Association of Target Lesion Characteristics Evaluated by Coronary Computed Tomography Angiography and Plaque Debris Distal Embolization During Percutaneous Coronary Intervention

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Background: The slow-flow or no re-flow phenomenon has been associated with distal embolization, especially of plaque debris, and with unfavorable clinical outcomes. Therefore, we examined the association between the coronary computed tomography angiography (CCTA) findings of the target lesion and distal embolization during percutaneous coronary intervention (PCI).

Methods and Results: Consecutive patients (n=55: 18 unstable angina, 19 stable effort angina, 18 silent ischemia) who underwent PCI with a filter-type distal protection device after evaluation of the target lesion by CCTA were analyzed. CCTA examined low-attenuation plaque (LAP), positive remodeling (PR), and ring-like enhancement of the target lesion. Distal embolization of thrombus and plaque debris was evaluated by pathological examination of material collected in the filter. Any distal embolization and distal embolization of plaque debris were respectively detected in 75% and 0% of patients with LAP or PR alone, in 95% and 17% of patients with both LAP and PR, and in 100% and 27% of patients with all of LAP, PR and ring-like enhancement. The sensitivity and specificity to predict plaque debris embolization by having both findings of LAP and PR was 100% and 46%, respectively.

Conclusions: The CCTA findings of the target lesion were associated with distal embolization and were very sensitive for predicting plaque debris embolization. (*Circ J* 2014; **78**: 2203–2208)

Key Words: Coronary computed tomography angiography; Distal embolization; Plaque debris; Thrombus

It has been reported that the no-/slow-flow phenomenon occurs in 0.5–1% of cases of elective percutaneous coronary intervention (PCI),¹ which is extremely deleterious to the result of PCI. Although distal embolization is the supposed cause,^{2–4} the usefulness of distal protection devices has not been established.^{5,6} A major problem with clinical trials to show the usefulness of such devices is selection of high-risk patients. We have previously reported the beneficial effect of a device in a selected high-risk group of acute MI patients with ruptured plaque at the target lesion.⁷ Distal embolization of plaque debris was frequently demonstrated in those patients.

Coronary computed tomography angiography (CCTA) can evaluate the characteristics of coronary plaques.^{8,9} Low-attenuation plaque (LAP), positive remodeling (PR) and ring-like enhancement have been reported as the CCTA findings associ-

ated with future coronary events.^{10,11} We have previously reported that these CCTA findings are associated with the presence of yellow plaque or ruptured plaque on angiography.¹²

In the present study, we examined the association between CCTA findings and distal embolization when using a filter-type distal protection device.

Methods

Study Patients

We analyzed 55 consecutive patients who underwent CCTA within 2 weeks before PCI using distal protection device between March 2010 and August 2012, excluding 3 patients without adequate CCTA images because of heavy calcification. The association between the CCTA findings of the PCI

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Table 1. Characteristics of the Patients Who Underwent CCTA and PCI

n	55
Male sex, n (%)	47 (85)
Age, years	61.4±7.0
Risk factors, n (%)	
Diabetes mellitus	19 (35)
Hypertension	46 (84)
Dyslipidemia	46 (84)
Current smoking	13 (24)
Body mass index	25.3±3.9
Lipid profile, mg/dl	
Total cholesterol	181±32
LDL-cholesterol	102±25
HDL-cholesterol	48±12
Triglycerides	159±112
Hemoglobin A1c, %	6.0±1.4
Diagnosis, n (%)	
Unstable angina	18 (33)
Stable effort angina	19 (35)
Silent myocardial ischemia	18 (33)
Medications, n (%)	
Statin	32 (58)
Aspirin	49 (89)
Clopidogrel/ticlopidine	40 (73)
ARB/ACEI	24 (44)
β-blocker	15 (27)
Ca-blocker	24 (44)

Continuous data are presented as mean±SD.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCTA, coronary computed tomography angiography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention.

target lesion and pathologically examined distal embolization was analyzed. Written informed consent was given by all the patients and the protocol was approved by the Osaka Police Hospital Ethics Committee.

