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Association of nonculprit plaque characteristics with transient slow flow phenomenon during percutaneous coronary intervention

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ABSTRACT

Background: The slow flow (SF) phenomenon is more prevalent in patients with acute coronary syndrome (ACS), who frequently exhibit vulnerable plaques in remote coronary arteries. We aimed to clarify the impact of nonculprit plaque characteristics on the occurrence of SF using multidetector computed tomography (MDCT).
Methods: The study population comprised 180 consecutive patients with non-ST-segment elevation ACS (NSTE-ACS) who underwent MDCT before intervention. The characteristics of culprit and nonculprit lesions were compared between patients with and without SF.
Results: SF was observed in 43 (23.8%) of the 180 patients. The prevalence of positive remodeling (PR), low-attenuation plaque (LAP), and napkin-ring sign (NRS) in culprit lesion was significantly higher in the SF group than in the non-SF group (86.1% vs. 39.4%; $p < 0.001$, 81.4% vs. 18.3%; $p < 0.001$, and 65.1% vs. 16.1%; $p < 0.001$, respectively). The same result was observed for nonculprit lesions (58.1% vs. 14.6%; $p < 0.001$, 45.2% vs. 6.6%; $p < 0.001$, and 14.3% vs. 4.9%; $p < 0.04$, respectively). Multivariate analysis revealed LAP [odds ratio (OR), 12.8; 95% confidence interval (CI), 3.7–54.7; $p < 0.001$], and NRS (OR, 5.1; 95% CI, 1.3–25.3; $p = 0.03$) in culprit lesions and PR (OR, 4.7; 95% CI, 1.1–22.2; $p = 0.04$) in nonculprit lesions were independently associated with SF.
Conclusions: The plaque characteristics of nonculprit lesions are associated with the occurrence of SF during percutaneous coronary intervention. Assessment of plaque characteristics of both culprit and nonculprit lesions using MDCT may be useful for the prediction of SF.

The coronary slow-flow (SF) phenomenon or the no-reflow phenomenon has been observed during percutaneous coronary intervention (PCI) in 12%–45% of cases, and it was more frequent in patients with acute coronary syndrome (ACS) [1–4]. SF is associated with unfavorable clinical outcomes, prolonged hospital stay, and increased mortality [5,6].

Recent advances in multidetector computed tomography (MDCT) have enabled the noninvasive assessment of coronary artery stenosis and plaque characteristics [7,8]. Low-attenuation plaque (LAP) and napkin-ring sign (NRS) as assessed by preprocedural MDCT were reported to be associated with SF in patients with angina [9,10].

It has been reported that patients with ACS frequently have high risk atherosclerotic plaques in their remote coronary arteries, suggesting that atherosclerosis is a part of the pan-coronary process [11,12]. The instability of plaques reflects not only local vascular factors but also pan-vascular factors, which have the potential to destabilize atherosclerotic plaques in nonculprit lesions [13]. Increased inflammatory marker levels were reported in patients with SF; therefore, SF is passively caused by not only focal factors such as plaque characteristics, but also pan-vascular factors such as coronary artery inflammation [14,15]. We hypothesized that pan-vascular factors associated with SF may have some influence on the plaque characteristics of nonculprit lesions.

MDCT enables the assessment of not only culprit lesions but also entire coronary trees. However, the relationship between the plaque characteristics of nonculprit lesions as assessed by MDCT and SF remains unclear. This study was designed to investigate the association between the plaque characteristics of nonculprit lesions and the occurrence of SF during PCI in patients with non-ST-elevation ACS (NSTE-ACS).

1. Methods

1.1. Study population

This retrospective, single-center study included 378 patients with NSTE-ACS who underwent PCI between April 2010 and April 2013.

Of these, MDCT was performed in 229 of these patients. MDCT is routinely used in our daily practice to assess the plaque characteristics of culprit lesions before PCI in patients with coronary artery disease (CAD) and a symptom of angina or positive stress test results. MDCT is also performed in the emergency room as a part of triple-rule-out CT to evaluate

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the coronary arteries, aorta, pulmonary arteries, and adjacent intrathoracic structures in the patients with acute chest pain.

