Morphologic and Functional Assessment of Coronary Artery Disease

– Potential Application of Computed Tomography Angiography and Myocardial Perfusion Imaging –

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Background: The role of combined evaluation of myocardial perfusion imaging (MPI; by single-photon emission computed tomography) and computed tomography angiography (CTA) for risk stratification of coronary artery disease was evaluated. For CTA, the extent of luminal stenosis, and also the features of high-risk plaques (HRP, including positive remodeling and low attenuation) were evaluated.

Methods and Results: A total of 304 patients (65 ± 11 years, male 72%, median follow-up: 24 months) who underwent CTA and MPI were enrolled in the study. Summed stress scores and summed difference scores (SDS) for MPI, stenosis, and HRP were evaluated, and event rates were compared. Cardiac events were defined as acute coronary event including cardiac death or non-fatal acute myocardial infarction, and unstable angina requiring revascularization. Of 304 patients, 51 (16.8%) underwent early revascularization. In the remaining 253 patients, an event occurred in 11 (4.3%). HRP (hazard ratio [HR], 4.75, $P=0.00171$) and stenosis (+) with SDS >0 (HR, 4.58, $P=0.0461$) were significant independent predictors of cardiac event. The event rate for stenosis (+) with SDS >0 was significantly higher than others (log-rank $P=0.0490$). The event rates were significantly different between HRP(+) and HRP(–) (16.1% vs. 2.7%, log-rank $P=0.0013$).

Conclusions: HRP on CTA was an independent predictor of acute coronary events, as was stenosis (+) with SDS >0 , and HRP had increased prognostic value over stenosis and abnormal MPI findings. (*Circ J* 2013; **77**: 411–417)

Key Words: Computed tomography angiography; High-risk plaque; Myocardial perfusion imaging; Risk stratification

Technological advances have substantially reduced the radiation burden of both computed tomography computed tomography angiography (CTA) and single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). Although CTA is a promising method for detection and exclusion of obstructive coronary artery disease (CAD) with high sensitivity and negative predictive value, one of the problems of CTA is low positive predictive value, often because of calcified lesions and motion artifacts.^{1–3} In contrast, one of the advantages of CTA is the feasibility of plaque characteristics,^{4–8} and CTA has the potential to detect high-risk plaque (HRP). In our previous study, low-attenuation

plaque (LAP) and positive vascular remodeling (PR) on CTA associated with plaques resulted in acute coronary syndrome (ACS),⁹ as did the culprit ACS lesions.¹⁰

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Traditionally, physiological or pharmacological myocardial stress tests using SPECT^{11–16} have been performed for the non-invasive detection of significant CAD for clinical evaluation before coronary revascularization. It is intriguing that the absence of inducible ischemia at MPI identifies subjects with a very low ($<1\%$ per year) event rate during the following 1

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Table 1. Patient Characteristics

	Total (n=304)
Age (years), mean±SD	65.3±10.6
Male, n (%)	220 (72.4)
Hypertension, n (%)	182 (59.9)
Dyslipidemia, n (%)	148 (48.9)
Diabetes, n (%)	81 (26.6)
Obesity, n (%)	72 (23.8)
Smoking, n (%)	81 (26.6)
Previous MI, n (%)	101 (33.2)
16/64/320 slice CT, n (%)	90/67/146 (39.7/22.1/48.2)

CT, computed tomography; MI, myocardial infarction; obesity, >25 kg/m².

year. It has been proposed that the events may occur in patients with inducible ischemia because the plaques vulnerable to imminent rupture may generally become larger before rupture. It is intuitively logical that the combination of these 2 non-invasive imaging techniques would allow for a more comprehensive evaluation of prognostic outcomes. For CTA, we evaluated both the extent of luminal stenosis and also the features of HRP including PR or LAP. In contrast, hemodynamically significant lesions were detected on MPI.

