Impaired Flow-Mediated Dilation and Severity and Vulnerability of Culprit Plaque in Patients with Coronary Artery Disease

Teruyoshi Nemoto, MD, Yoshiyasu Minami, MD, Minako Yamaoka-Tojo, MD, Toshimitsu Sato, MD, Yusuke Muramatsu, MD, Ryota Kakizaki, MD, Kazuhiro Fujiyoshi, MD, Takuya Hashimoto, MD, Kentaro Meguro, MD, Takao Shimohama, MD, Taiki Tojo, MD and Junya Ako, MD

Summary

The association between endothelial function, evaluated using flow-mediated dilatation (FMD), and the severity of coronary artery disease remains to be elucidated.

A total of 245 consecutive patients with stable angina were prospectively enrolled. FMD was evaluated in the brachial artery before percutaneous coronary intervention. Patients were divided into 2 groups according to the FMD value (lower FMD group [FMD < 2.0], n = 82; higher FMD group [FMD ≥ 2.0], n = 163). The severity of coronary artery disease was evaluated using findings of angiography and optical coherence tomography, and compared between the 2 groups.

The prevalence of left main (LM) disease was significantly higher in the lower FMD group than in the higher FMD group (8.5% versus 2.5%, P = 0.046), although the prevalence of multivessel disease was comparable between the groups. Lower FMD was independently associated with a higher prevalence of LM disease (odds ratio, 3.89; 95% confidence interval, 1.12-15.5; P = 0.033). A general linear model with multiple variables revealed that the minimal lumen area (MLA) in the culprit lesion was significantly smaller in patients with lower FMD than in those with higher FMD (regression coefficient b, −0.249 mm²; 95% confidence interval, −0.479−0.018 mm²; P = 0.035). The prevalence of vulnerable plaque characteristics was comparable between the 2 groups.

Patients with lower FMD had a higher incidence of LM disease and a smaller MLA in the culprit lesion. FMD may be a useful, noninvasive indicator for identifying patients with severe coronary artery disease.

Key words: Endothelial dysfunction, Optical coherence tomography, Vulnerable plaque

Endothelial dysfunction is an initial physiologic event in atherogenesis, and is systematically affected by common risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking. Ultrasound assessment of flow-mediated dilatation (FMD) of the brachial artery is a sensitive and noninvasive method of quantifying endothelium-dependent vasomotion, which reflects systemic endothelial function. FMD in brachial arteries is known as a predictor of adverse cardiovascular events and is considered to reflect coronary endothelial dysfunction. Thus, FMD evaluation is used for the risk stratification of patients with risk factors in daily clinical practice.

In addition to the association between FMD and future risks of cardiac events, several previous studies have suggested an association between FMD and the severity of coronary artery disease. Kaku et al. reported the inverse correlation between FMD of the brachial artery and the number of diseased vessels. Moreover, a recent study using intravascular ultrasound reported the association between a lower FMD value and a larger necrotic core in coronary plaque. Thus, FMD evaluation might become a useful, noninvasive method of determining the disease severity and plaque vulnerability in patients with coronary artery disease. However, to date, the association between FMD and disease severity according to the number of diseased vessels and plaque vulnerability according to the status of the necrotic core remains unclear. In the present study, we aimed to clarify in detail 1) the association between FMD and the severity of coronary lesion, as well as 2) the association between FMD and plaque vulnerability assessed using optical coherence tomography (OCT).
Methods

Study population: This was a prospective, observational study conducted between October 2016 and December 2017 at a single center. From a total of 280 consecutive patients who underwent percutaneous coronary intervention (PCI) for stable angina, we included 245 patients who underwent assessment of endothelial function based on FMD (Figure 1). Among them, we identified 82 patients with FMD < 2.0 (lower FMD group) and 163 patients with FMD ≥ 2.0 (higher FMD group). The FMD cutoff value of 2.0 was demonstrated to be a prognostic factor for the incidence of cardiovascular events in patients with advanced atherosclerosis.9) The study protocol was approved by the Human Research Committee of Kitasato University School of Medicine, and all patients provided written informed consent before the procedure.

