (19 ± 8 days), and 567 patients showed normal myocardial perfusion SPECT. Patients lost to follow-up were excluded at the time of the last follow-up assessment (n = 24). The final study population consisted of 543 patients (344 men, mean age 65 ± 10 years). An exclusion flow diagram was summarized in Figure 1. Blood samples were taken at the CTCA examination to measure serum creatinine, fasting lipids, glucose, glycated haemoglobin, and C-reactive protein (CRP). All patients received optimized medical therapy for atherosclerotic risk factors according to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines based on structured interviews by the attending physicians. Each patient was followed once every 2 months until the end of the study or the occurrence of ACS events using structured interviews and clinical examinations by physicians. This study design was approved by the Institutional Review Board of Osaka Ekisaikai Hospital.

Scan protocol and image reconstruction

The CTCA was performed using a SOMATOM Sensation 64 system (Siemens Medical Systems, Forchheim, Germany), with the following scan parameters: 64 × 0.6 mm collimation, tube voltage of 120 kV, gantry rotation time of 330 ms, and tube current of 770–850 mA. For the contrast-enhanced scans, 50–80 mL of non-ionic contrast agent (Omnipaque 350, Daiichi Sankyo Co, Tokyo, Japan) was injected intravenously at a flow rate of 3.5–5.5 mL/s followed by 30 mL of saline. Delay time was defined using the bolus tracking technique with a region of interest positioned at the level of the ascending aorta in the monitoring scan and using a manually triggered threshold of 100 Hounsfield units (HU) for the main scanning. All patients received 5 mg of bispiron-propronal orally before the computed tomography (CTCA) scan, and patients with a heart rate >70 beats/min received 2 mg of metoprolol intravenously. In addition, patients received 0.6 mg of sublingual nitroglycerin. All scans were performed during a single breath hold. The raw data were reconstructed using algorithms optimized for electrocardiography-gated multi-slice spiral reconstruction. Retrospective gating was used and the estimated radiation dose was 9 mSv.

Analysis of CTCA

All three major vessels were assessed in every patient using the modified 17-segment AHA model for coronary segment classification. In each coronary artery segment, coronary atherosclerotic plaque was defined as a tissue structure >1 mm² that existed either within the coronary artery lumen or adjacent to the coronary artery lumen and that could be discriminated from the surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. The severity of luminal-diameter stenosis was visually divided into (i) <50% luminal stenosis, (ii) 50–69% luminal stenosis, or (iii) >70% luminal stenosis. The vessel was displayed on axial images and multi-planar reconstruction images, and diameter stenosis was estimated using proximal and distal reference segments. The reference segment was the most adjacent points to the maximal stenosis at which there was minimal or no plaque. Each plaque was classified as follows: (i) non-calcified plaque = plaque with lower density compared with the contrast-enhanced vessel lumen without any calcification (>150 HU), (ii) calcified plaque = plaque with predominantly calcification, or (iii) mixed plaque = plaque with a small amount of calcification elements within a single plaque.

In non-calcified and mixed plaques, the presence or absence of the following three vulnerable features was analysed: LAP, PR, and ring-like sign. First, non-calcified plaques were divided into LAP (plaque with <30 HU) and intermediate-attenuation plaques (plaques between 30 and 150 HU). To identify the presence of LAP, a region of interest was placed on at least five randomly selected points within each plaque, and the mean value was defined as the plaque density. Secondly, the remodelling index was defined as the ratio of the vessel diameter at the plaque site to the reference diameter set proximal to the lesion in a normal-appearing vessel segment. The presence of PR was defined as a remodelling index >1.1. Finally, a ring-like sign represented a plaque core with low attenuation surrounded by a rim-like area of higher attenuation. The ring-like sign was defined by the following criteria: (i) the presence of a ring of high attenuation around certain coronary artery plaques and (ii) CTCA attenuation of the ring, presenting higher than those of the adjacent plaque and no >150 HU.

Figure 2 shows a representative case of vulnerable featured plaque on CTCA that resulted in an ACS event.