Methods

This retrospective study included a total of 304 patients who underwent both CTA and MPI within 3 months and who were followed up for at least 12 months. Patients who had undergone coronary bypass graft before CTA and MPI were excluded. Patients were referred for evaluation on CTA and MPI for suspected CAD. We collected information on the presence of categorical cardiac risk factors in each individual including hypertension, dyslipidemia, diabetes mellitus, smoking status, and body mass index as well as past history of myocardial infarction (MI). Hypertension was defined as blood pressure-lowering medication usage, or blood pressure $\geq 140/90$ mmHg (systolic/diastolic). Dyslipidemia was defined as lipid-lowering medication usage, low-density lipoprotein ≥ 140 mg/dl, or total cholesterol ≥ 220 mg/dl. Diabetes was defined as glucose-lowering medication usage, or HbA_{1c} ≥ 6.5 . Smoking was defined as self-reported history of current smoking. Institutional review board approval was obtained.

CTA, Interpretation and Detection of Stenosis

We used 320-slice CT in 146 patients, 64-slice CT in 67, and 16-slice CT in 90 patients. 320-slice CT (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) was performed with a collimation of 320×0.5 mm, pixel size of 0.35×0.35 mm, rotation time of 350 ms. Tube voltage was 120 or 135 kV and maximum tube current was 300–580 mA depending on body weight. For contrast-enhanced scanning, 245 mgI/kg of contrast media was injected in 12 s followed by saline of 20 ml at 3.0 ml/s. Axial scan was performed with prospective gated scan for 1 heart beat at heart rate of <65 beats/min for half reconstruction, and in 2 or 3 heart beats for heart rate ≥ 65 beats/min for segment reconstruction.

64-slice CT (Aquilion 64, Toshiba Medical Systems, Japan) was used with a collimation of 64×0.5 mm, detector pitch of 9.8–11.2, pixel size 0.39×0.39 mm, rotation time 350, 375 or 400 ms, tube current of 400 or 450 mA, and voltage 120 or

135 kV. For contrast-enhanced scanning, 60 ml of contrast media was injected at 4.0 ml/s followed by 20 ml at 2.0 ml/s. In the remaining 911 patients, 16-slice CT (Aquilion 16, Toshiba Medical Systems, Japan) was used with a collimation of 16×0.5 mm, detector pitch of 3.2–3.6, pixel size 0.39×0.39 mm, rotation time 400 ms, tube current 360 mA, and voltage 135 kV. For contrast-enhanced scanning, 60 ml of contrast media was injected at 3.0 ml/s followed by 40 ml at 1.5 ml/s. Patients received β -blocker 1 h before CT if the heart rate was >60 beats/min. The raw CT data were reconstructed using algorithms optimized for retrospective electrocardiogram (ECG)-gated segment reconstruction. The reconstructed CT image data were transferred to a computer workstation for post-processing (ZIOSTATION System 1000 or ZIO M900, Amin/ZIO, Japan).

MPI was carried out in the axial, coronal and sagittal, cross-sectional, and curved planes. Coronary arteries with a diameter of 2 mm were visually evaluated for the presence of stenoses $\geq 70\%$. Calcified lesions or stent lesions for which it was difficult to detect the patency were classed as stenosis.

For plaque assessment, the presence of LAP and PR were observed regardless of luminal stenosis.

LAP was defined as plaque with minimum CT density <30 Hounsfield units [HU] based on our previous study.^{8–10}

Coronary arterial remodeling was defined as a change in the vessel area at the plaque site in comparison to the reference segment set proximal to the lesion in a normal-appearing vessel segment (reference area). Manual inspection of the cross-section was used for defining the remodeling index (lesion area/reference area). The remodeling index was reported as positive when the area at the plaque site was at least 20% larger than the reference segment. HRP was defined as plaque with LAP and/or PR.

CTA interpretation was performed by consensus between 2 cardiologists who were unaware of the MPI findings and event data.