CCTA Examination and Evaluation

CCTA was performed with a 64-detector row CT scanner (Light speed VCT, GE Healthcare Japan, Tokyo, Japan). All patients with a heart rate >60 beats/min were given metoprolol 20 mg orally 2 h before CT scan. At the time of examination, patients with heart rates >70 beats/min were given 2 mg of intravenous propranolol. All patients received 0.3 mg nitroglycerin sublingually immediately before scanning. CCTA data were acquired using X-ray beam collimation (width 0.625×64 mm, gantry rotation time 0.35 s, tube voltage 100–120 mV, effective tube current 280–750 mA using ECG modulation) and the pitch ranged from 0.18 to 0.26 depending on the patient's heart rate. The estimated mean radiation dose was 15–18 mSv.

A non-contrast scan was initially performed to determine the anatomic landmarks for the contrast-enhanced study. Immediately thereafter, test bolus tracking with 15 ml of non-ionic contrast agent was performed to calculate the exact arrival time of contrast agent in the coronary arteries, with the region of interest in the proximal part of the ascending aorta. Finally, a contrast-enhanced scan with retrospective ECG gating was performed after administration of contrast medium (0.8 ml·kg body weight⁻¹·12s⁻¹) during a single breath hold. Image reconstruction

Table 2. Lesion and Procedural Characteristics of the Patients Who Underwent CCTA and PCI

No. of lesions	55
Target vessel, n (%)	
Left anterior descending coronary artery	22 (40)
Left circumflex coronary artery	9 (16)
Right coronary artery	24 (44)
Angiographic findings	
AHA/ACC classification, A/B1/B2/C	17/20/15/3
Diameter stenosis, %	67.8±15.6
Reference diameter, mm	3.2±0.7
Lesion length, mm	22.5±10.2
IVUS findings	
Minimum lumen area, mm ²	2.8±0.5
Maximum plaque area, mm ²	14.1±4.3
CT findings	
Low-attenuation plaque, n (%)	34 (62)
Positive remodeling, n (%)	35 (64)
Ring-like enhancement, n (%)	20 (36)
Procedural data	
No. of aspiration thrombectomies	0.3±0.8
Stent diameter, mm	3.2±0.4
Total stent length, mm	27.6±16.4
Maximum inflation pressure, atm	17.2±3.5

Continuous data are presented as mean±SD.

IVUS, intravascular ultrasound. Other abbreviations as in Table 1.

tion was performed with image-analysis software (CardIQ, GE Healthcare Japan) on a dedicated computer workstation (Advantage Workstation Ver. 4.2, GE Healthcare Japan). A standard kernel was used as the reconstruction filter. Depending on heart rate, either a half-scan or multi-segment reconstruction algorithm was selected or the optimal cardiac phase with the least motion artifacts was chosen individually.

Coronary arterial remodeling was evaluated by cross-sectional images. The remodeling index was calculated as the ratio of outer vessel diameter at the plaque site to the mean diameter of proximal and distal reference sites. PR was defined as remodeling index >1.05.¹³ The CT attenuation value of a plaque was measured at 5 points and averaged. LAP was defined as a CT attenuation value <40 HU.¹⁴ Ring-like enhancement was defined as previously reported.¹⁵ Briefly, it is the presence of a ring with high attenuation around certain plaque with an attenuation value higher than that of adjacent plaque but no greater than 130 HU to exclude calcium deposition.

Catheterization and PCI

Catheterization was performed by femoral, brachial, or radial artery approach using 6 or 7Fr sheath and catheters. Coronary angiogram was recorded by the Innova Cardiovascular imaging system (GE Healthcare Japan). Intravascular ultrasound (IVUS) is routinely used as a guide for all PCI procedures in our hospital. Distal protection was performed in all enrolled patients with a filter-type distal protection device Filtrap (Lifeline, Tokyo, Japan) during the PCI procedure. Filtrap is a single-use steerable 0.014" fixed-wire equipped with a filter basket. During the PCI procedure, plaque debris and thrombus are collected by the filter basket, while blood flows freely through the porous membrane of the filter. At the end of procedure, the filter retaining the embolic material is removed from the target vessel and processed for pathologic examination. Device suc-

Figure 1. Representative case of a 68-year-old male patient with unstable angina. Coronary computed tomography angiography (CCTA) detected a significant stenosis in the proximal left anterior descending coronary artery with a plaque that had low attenuation (CT value=24 HU; the sites of CT value measurement are shown by yellow circles), positive remodeling, and ring-like enhancement (**A**). Percutaneous coronary intervention (PCI) of the stenotic lesion (**B**, red arrow) was performed with a filter-type distal protection device (**B**, yellow circle). Plaque debris was macroscopically detected in the filter of the distal protection device after PCI (**C**). Pathologically, the debris contains platelet and fibrinous clot, foamy cells, and cholesterol crystals (**D**).