Assessment of endothelial function based on FMD: Endothelial function was evaluated using high-resolution ultrasound with a 10-MHz linear array transducer probe (UNEX EF; Unex Co. Ltd., Nagoya, Japan) before PCI as previously described.10,11) The patients were instructed to fast for at least 4 hours before undergoing FMD assessment, and to abstain from smoking cigarettes and ingesting alcohol, caffeine, or antioxidant vitamins for at least 6 hours before the measurements. Before the evaluation, the patients were asked to rest for 30 minutes in the supine position in a quiet, dark, air-conditioned room (22°C-25°C).12) The FMD procedure was performed in the morning or evening (between 6 and 8 am or between 5 and 6 pm). A forearm cuff was then inflated for 5 minutes at 50 mmHg above the systolic blood pressure just before the FMD measurement. After cuff deflation, the diastolic diameter of the brachial artery was semiautomatically recorded continuously for 2 minutes by using an instrument equipped with software for monitoring the brachial artery diameter. The percentage change in FMD (%FMD) was then estimated as the percentage change in the vessel diameter over the baseline value at maximum dilatation during reactive hyperemia. All measurements were performed by an independent clinical psychologist who was blinded to the findings of coronary angiography and OCT.

Angiographic analysis: Coronary angiograms before balloononing or stent implantation were analyzed using quantitative coronary angiography with a computerized, edge-detection, quantitative, coronary angiographic analysis system (CASS System; Pie Medical Instruments, Maastricht, The Netherlands).

OCT image acquisition and assessment: In the present study, OCT imaging of the culprit lesion was performed in 164 patients. Among them, 156 patients were included in the OCT analysis after excluding 8 patients with poor image quality. OCT imaging was performed using a frequency domain OCT system (C7-XR OCT Intravascular Imaging System; St. Jude Medical, St. Paul, MN, USA) after the intracoronary administration of 100-200 μg nitroglycerin before balloon dilation or stenting. All images were analyzed using offline proprietary software (St. Jude Medical). Qualitative and quantitative analyses were performed at 1-mm intervals. The morphologies of all plaques on OCT were analyzed using previously established criteria.13,14) Fibrous cap thickness was measured at the thinnest part 3 times, and the average value was calculated. Thin-cap fibroatheroma (TCFA) was defined as a lipid plaque with lipid arc > 90° and fibrous cap thickness < 65 μm. The presence of bright spots within the fibrous cap with backward shadowing was considered indicative of macrophage accumulation.15) Microchannels were defined as small black holes or tubular structures of 50-100 μm diameter that were present within a plaque in at least 3 consecutive cross-sectional frames.15) Cholesterol crystals were defined as thin and linear regions of high light intensity without signal attenuation.16) Calcifications were defined as signal-poor or heterogeneous areas delimited by sharp borders. Calcified lesions subtending an arc < 90° and extending in length for 1-4 mm were classified as spotty calcium.17) Thrombus was defined as a mass > 250 μm attached to the luminal surface or floating within the lumen.14,16) Definitions: Diseased vessels were identified on the basis of the presence of significant stenosis (≥ 75% diameter stenosis) on angiograms or a history of stenting. Hyper-tension was defined as arterial blood pressure > 140/90 mmHg or use of antihypertensive medication. Dyslipidemia was defined as high-density lipoprotein cholesterol < 40 mg/dL, low-density lipoprotein cholesterol > 140 mg/dL, or triglycerides > 150 mg/dL, or use of dyslipidemia medication. Diabetes mellitus was defined as symptoms of diabetes plus usual plasma glucose concentration > 200 mg/dL, fasting plasma glucose concentration > 126 mg/dL, 2-hour plasma glucose concentration > 200 mg/dL during a 75-g oral glucose tolerance test, or use of diabe-tes medication. Smoking was defined as current or past smoking habit.

Statistical analysis: Continuous variables with a normal distribution are expressed as mean ± standard deviation, whereas the median value with interquartile range is reported when data were not normally distributed. Continuous variables were analyzed using t test or Mann-Whitney U test. Categorical outcome data were summarized as
counts (percentages), and between group comparisons were performed using Fisher’s exact test or the chi-square test, as appropriate, depending on the expected frequency distribution under the null hypothesis. Multivariable logistic regression analysis was performed to determine the independent factor of left main (LM) disease. Clinical variables with $P < 0.10$ in univariate analysis were included in the multivariable model. A general linear model with multiple predictor variables was used to determine the independent factors of the minimal lumen area (MLA) in the culprit lesion. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using JMP 13.0 version (SAS Institute, Cary, NC, USA).