Adenosine Stress MPI

Adenosine stress-201Tl SPECT was performed in all patients. Adenosine was given i.v. at 0.12 mg·kg⁻¹·min⁻¹ for 6 min, and 201Tl was injected at 3 min into the infusion. ECG signal and blood pressure were monitored before and throughout the infusion. Cardiac scintigraphy was performed using a dual-headed SPECT gamma camera (ADAC, VERTEX- plus EPIC, USA) adhering to the standard protocol. The initial image was obtained at 10 min after the 201Tl injection in the supine position, and a delayed image was obtained 4 h later. Seventy-two data projections were obtained with a 64×64 matrix over 360°. Data were acquired for 25 s for each projection. The energy window was set at the 67-keV photopeak of 201Tl with a 15% window. Reconstruction was performed using a Butterworth filter at a cut-off frequency of 0.70 cycles/cm and an order of 8. No attenuation or scatter correction was used.

SPECT was assessed using a 17-segment model.¹⁷ Distribution was evaluated visually on a 5-point scale for stress (summed stress score; SSS) and delayed images (summed rest score; SRS): 0, normal; 1, slight reduction of tracer uptake; 2, moderate reduction of uptake; 3, severe reduction of uptake; 4, absence of uptake. Summed difference score (SDS) was obtained as follows: SDS=SSS–SRS. SSS ≥ 4 and SDS >0 were defined as abnormal on MPI. Images were analyzed independently by 2 cardiologists who were unaware of the CTA and event data.

Table 2. Profile for Presence vs. Absence of Cardiac Event

	Event (+)	Event (–)	P-value
n	11	242	
SSS ≥ 4 , n (%)	7 (63.6)	108 (44.6)	0.2156
SDS > 0 , n (%)	5 (45.5)	75 (31.0)	0.3130
Stenosis, n (%)	8 (72.7)	142 (58.7)	0.3536
Stenosis (+) with SSS ≥ 4 , n (%)	6 (54.6)	77 (31.8)	0.1164
Stenosis (+) with SDS > 0 , n (%)	5 (45.5)	47 (19.4)	0.0366
HRP, n (%)	5 (45.5)	26 (10.7)	0.0006
Age (years), mean $\pm$ SD	68.1 $\pm$ 6.1	65.5 $\pm$ 10.6	0.3132
Male, n (%)	10 (90.9)	171 (70.7)	0.1455
Hypertension, n (%)	9 (81.8)	173 (59.0)	0.1303
Dyslipidemia, n (%)	8 (72.7)	117 (48.4)	0.1137
Diabetes, n (%)	1 (9.1)	63 (26.0)	0.2062
Obesity, n (%)	4 (36.4)	49 (20.3)	0.2020
Smoking, n (%)	4 (36.4)	62 (25.6)	0.4274
Previous MI, n (%)	6 (54.6)	73 (30.2)	0.0879

HRP, high-risk plaque; SDS, summed difference score; SSS, summed stress score. Other abbreviations as in Table 1.

Table 3. Significant Independent Predictors of Cardiac Events

	SE	P-value	HR	95% CI
Stenosis (+) with SDS > 0	0.30	0.0461	3.58	1.02–11.98
HRP	0.31	0.0171	4.75	1.35–16.05
Previous MI	0.31	0.2982	1.90	0.56–6.69

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,2.

Follow-up

A cardiac event was defined as an unexpected acute coronary event including cardiac death or non-fatal acute MI, and unstable angina requiring revascularization. A 12-lead ECG and cardiac-specific troponin were obtained in all patients presenting to the emergency room with chest discomfort. Patients with typical acute chest pain and persistent ST-segment elevation on ECG and elevation of troponin (TnI > 0.1) were defined as having ST-elevation MI. Patients with typical acute chest pain presenting without ST-segment elevation on the ECG but elevation of troponin (TnI > 0.04) were defined as having non-ST-elevation MI. Unstable angina was defined according to the European Society of Cardiology guidelines as acute chest pain with or without the presence of ECG abnormalities, and negative cardiac enzyme levels.¹⁸ Patients with stable complaints undergoing early elective revascularization within 60 days after CTA or MPI were excluded from survival analysis.