Exclusion criteria for MDCT included cardiac arrhythmias (i.e. atrial fibrillation or frequent paroxysmal premature beats), contraindications for iodinated contrast medium, poor renal function (serum creatinine > 1.5 mg/dl), unstable hemodynamic conditions and on-going ischemic symptom.

NSTE-ACS was defined as an unstable pattern of chest pain and included rest angina, new-onset severe angina, or angina of increasing intensity, duration, and/or frequency without ST-segment elevation on electrocardiography (ECG) [16].

MDCT was performed in 229 of these patients. After undergoing MDCT, 29 patients were excluded because of heavily calcified lesions (n = 7), in-stent restenosis/lesions adjacent to a stent (n = 18), and ostial lesion/bifurcation lesions for which remodeling index could not be calculated (n = 4). Twenty patients were excluded at the time of PCI because of the absence of normal flow [thrombolysis in myocardial infarction (TIMI) flow grade 3] noted before the intervention, which meant that SF could not be assessed accurately [17].

The final study population is comprised of 180 patients (141 men; mean age, 70 ± 10 years) with NSTE-ACS who underwent MDCT before PCI (Fig. 1).

This study was approved by our hospital's ethical committee, and written informed consent was obtained from all patients.

1.2. MDCT scanning and imaging protocol

MDCT was performed using a 128-slice dual source detector CT (SOMATOM Definition Flash Dual Source 128-slice scan, Siemens, Forchheim, Germany). All patients received sublingual nitroglycerin (0.3 mg) just before scanning. Patients with a heart rate of >100 beats/min received intravenous landiolol (0.125 mg/kg). For the contrast-enhanced scanning, a 0.7 ml/kg bolus of contrast medium (Iopamidol, 370 mg I/ml, Bayer Healthcare, Berlin, Germany) was intravenously injected at a flow rate of 0.07 ml/kg/s followed by a 50 ml injection of saline at the same flow rate. We acquired contrast-enhanced data during an inspiratory breath hold. The volume data set was acquired in helical mode (128 × 0.6 mm collimation; rotation time, 280 ms; tube voltage, 120 kV). The estimated radiation dose ranged from 1 to 10 mSv.

1.2.1. Image analysis of coronary arteries using MDCT

Image reconstruction was performed using image-analysis software on a dedicated computer workstation (Virtual Place Raijin plus, AZE, Tokyo, Japan). Analysis of MDCT image data was performed by two experienced readers. According to the recommendations of the American Heart Association (AHA), coronary arteries were divided using the 17 segment modified AHA classification [18]. In each segment, a coronary atherosclerotic plaque was defined as tissue structures of >1 mm^2 located either within or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue [19]. Each plaque was separated by at least 5 mm from the edge of any other plaque or stent edge.

Plaques were classified as non-calcified plaques (plaques having lower density compared with the contrast-enhanced vessel lumen without any calcification), calcified plaques (plaques with high density) or mixed plaques (plaques with non-calcified and calcified elements within a single plaque) [20]. The cross sectional areas (CSA) of the external elastic membrane (EEM), the plaque + media (P + M) and the lumen were measured using the axial images. The remodeling index (RI) was defined as the EEM CSA of the target lesion divided by the average of the EEM CSAs of the proximal and distal references. Positive remodeling (PR) was defined as a RI > 1.1 [21]. The P + M CSAs were calculated as a difference between EEM CSA and lumen CSA. The CT attenuation value of a plaque was measured at five points and the lowest values at three points were averaged. LAP was defined as a plaque with a CT attenuation value of <30 Hounsfield units (HU) [20,22].

NRS was defined as the presence of low CT attenuation in the center of the plaque close to the lumen surrounded by a rim area of higher attenuation [23]. Representative cases of PR, LAP, and NRS are shown in Fig. 2.

In the cases of discordance between the investigators, a consensus reading was obtained from a third independent investigator.