All CTCA data sets were analysed on a per-segment basis by two independent experienced readers (A.T. and K.S.) who had >5-year experience in CTCA analysis with the number of CTCA examinations compatible with ACCF/AHA clinical competence statement training level 3. In case of disagreement or intermediate CTCA results, the plaques were reevaluated for the consensus judgement. They were blinded to clinical characteristics and the results of SPECT until the end of patient’s enrolment period in this study (March 2011).

Myocardial perfusion image acquisition and analysis

Each patient underwent ECG-gated myocardial perfusion SPECT with symptom-limited exercise on a bicycle. The endpoints included excessive fatigue, dyspnoea, moderate-to-severe angina, hypotension, diagnostic ST depression, or significant arrhythmia. At peak exercise, thallium-201 (201TL) was injected intravenously, and the patient was encouraged to exercise for another 1 min. Initial images were obtained immediately after the termination of exercise and delayed images were obtained 4 h later. Patients were asked to refrain from ingesting caffeine-containing beverages for at least 12 h, nitrates and calcium channel blockers for 24 h, and β-blockers for 48 h, before the myocardial perfusion study. Gated SPECT studies were performed with a 2-head gamma camera (GCA-7200; Toshiba Medical Systems, Otawara, Japan) equipped with low-energy, general-purpose collimators, with the detectors set to form a 180° angle. Sixty equidistant projections were acquired over...
360° in a 64 × 64 matrix. Acquisition of images was performed with 30 s per step, in 6° angular steps. For all patients, SPECT image set was reconstructed at a dedicated workstation (GCA-7200; Toshiba Medical Systems, Otawara, Japan) into short-axis, vertical long-axis, and horizontal long-axis sections encompassing the entire left ventricle. No attenuation correction was applied. In addition, polar maps of perfusion were produced using a dedicated software package (GCA-7200; Toshiba Medical Systems, Otawara, Japan).

Myocardial perfusion SPECT image interpretation was visually performed by two experienced cardiologists (H.T. and S.F.) with 10 years of experience in cardiac radionuclide imaging who were blinded to CTCA findings. If the discordance between two experienced cardiologists did not resolve, SPECT finding was defined as ‘inconclusive results’. Also, patients who did not reach to the target heart rate, defined as \(220 - \text{age (years)} \times 0.85\), were classified into ‘inconclusive results’. Normal myocardial perfusion SPECT was defined as myocardial perfusion without any perfusion abnormalities. Further, increased lung uptake of 201Tl, transient left ventricular dilatation at initial image, and decreased myocardial 201Tl washout were defined as abnormal myocardial perfusion that suggest multi-vessel CAD.4,15,16 When there was discordance between them, a consensus reading was obtained.

Endpoints
The pre-specified endpoint of this study was the occurrence of an ACS event defined as cardiac death, non-fatal myocardial infarction, and unstable angina requiring revascularization. Myocardial infarction was defined by the ACCF/AHA guideline, and unstable angina was defined according to the Braunwald classification. The culprit lesion was comprehensively determined on the basis of the association of invasive coronary angiography with electrocardiographic changes, echocardiography, or myocardial ischaemia as detected during a stress test. When culprit lesion was difficult to determine by imaging modalities, stress test was performed after medical therapy to stabilize the patient’s condition. Unstable angina requiring revascularizations was included in endpoints. All events of unstable angina were proved by invasive coronary angiography.

Statistical analysis
Categorical variables are presented as number (%) and continuous variables as mean ± SD. The \(\chi^2\) test was used for comparison of categorical variables. Between-group comparisons were made using the independent-samples t-test or Mann–Whitney U test as appropriate. Multivariate Cox proportional hazard analysis was performed to identify predictors of ACS events on per-patient based analysis, including hypertension, 50–69% luminal stenosis, 2- or 3-vessel disease, and vulnerable featured plaques. The Kaplan–Meier survival method was used to compare survival according to the existence or absence of vulnerable features on CTCA for per-segment and per-patient-based analyses, using the log-rank test. A P value < 0.05 was considered statistically significant. The sample size was calculated to provide adequate statistical power for identifying plaque characteristics that result in ACS events on the basis of a range of assumptions about the frequency of vulnerable plaques: power of 80%, hazard ratio of 5.0, ACS event rate for vulnerable plaques.
featured plaques of 5%, and a two-sided alpha of 0.050. If a vulnerable featured plaque is detected in 30% of patients with CAD, 518 patients would be needed. Allowing for a 5% attrition rate, we calculated that we would need to enrol 545 patients.