Statistical Analysis

JMP (version 9.0) was used for all statistical analysis. Categorical variables are expressed as percentages. Continuous variables are expressed as mean $\pm$ SD. Chi-squared statistics were used for comparison of categorical variables, and Student's unpaired t-test for that of continuous variables. Those variables significant at $P < 0.1$ were included in multivariate Cox proportional hazards regression to evaluate for factors that were independently associated with the cardiac event. The Kaplan-Meier method was used for event-free analysis, and comparison between groups was done with the log-rank test. All P-values were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

A total of 304 patients (65 $\pm$ 11 years, male 72%) were included in this study. The median follow-up period was 24 months. Of these, 182 patients had hypertension, 148 dyslipidemia, 81 had diabetes mellitus, and 72 were obese. Eighty-one subjects were active smokers and 101 had a history of previous MI (Table 1). SSS ≥ 4 was noted in 160 patients (52.6%), SDS > 0 in 120 (39.5%), and stenosis on CTA in 198 (65.1%). HRP was detected in 41 patients (13.5%). Of 304 patients, 51 (16.8%) underwent early revascularization. In the remaining 253 patients, median follow-up was 27 months. During this period, an event occurred in 11 patients (4.3%; 9 non-fatal MI and 2 unstable angina pectoris). Culprit lesions of acute event were confirmed on ECG, echocardiography, and coronary angiography, and all culprit lesions in HRP patients were located at HRP.

Comparison of imaging findings and clinical profile for presence vs. absence of cardiac events is given in Table 2. Stenosis (+) with SDS > 0 (45.5% vs. 19.4%, $P = 0.0366$), HRP (45.5% vs. 10.7%, $P = 0.0006$), and previous MI (54.6% vs. 30.2%, $P = 0.0879$) were the variables with $P < 0.1$. Upon multivariate Cox regression analysis of these 3 selected variables in 253 patients, HRP (hazard ratio [HR], 4.75; 95% confidence interval [CI]: 1.35–16.05, $P = 0.0171$) and stenosis (+) with SDS > 0 (HR, 3.58; 95% CI: 1.02–11.98, $P = 0.0461$) were significant independent predictors of cardiac events (Table 3).

The Kaplan-Meier survival curves illustrate the different survival rates for cardiac event. There were no significant differences in event rate between SSS ≥ 4 and SSS < 4 (6.1% vs. 2.9%, log-rank $P = 0.2322$), SDS > 0 and SDS = 0 (6.3% vs. 3.5%, log-rank $P = 0.3238$), and stenosis (+) and (–) (5.3% vs. 2.9%, log-rank $P = 0.3745$; Figures 1A–C). For the combination of

Figure 1. Kaplan-Meier curve for cardiac event based on computed tomography angiography and myocardial perfusion imaging findings. There were no significant differences in the event rate between (A) SSS ≥ 4 and <4 (6.1% vs. 2.9%, log-rank $P=0.2322$), (B) SDS >0 and $=0$ (6.3% vs. 3.5%, log-rank: $P=0.3238$), and (C) stenosis (+) and (-) (5.3% vs. 2.9%, log-rank: $P=0.3745$). (D) The event rate for stenosis (+) and SSS ≥ 4 was not significantly different from stenosis (-) and SSS >4 (log-rank $P=0.2010$). (E) The event rate for stenosis (+) and SDS >0 was significantly higher than that for stenosis (-) or SDS $=0$ (log-rank $P=0.0490$). (F) The event ratio was significantly different between HRP(+) and HRP(-) (16.1% vs. 2.7%, log-rank $P=0.0013$). HRP, high-risk plaque; SDS, summed difference score; SSS, summed stress score.