Figure 2. Frequency of distal embolization at the site of various coronary computed tomography angiography (CCTA) findings. Distal embolization of plaque debris was detected only when the target lesion had both findings of low-attenuation plaque (LAP) and positive remodeling (PR). The sensitivity and specificity to predict plaque debris embolization by having both findings was 100% and 46%, respectively. The sensitivity and specificity to predict plaque debris embolization by having all 3 findings of LAP, PR, and ring-like enhancement was 57% and 77%, respectively.

cess was defined as successful deployment and retrieval of Filtrap without angiographic complications such as dissection and vasospasm. The no-/slow-flow phenomenon was defined as the apparent reduction of coronary flow speed observed on angiography (ie, TIMI flow grade <3) at the end of the PCI procedure after removal of the distal protection device. Filter no-/slow-flow was defined as the no-/slow-flow phenomenon before removal of the distal protection device.

Pathologic Examination and Evaluation

The tip of the Filtrap device (filter) was cut and processed for pathologic examination. The collected material was gently removed from the filter and processed for histological examination. It was stained with hematoxylin-eosin, Masson trichrome, and elastica van Gieson. Two expert pathologists blinded to the patients' characteristics analyzed the specimens independently, and in case of disagreement, they discussed until they reached consensus. The specimens were analyzed for the presence of thrombus and plaque debris. Thrombus was detected by the presence of fibrin or platelets. Plaque debris was detected by the presence of atherosclerotic plaque tissue (extracellular matrix, necrotic gruel, fibrous fragments, foam cells, cholesterol crystals, or calcium deposits). Distal embolization in the present study was defined as the presence of captured material (thrombus or plaque debris) in the filter device.

Statistical Analysis

Continuous data are presented as mean $\pm$ SD. Comparisons between groups were done by unpaired Student's t-test, the chi-square test, or Kruskal-Wallis test. $P < 0.05$ was regarded as statistically significant. Analysis was done with SPSS version 16.0J for Windows (SPSS Inc, Chicago, IL, USA).

Results

Study Patients

Positioning of the Filtrap was attempted in 55 patients and device success was attained in all of them. Although filter no-/slow-flow was detected in 11 (20%) patients, the no-/slow-flow phenomenon after filter removal was not detected in any patient. Patients' characteristics are presented in Table 1 and lesion and procedural characteristics are presented in Table 2. A representative case is presented in Figure 1.

CCTA and Pathologic Findings

Distal embolization was detected in 42 (76%) patients. Thrombus embolization was detected in 35 (64%) patients and plaque debris embolization was detected in 7 (13%) patients. The incidence of distal embolization (thrombus or plaque debris) in the patients with each combination of CCTA findings (LAP, PR, and/or ring-like enhancement) is presented in Figure 2. Distal embolization of plaque debris was detected only when the target lesion had both findings of LAP and PR. The sensitivity and specificity to predict plaque debris embolization by having both findings of LAP and PR was 100% and 46%, respectively. The sensitivity and specificity to predict plaque debris embolization by having all 3 findings of LAP, PR, and ring-like enhancement was 57% and 77%, respectively.

The minimum lumen area (2.8 ± 0.5 , 2.9 ± 0.6 , 2.8 ± 0.5 , 2.7 ± 0.5 mm²) and maximum plaque area (14.1 ± 4.3 , 9.6 ± 1.7 , 13.9 ± 5.4 , 14.3 ± 4.4 mm²) measured by IVUS were not different among the patients with each combination of CCTA findings (none, LAP or PR, both LAP and PR, and all of LAP, PR, and ring-like enhancement).

Although the serum troponin T level on next day after PCI was not different among the patients with each combination of CCTA findings, the incidence of filter no-/slow-flow was higher in the patients with more CCTA findings (Table 3). Among non-ACS patients, filter no-/slow-flow was more frequently detected in the patients with plaque debris embolization than in those without (83% vs. 10%, $P = 0.004$).