Results

Baseline plaque compositions on CTCA

Of the 543 patients, 9231 segments were adequately analysed where 1107 plaques were detected (2.0 plaques per patient). The severity of luminal narrowing was <50% in 774 (70%) plaques and between 50 and 70% in 331 (30%) plaques. No plaques had luminal narrowing with >70%. At least one of the vulnerable features, including PR, LAP, or ring-like sign, was detected in 274 plaques (24%) in 182 patients (33%; 0.4 plaques per patient). PR was detected in 183 (16%) plaques, LAP in 133 (12%), and ring-like sign in 30 (2.7%). Of these, 44 plaques (3.9%) had any 2 vulnerable features, and 14 plaques (1.2%) had all 3 vulnerable features, respectively. These results are summarized in Figure 3. The plaques with any vulnerable features were 85 (31%) in the right coronary artery, 25 (9.1%) in the left main coronary artery, 118 (43%) in the left anterior descending coronary artery, and 45 (16%) in the left circumflex coronary artery.

Patients’ characteristics and ACS events

Patients were divided into two groups: with or without plaques with at least one of vulnerable features on CTCA (Table 1). Patients with at least one of vulnerable features had lower HDL-cholesterol levels than those with no vulnerable features (49 ± 14 vs. 56 ± 18 mg/dL, \( P = 0.014 \)). There were no significant differences in other clinical characteristics, the medications that the patients were taking after CTCA and myocardial perfusion SPECT, and laboratory examinations between patients with and without vulnerable features. Also, clinical characteristics, plaque features and drugs of patients with ACS event, lost at the follow-up, and positive SPECT results are shown in Supplementary data online, Table S1.

Of the 543 patients, the composite ACS event was examined after a mean follow-up of 3.4 ± 0.8 years (range 1–5.4 years; median 3.4
years). During this period, 23 ACS events occurred (1.2% per year), comprising myocardial infarction in 12 patients and unstable angina requiring revascularizations in 11 patients. Three of 12 patients with myocardial infarction died during the hospitalization thereafter. All culprit lesions were confirmed by emergent invasive coronary angiography. Of the 23 ACS events, the number of vulnerable features on CTCA in the culprit lesion was 3 in 5 (22%) patients, 2 in 8 (35%) patients, 1 in 7 (30%) patients, and 0 in 3 (13%) patients. Of the 182 patients with plaques with vulnerable features, 20 patients (8.8%) developed ACS events, 1 patient (0.5%) had ACS within 30 days, and 0 in 3 (13%) patients.

Supplementary data online, Table S2 shows the patient-based univariate analysis compared between patients with and without ACS event. Patients with ACS event had higher prevalence of hypertension (P = 0.046), 50–69% luminal stenosis (P < 0.001), 2- or 3-vessel disease (P < 0.001), and vulnerable featured plaques (P < 0.001) than those without ACS event. In patient-based multivariate analysis, the presence of plaque with vulnerable features on CTCA was a significant predictor for future ACS events (P = 0.001) (Table 2). Figure 4 shows the Kaplan–Meier curve of patients according to the presence of plaques with vulnerable features (Figure 4A), the extent of atherosclerotic burden (Figure 4B), and the severity of luminal stenosis (Figure 4C), respectively. Kaplan–Meier analysis confirmed that patients with vulnerable featured plaques on CTCA had a worse outcome compared with those without vulnerable featured plaques (P < 0.001) in Figure 4A. The event rate in patients with and without vulnerable featured plaques was 3.2 and 0.24% per year, respectively.