1.2.2. Interventional protocol

All the patients were pretreated with aspirin (100 mg) and clopidogrel (75 mg) before intervention. Intravenous boluses of unfractionated heparin were administered to maintain an activated clotting time of >250 s during PCI. Coronary angiography was performed using standard techniques. Vessel narrowing was measured using quantitative coronary angiography analysis. Obstructive stenosis was defined as luminal diameter narrowing of >50% in comparison with the reference vessel diameter. A single obstructive coronary stenosis was identified as the culprit lesion, and nonculprit lesions were defined as untreated lesions with >50% diameter stenosis. Culprit and nonculprit lesions were identified on the basis of electrocardiographic changes, and angiographic analyses [24].

Lesions were classified according to the modified ACC/AHA grading system as type A, B1, B2, or C [25]. The interventional procedure was performed using a femoral or radial approach with a 6- or 7-F guiding catheter. Direct stenting was performed in most patients, and pre- and post-dilatation were performed according to the operator's discretion. The lesion length and reference vessel diameter were measured using quantitative coronary angiography. The stent diameter and balloon inflation pressure were recorded.

1.2.3. Definition of SF

SF was defined as coronary flow with TIMI flow grade 0–2 with ST-segment elevation on the ECG during the procedure, except for dissection, spasm, thrombus, or residual stenosis [8,26,27]. TIMI flow grade was assessed by two experienced cardiologists.

1.3. Clinical end points

The clinical end points of this study were major adverse cardiac events (MACE) at 90 days, defined as death, myocardial infarction (MI), or the need for repeat revascularization.

1.3.1. Statistical analysis

Results were presented as mean ± SD and median (25th to 75th percentiles). Univariate analysis was performed using the Student's *t*-test. Categorical data were compared against a chi-square distribution. Clinical variables were entered into a multivariate logistic regression model of SF to test their independent effects. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to assess the predictive value. A p-value of <0.05 was considered statistically significant.

To determine interobserver and intraobserver variability of plaque characteristics and SF, 50 random segments and 50 random coronary angiographies were analyzed by two independent readers and the same observer at two different time points. Interobserver and intraobserver variability of MDCT analyses were evaluated using Cohen κ statistics.

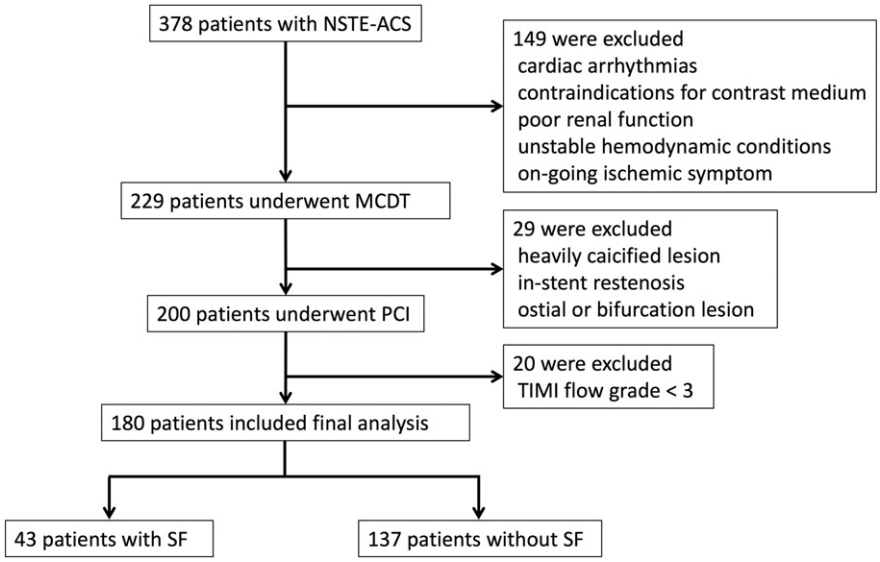

Fig. 1. Flow chart of patient selection. NSTE-ACS, Non-ST elevation acute coronary syndrome; TIMI, Thrombolysis In Myocardial Infarction.