Discussion

According to the results of the present study, distal embolization of plaque debris was detected in 17% of patients who had both of LAP and PR and in 27% of patients who had all of LAP, PR and ring-like enhancement signs on CCTA. Remarkably, distal embolization of plaque debris was detected only when

Table 3. Incidence of Filter No-/Slow-Flow and the Serum Troponin T Level in Patients With Each Combination of CCTA Findings

	None	LAP/PR	LAP+PR	LAP+PR+Ring
No. of lesions	14	8	18	15
Incidence of filter no-/slow-flow, n (%)	0 (0)	1 (13)	5 (28)	5 (33)*
Serum troponin T level,† ng/ml	0.08 $\pm$ 0.09	0.29 $\pm$ 0.64	0.06 $\pm$ 0.11	0.15 $\pm$ 0.23

* $P = 0.02$ vs. none. Continuous data are presented as mean $\pm$ SD.†Measured on the day after PCI.

CCTA, coronary computed tomography angiography; LAP, low-attenuation plaque; PR, positive remodeling; Ring, ring-like enhancement.

the target lesion had both findings of LAP and PR.

Factors Associated With Embolization

According to previous reports, distal micro-embolization occurs in 0–70%,¹⁶ and the no-/slow-flow phenomenon in 0.5–1% of PCI cases.¹⁷ As we have previously reported,¹⁸ the no-/slow-flow phenomenon occurs more frequently in patients with ruptured plaque at the target lesion of PCI than in patients without it; and distal embolization of plaque debris is detected more frequently in those patients. Therefore, embolization of plaque debris may be an important cause of the no-/slow-flow phenomenon, which has been associated with deterioration of left ventricular function and worsening of clinical outcome. In the present study, the presence of LAP, PR and ring-like enhancement was demonstrated as predictive of plaque debris embolization. These CCTA findings were significantly associated with the presence of ruptured plaque, as we previously reported.¹² In both that report and the present study, the incidence of ruptured plaque and that of plaque debris embolization was 25% and 17%, respectively, in patients who had both LAP and PR, and in 60% and 27%, respectively, of patients with all 3 findings of LAP, PR and ring-like enhancement. This is consistent with our previous finding that plaque debris embolization and the no-/slow-flow phenomenon occurs more frequently in patients with ruptured plaque.^{7,18}

There are some previous reports on the frequency of thrombus or plaque debris embolization. Embolization of thrombus was pathologically detected with a distal protection device in 95% of acute MI patients,⁷ in 79% of unstable angina patients,¹⁹ and in 70% of stable angina patients.¹⁹ The embolization of plaque debris was pathologically detected with a distal protection device in 69% of acute MI patients,⁷ in 73% of ST-elevation MI patients,²⁰ in 21% of unstable angina patients,¹⁹ and in 30% of stable angina patients.¹⁹ The embolization of thrombus or plaque debris was detected in 100% of acute MI patients by high-intensity transient signals (HITS) using Doppler guide wire.¹ These previously reported results are consistent with the results of the present study.

The clinical outcome of distal embolization could not be evaluated in the present study, because the distal protection device should have prevented real embolization into microvessels. Indeed, peri-procedural MI, as shown by the serum troponin T levels on the day after PCI not being different among the patients with each combination of CCTA findings. However, the incidence of filter no-/slow-flow was significantly associated with the CCTA findings. Furthermore, our findings were consistent with a recent report in which LAP and PR were detected more often in the patients who suffered no-/slow-flow than in those who did not.²¹ Therefore, these very simple markers (LAP and PR) could be important for evaluating the risk of the no-/slow-flow phenomenon during PCI, which can be performed less invasively by magnetic resonance imaging,²² and might be prevented by a distal protection device or more simply by laser angioplasty.²³ These issues are expected to be investigated in the near future.

Study Limitations

Our study population was limited to those who underwent both CCTA and PCI and thus a selection bias might be possible. Some of the thrombus detected in the filter device might have been from-situ thrombus formation rather than embolized thrombus, which might have resulted in overestimation of the frequency of thrombus embolization; therefore, we focused more on plaque debris embolization. We did not measure plaque volume, which have influenced the results, because the accu-

racy of plaque volume measurement by CCTA is still uncertain. Because this study was not designed to evaluate IVUS findings, adequate IVUS images were not available for study patients examined by various IVUS systems from different manufacturers, but mainly by manual pullback. We have not demonstrated the effectiveness of distal protection devices to prevent the no-/slow-flow phenomenon, which must be demonstrated in future randomized controlled clinical trials.

Conclusions

CCTA findings were well associated with distal embolization. The presence of both findings of LAP and PR was highly sensitive for predicting plaque debris embolization.

Disclosures

None of the authors has any conflict to disclose.

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None.

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