The results of segment-based univariate and multivariate analyses are provided in Supplementary data online, Tables S3 and S4. The segment-based Kaplan–Meier analysis according to the presence or absence of the three CTCA features for future ACS events is shown in Figure 5. The presence of any of the three vulnerable features on CTCA correlated with ACS, with a graded relationship with the number of vulnerable features (Figure 5). The results of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of vulnerable plaques for predicting ACS events are summarized in Table 3. The presence of >1 vulnerable feature showed a high PPV of 87%, and the absence of two or three vulnerable features showed a high NPV of 97% for predictive value of developing future ACS event.

**Discussion**

This CTCA study revealed that ACS events occurred at the rate of 1.2% per year in patients with normal myocardial perfusion image. Patients having a vulnerable plaque on CTCA showed poorer prognoses compared with those without vulnerable plaque, and most...
ACS events occurred at the plaque showing vulnerable features on baseline CTCA.

CTCA predictors for ACS events
Assessment of coronary artery stenosis and plaque characteristics by CTCA has been well validated in prior studies against intracoronary ultrasonography/virtual histology and optical coherence tomography. Early CTCA reports indicated that the presence and extent of obstructive CAD defined by coronary plaques causing >50% reduction in the luminal diameter is a valuable prognostic marker of incident death or major adverse cardiovascular events. Recent CTCA studies identified plaque compositions, including PR, LAP, and ring-like sign as vulnerable features associated with plaques that are prone to rupture, independent of the severity of coronary artery luminal stenosis. These findings were

Table 2  Patient-based multivariate predictors of ACS events during follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.7 (0.55–5.36)</td>
<td>0.34</td>
</tr>
<tr>
<td>50–69% luminal stenosis</td>
<td>1.9 (0.54–6.94)</td>
<td>0.30</td>
</tr>
<tr>
<td>2- or 3-vessel disease</td>
<td>2.2 (0.75–6.66)</td>
<td>0.14</td>
</tr>
<tr>
<td>Vulnerable featured plaques</td>
<td>9.4 (2.66–33.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The variables entered into patient-based multivariate Cox proportional hazards model when they indicated P < 0.05 in Table 2. Less than 50% luminal stenosis was excluded because it was initially associated with 50–69% luminal stenosis. The final variables entered were hypertension, 50–69% luminal stenosis, 2- or 3-vessel disease, and vulnerable featured plaques. ACS, acute coronary syndrome; CI, confidence interval.

Figure 4  Kaplan–Meier analyses for future ACS events. (A) The Kaplan–Meier curve according to the presence of plaques with vulnerable features (no vulnerable features, 1 vulnerable feature, and ≥2 vulnerable features). (B) The Kaplan–Meier curve in the comparison between patients with 1-vessel disease vs. patients with two- to three-vessel disease. (C) The Kaplan–Meier curve of patients with plaques >50% (50–69%) luminal stenosis vs. patients with plaques <50% luminal stenosis. ACS, acute coronary syndrome.
supported by the investigation with intravascular ultrasound demonstrated that coronary lesions responsible for cardiac events were associated with the large plaque burden, a small lumen area, and thin-cap fibroatheroma morphology. It should be emphasized, however, that almost all of these studies investigated plaque extent and stenosis severity, and there are only limited data on the relationship between atherosclerotic plaque morphology and regional myocardial ischaemia attributed to the atherosclerotic lesion in patients with CAD. Specifically, the use of CTCA has methodological limitations with regard to the use of diameter stenosis for assessing coronary artery stenosis severity. This was the first study that used SPECT to confirm that most coronary atherosclerotic lesions associated with future ACS events were physiologically non-obstruction. In this study, 29% of plaques (n = 331) with luminal narrowing between 50 and 70% showed normal perfusion patterns. This finding was similar to previous observations. Schuijf et al. underwent both CTCA and myocardial perfusion imaging on SPECT in 114 patients. They found ≈50% of patients with plaques with >50% luminal narrowing on CTCA who showed a normal findings.