stenosis and SSS, the event rate for stenosis (+) with SSS ≥ 4 , stenosis (+) with SSS <4 , stenosis (-) with SSS ≥ 4 , and stenosis (-) with SSS <4 was 7.1%, 3.0%, 3.2%, and 2.8%, respectively. For stenosis and SDS, the event rate for stenosis (+) with SDS >0 , stenosis (+) with SDS $=0$, stenosis (-) with SDS >0 , and stenosis (-) with SDS $=0$ was 9.6%, 3.1%, 0%, and 4.0%, respectively. Although the event rate for stenosis (+) with SSS ≥ 4 was not significantly different compared to the others (log-rank $P=0.2010$), the event rate for stenosis (+) with SDS >0 was significantly higher than others (log-rank $P=0.0490$; **Figures 1D,E**). The event rates were significantly different between HRP(+) and HRP(-) (16.1% vs. 2.7%, log-rank $P=0.0013$; **Figure 1F**). The combination of HRP and other CT and MPI parameters had increased prognostic value for the cardiac event (**Figure 2**). Each stenosis (-) or normal MPI group was divided into 2 groups based on HRP, and the event rate was then compared between 3 groups as follows. The event rate for SSS ≥ 4 , SSS <4 with HRP, and SSS <4 without HRP was 6.1% vs. 22.2% vs. 0% (log-rank $P<0.0001$). The event rate for SDS >0 , SDS $=0$ with HRP, and SDS $=0$ without HRP was 6.3% vs. 20.8% vs. 0.7% (log-rank $P<0.0001$). For stenosis (+), stenosis (-) with HRP, and stenosis (-) without HRP, the event rate was 5.3% vs. 30.0% vs. 0%, respectively (log-rank $P<0.0001$). For stenosis (+) with SSS ≥ 4 , stenosis (-) or SSS <4 with HRP, and stenosis (-) or SSS <4 without HRP, the event rate was 7.1% vs. 25.0% vs. 0% (log-rank $P<0.0001$). For stenosis (+) with SDS >0 , stenosis (-) or SDS $=0$

with HRP, and stenosis (-) or SDS $=0$ without HRP, the event rate was 9.6% vs. 17.9% vs. 0.6% (log-rank $P<0.0001$). **Figure 3** shows a representative case of non-fatal MI after CTA and MPI. There was no significant stenosis on CTA (**Figures 3A,B**) or abnormal MPI findings. The lesion with LAP and PR at right coronary artery, however, resulted in ACS at 20 months, and a stent was implanted (**Figures 3C,D**).

Discussion

The present study has shown that HRP on CTA had increased prognostic value over stenosis on CTA or MPI findings. HRP was an independent predictor of acute event.

MPI is a well-established tool for risk stratification in patients with CAD as well as for detection of ischemia.¹¹⁻¹⁶ The absence of inducible ischemia at MPI identifies subjects with very low ($<1\%$ per year) event rate during the following 1 year. In contrast, because CTA has been proposed as a useful tool to evaluate coronary artery stenosis, the comparison of stenosis on CTA and induced ischemia on MPI have been reported in several studies.¹⁹⁻²⁴ For risk stratification by CT, evaluation of prognosis for CAD has been studied using calcium scoring on plane CT. Budoff et al reported that calcium score is an independent predictor of cardiac death, and higher calcium score is associated with worse prognosis.²⁵ There are also some reports about prognosis with CTA findings recently.²⁶⁻³¹ Min et al showed that the severity of coronary artery stenosis and

Figure 2. Kaplan-Meier curve for cardiac event based on high-risk plaque (HRP). Each stenosis (-) or normal myocardial imaging patient group was divided into 2 groups based on HRP, and the event rate was then compared between 3 groups. HRP on computed tomography angiography had increased prognostic value over (A) summed stress score (SSS), (B) summed difference score (SDS), (C) stenosis, (D) stenosis and SSS, and (E) stenosis and SDS.