**Results**

**Clinical characteristics:** Among 245 patients, the lower FMD group (FMD < 2.0) and higher FMD group (FMD ≥ 2.0) included 82 patients and 163 patients, respectively. There was no significant difference in clinical characteristics other than the mean value of high-density lipoprotein cholesterol between the 2 groups (Table I).

**Angiographic and procedural findings:** Comparisons of angiographic and procedural findings between the 2 groups are shown in Table II. The prevalence of LM disease was significantly higher in the lower FMD group than in the higher FMD group (8.5 versus 2.5%, $P = 0.046$), although the prevalence of multivessel disease was comparable between the 2 groups. The values in quantitative coronary angiography were comparable between the 2 groups.

**Independent factors of LM disease:** The results of univariate and multivariate analyses for identifying the independent clinical factors of LM disease are shown in Table III. Lower FMD was independently associated with the presence of LM disease (odds ratio, 3.89; confidence interval, 1.12-15.5; $P = 0.033$).

**OCT analysis of culprit lesion:** Comparisons of the results of quantitative and qualitative OCT analyses of culprit lesions are shown in Table IV. The MLA was significantly smaller in the lower FMD group than in the higher FMD group (1.30 ± 0.44 versus 1.55 ± 0.72 mm², $P = 0.027$). The prevalence of vulnerable plaque characteristics including TCFA was comparable between the 2 groups (11.5 versus 12.5%, $P = 0.845$).

**Independent factors of MLA:** The results of the general linear model with multiple predictor variables for MLA are shown in Figure 2. The MLA in the culprit lesion was significantly smaller in patients with lower FMD than in those with higher FMD (regression coefficient b, −0.249 mm²; 95% confidence interval, −0.479−−0.018 mm²; $P = 0.035$).

**Discussion**

The main findings of this study are as follows: 1) Lower FMD was independently associated with the prevalence of LM disease. 2) Patients with a lower FMD had a smaller MLA in the culprit lesion than patients with a higher FMD. 3) No association was found between lower FMD and higher prevalence of vulnerable characteristics in the culprit lesion.
### Table II. Angiographic and Procedural Findings

|                               | Lower FMD (n = 82) | Higher FMD (n = 163) | P value |
|-------------------------------|--------------------|----------------------|---------|
| 1-Vessel disease, n (%)       | 28 (34)            | 46 (28)              | 0.094   |
| 2-Vessel disease, n (%)       | 28 (34)            | 79 (48)              |         |
| 3-Vessel disease, n (%)       | 26 (32)            | 38 (23)              |         |
| Type A/B1, n (%)              | 9 (11)             | 29 (18)              | 0.154   |
| Type B2/C, n (%)              | 73 (89)            | 134 (82)             |         |
| LM disease, n (%)             | 7 (8.5)            | 4 (2.5)              | 0.046   |
| CTO, n (%)                    | 10 (12)            | 26 (16)              | 0.427   |

Quantitative coronary angiography

|                               | Lower FMD | Higher FMD | P value |
|-------------------------------|-----------|------------|---------|
| Reference vessel diameter, mm | 2.67 ± 0.56 | 2.67 ± 0.51 | 0.879   |
| Minimum lumen diameter, mm    | 0.86 ± 0.42 | 0.87 ± 0.52 | 0.866   |
| Percent-diameter stenosis, %  | 67.4 ± 15.9 | 67.5 ± 18.1 | 0.970   |
| Lesion length, mm             | 28.6 ± 14.0 | 30.1 ± 15.2 | 0.487   |
| Stent diameter, mm            | 2.83 ± 0.42 | 2.90 ± 0.42  |         |
| Stent length, mm              | 38.8 ± 18.7 | 40.6 ± 21.6 | 0.522   |

CTO indicates chronic total occlusion; FMD, flow-mediated dilatation; and LM, left main trunk.