In recent investigations using CTCA and intravascular ultrasound, the event rate of recurrent coronary events (except revascularizations for stent restenosis) among ACS patients ranged from 2.2–5.5% per year, which was comparable to that of patients with vulnerable featured plaques in the present study (3.2% per year). Data from large-scale clinical trials that used statins for secondary prevention in patients with previous myocardial infarction showed similar event rate (2.0–2.9% per year). These findings could justify the assessment of vulnerable plaques without abnormalities using myocardial perfusion for predicting future ACS events. If CTCA would detect plaques showing vulnerability, more aggressive intervention and/or close monitoring might be required even with normal finding on myocardial perfusion SPECT.

**ACS outcome in comparison with previous studies**

The rate of ACS events in the present study (1.2% per year) seems to be slightly higher than that reported in previous studies among patients with normal myocardial perfusion SPECT varied from 0 to 0.93% per year, in which unstable angina was not included as the primary endpoint, at least partially due to the subjective judgement of unstable angina. The optimal management is required in patients with unstable angina to prevent serious adverse outcomes. The endpoint of this study included only unstable angina requiring revascularization.

<table>
<thead>
<tr>
<th>CCTA characteristics</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>8.7</td>
<td>99</td>
<td>69</td>
<td>84</td>
<td>11</td>
</tr>
<tr>
<td>LAP</td>
<td>7.1</td>
<td>98</td>
<td>56</td>
<td>84</td>
<td>6.5</td>
</tr>
<tr>
<td>Ring-like sign</td>
<td>30</td>
<td>98</td>
<td>39</td>
<td>98</td>
<td>23</td>
</tr>
<tr>
<td>Any one of vulnerable features</td>
<td>7.3</td>
<td>99</td>
<td>86</td>
<td>76</td>
<td>20</td>
</tr>
<tr>
<td>Two or three vulnerable features</td>
<td>28</td>
<td>99</td>
<td>56</td>
<td>97</td>
<td>30</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CTCA, computed tomographic coronary angiography; LAP, low-attenuation plaque; NPV, negative predictive value; PPV, positive predictive value; PR, positive remodelling.
in SPECT analysis. Quantitative analysis should be performed in the future studies. In this study, however, none of the patients had severe coronary stenosis of >70% or multi-vessel CAD. Therefore, these technical limitations might not affect the results of the present study. Secondly, we observed three ACS events (unstable angina) from the calcified plaques during the 3-year follow-up. Despite calcified nodules being recognized as a type of causing coronary thrombosis not caused by plaque rupture or erosion, inconsistent results have been observed for the association between calcified nodules and future ACS events. Three vulnerable features were evaluated in non-calcified and mixed plaques in the present study. Vulnerable features were not assessed in plaques with predominant calcification (calcified plaque), because plaques carrying heavy calcification are difficult to assess by CTCA. Therefore, the impact of vulnerable features in plaques with calcification on ACS outcome remained unclear. Further investigation is required to elucidate the relationship between the amount and characteristics of calcification and its impact in the prediction of future ACS events. Thirdly, all of the 24 patients that were lost in the follow-up had no vulnerable featured plaques on CTCA. However, patients with normal CTCA (no plaques) and those with abnormal SPECT results were not followed, and their prognostic data were unknown. Fourthly, the severity of CAD risk factors and concomitant medications for diabetes were not taken into account for the analysis, although these factors may influence the outcome in patients with CAD. Finally, radiation exposure may preclude the widespread use of CTCA in clinical practice. Recent CTCA algorithms, including prospective gating methods and tube current modulation, may overcome this limitation.

Conclusions
This CTCA study revealed that vulnerable plaques on CTCA, even those that were normal on myocardial perfusion imaging, were associated with future ACS events. We should pay more attention to plaques showing normal myocardial perfusion image but vulnerability.

Supplementary data
Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

Acknowledgements
We appreciate the assistance of following colleagues in the recording and management of CTCA data sets and patient records: Makoto Sakamoto MT, Keisuke Iwata MT, and Chihiro Kakoiyama, RN (Osaka Ekisaikai Hospital).

Conflict of interest: The authors declare no conflict of interest.

References