Figure 3. Patient who developed acute coronary syndrome after computed tomography angiography (CTA) and myocardial perfusion imaging (MPI). (A,C) Curved MPR of right coronary artery on CTA. (B,D) Right coronary artery on coronary angiography. (A,B) Lesion with positive remodeling and low-attenuation plaque at right coronary artery without luminal stenosis. MPI was normal. (C,D) This lesion resulted in non-fatal myocardial infarction 20 months after CTA and MPI, and a stent was implanted.

their vessel numbers were associated with cardiac event rate or cardiac death.²⁶ Lin et al reported that in patients without prior documented CAD and without obstructive CAD on CTA, mortality risk was higher in patients with non-obstructive plaque than in no-plaque patients.³⁰ A meta-analysis of 18 studies evaluating 9,592 patients reported that the risk of adverse cardiac event was associated with the extent and severity of underlying CAD.³¹ A recent study by van Werkhoven et al reported the increased prognostic value of CT over MPI.³² That study followed 541 patients at intermediate risk for CAD undergoing both CTA and MPI. Luminal stenosis on CTA was detected in 31% of patients and abnormal MPI (SSS ≥ 4) in 33%. After exclusion of 43 patients (8.3%) who underwent early revascularization, an event occurred in 23 patients (5.2%). The annual event rate in patients with normal and abnormal MPI was 1.5% vs. 6.0%, and in patients with none or mild stenosis and a significant stenosis it was 3.0% vs. 6.3%. They concluded that both stenosis on CTA and abnormal MPI (SSS ≥ 4) were independent predictors of events, and the combined use of the 2 modalities significantly enhanced the prediction of major adverse cardiac events.

CTA has the potential to detect not only luminal stenosis but also HRP. In our previous study, 10,688 segments in 1,059 patients were followed for a mean of 27 months.⁹ Of 72 segments with HRP (LAP and/or PR), 11 (15%) resulted in ACS within 2 years. We concluded that HRP was an independent predictor of ACS. In most cases, ACS occurred at the lesions without significant luminal stenosis on previous coronary angiography or CTA. In these cases, it might be difficult to see abnormalities on MPI. Medication for HRP has not been well-established as yet. We previously reported that statin reduced necrotic core volume evaluated on serial CTA.³³ High incident ratio of ACS at HRP might support the "plaque-sealing theory", with percutaneous coronary intervention for lesions without significant stenosis and/or ischemia. Invasive intervention for the coronary artery, however, is not recommended at this point. Optimal invasive and non-invasive therapy for HRP to prevent ACS should be considered. In the present study, HRP on CTA was an independent predictor of acute coronary event, as was stenosis (+) and SDS > 0 , and HRP had increased prognostic value over stenosis and abnormal MPI findings. Although it has been reported that normal MPI identifies subjects with a very low event rate, the present study has demonstrated that HRP is useful to predict ACS even in patients with normal MPI.

Study Limitations

First, this single center study included a small number of patients. The event rate was also low ($n=11$). A large multicenter trial is needed. Second, the indication of CTA is limited in patients with chronic kidney disease, difficulty in breath-holding, or arrhythmia. Only MPI should be performed in these cases.

The radiation dose in CTA and MPI is not negligible, but dose reduction in CTA is ongoing. MPI could also be displaced by new techniques such as MPI by CTA^{34,35} to reduce the radiation dose. Third, information on medical intervention was not provided. Use of anti-ischemic or lipidemic agent after CT is important for the inhibition of future cardiac events, but this information was not documented in all patients. Fourth, we used non-gated 201Tl SPECT for the assessment of MPI. The diagnostic accuracy of SPECT to detect ischemia has been reported as a sensitivity of 80–90% and specificity of 70–95% for non-gated SPECT. It has been reported that the diagnostic accuracy of gated SPECT is higher than that of non-gated

SPECT. It is possible that there was underestimation of abnormal findings on non-gated SPECT. Finally, this was a retrospective study. The diagnostic tool for CAD was selected independently by each physician. Some patients underwent only CTA or MPI, and these patients were not included in this study. For more precise investigation, a prospective study is needed.

Conclusions

HRP on CTA is an independent predictor of acute coronary event, as is stenosis (+) and SDS > 0 , and HRP has increased prognostic value over stenosis and abnormal MPI findings. Although it has been reported that normal MPI identifies subjects with very low risk of cardiac event, the present paper has demonstrated that HRP is useful to predict ACS even in patients with normal MPI.

Disclosures

There is no conflict of interest.

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