### Table III. Univariate and Multivariate Analyses for Left Main Disease

|                                 | Univariate analysis | Multivariate analysis |
|---------------------------------|---------------------|----------------------|
|                                 | Odds ratio | 95% CI | P value | Odds ratio | 95% CI | P value |
| Age                             | 1.03       | 0.974-1.10 | 0.317   |           |         |         |
| Male gender                     | 1.16       | 0.287-7.78 | 0.849   |           |         |         |
| Body mass index                 | 0.903      | 0.741-1.10 | 0.298   |           |         |         |
| Hypertension                    | 2.79       | 0.515-51.7 | 0.270   |           |         |         |
| Dyslipidemia                    | 0.603      | 0.176-2.37 | 0.444   |           |         |         |
| Diabetes mellitus               | 1.33       | 0.390-4.73 | 0.645   |           |         |         |
| CKD (eGFR < 60 mL: minute^-1:1.73 m^-2) | 0.792     | 0.223-2.70 | 0.706   |           |         |         |
| Smoking                         | 0.550      | 0.152-2.21 | 0.378   |           |         |         |
| Family history of IHD           | 1.39       | 0.292-5.18 | 0.649   |           |         |         |
| History of MI                   | 1.1        | 0.281-3.75 | 0.882   |           |         |         |
| History of PCI                  | 9.66       | 1.81-17.9  | 0.005   | 10.0       | 1.86-18.6 | 0.004 |
| Lower FMD                       | 3.71       | 1.05-13.1  | 0.037   | 3.89       | 1.12-15.5 | 0.033 |

CI indicates confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilatation; IHD, ischemic heart disease; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

### Table IV. OCT Analysis of the Culprit Lesion

|                                 | Lower FMD (n = 52) | Higher FMD (n = 104) | P value |
|---------------------------------|--------------------|----------------------|---------|
| Minimal lumen area, mm²         | 1.30 ± 0.44        | 1.55 ± 0.72          | 0.027   |
| Minimal lumen diameter, mm      | 1.26 ± 0.21        | 1.35 ± 0.31          | 0.059   |
| % Area stenosis, n (%)          | 74.4 ± 9.0         | 71.4 ± 10.6          | 0.090   |
| Lesion length, mm               | 34.7 ± 14.2        | 34.1 ± 14.1          | 0.813   |
| FCT, μm                         | 90.0 ± 42.4        | 100.0 ± 69.8         | 0.626   |
| Maximum lipid arc, °             |                     |                      |         |
| Lipid-rich plaque, n (%)        | 15 (29)            | 31 (30)              | 0.872   |
| TCFA (< 65 μm), n (%)           | 6 (12)             | 13 (13)              | 0.845   |
| Macrophage, n (%)               | 16 (31)            | 38 (37)              | 0.448   |
| Microchannel, n (%)             | 14 (27)            | 25 (24)              | 0.721   |
| Cholesterol crystals, n (%)     | 7 (13)             | 11 (11)              | 0.613   |
| Calcification, n (%)            | 45 (87)            | 87 (84)              | 0.730   |
| Spotty calcium, n (%)           | 41 (79)            | 81 (79)              | 0.977   |
| Thrombus, n (%)                 | 1 (1.9)            | 2 (1.9)              | 0.994   |

FCT indicates fibrous cap thickness; FMD, flow-mediated dilatation; OCT, optical coherence tomography; and TCFA, thin-cap fibroatheroma.
FMD and severity of coronary artery disease: Several previous studies have demonstrated the association between FMD and the number of diseased coronary arteries. In the present study, we further found an independent correlation between lower FMD and smaller MLA, assessed using OCT, in the culprit lesion. Although volumetric analysis of plaques was not performed owing to the limited penetration depth of OCT light, this could be explained by a simple hypothesis, as follows: severely impaired endothelial dysfunction caused greater progression of the culprit plaque, resulting in severe stenosis. Because OCT analysis showed a limited number of plaques with large lipid or TCFA, the majority of the plaque might consist of calcification and fibrous tissue. Another novel finding of the present study was the higher prevalence of LM disease in patients with lower FMD. Plaque progression in the LM trunk has been demonstrated to be highly affected by the complex flow dynamics and by local endothelial shear stress. Thus, severe endothelial dysfunction with the combination of focal physiologic factors might cause enhanced plaque progression resulting in the stenosis of the LM trunk in patients with lower FMD. These findings of smaller MLA and higher prevalence of LM disease may partly explain the worse clinical outcomes in patients with FMD < 2.0 shown in a previous clinical study. In contrast to previous studies, the prevalence of 2-vessel and 3-vessel disease was comparable between the lower FMD group and the higher FMD group in the present study. Although the exact reason for this discrepancy remains unclear, the cohort differences among studies might have played a role. Because we exclusively included patients with known coronary artery disease requiring PCI, the mean age (69 ± 11 years) was older than that in previous studies (58-64 years). In addition, the prevalence of 2-vessel and 3-vessel disease (44% and 26%, respectively) is greater than the reported prevalence in those studies (24-28% and 23-24%, respectively). Thus, the inclusion of an older population with advanced coronary artery disease might have diluted or confounded the correlation between FMD and the number of diseased vessels in the present study. Further studies are required to clarify the potential of FMD to differentiate the number of diseased vessels in this current aging population.

FMD and focal plaque vulnerability: In a study using spectral analyses of intravascular ultrasound radiofrequency data, the association of lower FMD and larger necrotic core with a higher prevalence of TCFA was demonstrated in both culprit and nonculprit plaques. The authors concluded that impaired endothelial function in brachial arteries might be associated with whole coronary plaque vulnerability and subsequent poor clinical outcomes in patients with coronary artery disease. In contrast, the prevalence of vulnerable characteristics, including TCFA and macrophage accumulation in the culprit lesion, assessed using OCT, was comparable between the lower FMD group and the higher FMD group in the present study. This means that the potential of FMD to assess focal vulnerability and active inflammation in culprit plaques may be limited, at least in the present type of cohort. There might be 2 potential reasons for the discrepancy in findings between the previous study and the present study other than the difference in imaging modality. First, the present study exclusively included patients with stable angina because we thought that FMD evaluation in patients with acute coronary syndrome is practically difficult owing to the emergent situation associated with multiple venous routes and arterial sheath insertion. Thus, the prevalence of vulnerable plaque characteristics in the present study was lower than that in the previous study (e.g., the prevalence of TCFA was 12% in the present study and 43% in the previous study). Second, multiple anti-inflammatory drugs, including statins, had already been prescribed for most patients in the present cohort. Because those drugs could immediately stabilize the vulnerable coronary plaque, the possible association between FMD and plaque vulnerability might have been confounded in the present study in contrast to a previous study showing a sharp relationship between these factors.

Clinical implication: Ultrasound assessment of FMD in the brachial arteries is a sensitive and noninvasive method
of evaluating endothelium-dependent vasomotion, which reflects systemic endothelial function. A recent meta-analysis has demonstrated that FMD has a prognostic potential in predicting future cardiac events and that the pooled relative ratio of cardiovascular events and all-cause mortality per 1% increase in brachial FMD was 0.90 (0.88-0.92) after adjusting for potential confounders. Thus, FMD evaluation is widely used for the risk stratification of patients with conventional risk factors of atherosclerosis in daily clinical practice. In addition to this prognostic utility of FMD for future cardiac events, several previous studies and the present study suggested the potential utility of FMD in identifying patients with severe coronary artery disease. In particular, the application of very low FMD as a cutoff could discriminate patients requiring prompt pharmacological intervention or revascularization.

**Limitations:** The present study has some limitations. First, we enrolled patients with known coronary artery disease undergoing PCI at a single center. Thus, the findings of the present study cannot be generalized. Second, patients with stable angina were exclusively enrolled in the present study because of the practical difficulty of enrolling patients with acute coronary syndrome. This could minimize the potential of FMD to identify subjects with vulnerable plaque, as we mentioned above. Further studies with different cohorts are needed to overcome this issue. Third, we applied FMD < 2.0 as the cutoff because we focused on patients with advanced atherosclerosis. Although previous studies have revealed the feasibility of this cutoff in identifying patients at risk, the use of a different cutoff may yield different results. Fourth, the clinical impact of the present findings was not investigated.

**Conclusions**

Patients with lower FMD had a higher incidence of LM disease and a smaller MLA in the culprit lesion. FMD may be a useful noninvasive indicator for identifying patients with severe coronary artery disease.

**Disclosure**

Conflicts of interest: None.

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