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Atherosclerosis

Impact of Transradial Catheterization on Vascular Function of the Brachial Artery Assessed by Flow-Mediated Dilatation

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Background: Few studies have evaluated long-term vascular function after radial access catheterization. Furthermore, the impact of repeated catheterization remains unknown. We investigated flow-mediated dilatation (FMD) of the brachial artery after transradial catheterization.

Methods: We prospectively enrolled 50 patients with suspected coronary artery disease referred for diagnostic coronary angiography. No ad-hoc percutaneous coronary interventions (PCI) had been performed at the time of the index procedure. In 30 patients (63.8%), PCI and/or repeated follow-up diagnostic catheterization were subsequently performed via the radial artery used at the index catheterization. FMD was successfully measured before catheterization, at 24 h after catheterization, and after long-term follow-up (mean, 32 months; range, 24-43) in 47 patients. FMD at follow-up was compared between patients receiving only one procedure and those receiving multiple procedures via the same arteries.

Results: FMD was significantly decreased after catheterization and recovered well in long-term follow-up (3.7 ± 1.6%, 3.0 ± 1.7%, and 3.9 ± 1.6%). There was no significant difference in follow-up FMD between the patients undergoing single catheterization and those with multiple procedures (3.4 ± 1.3 vs. 4.3 ± 1.7, p = 0.06). When the patients were divided into two groups according to the median follow-up FMD value, no significant predictive factor was identified for worse FMD.

Conclusions: After transradial catheterization, FMD of the brachial artery temporarily decreased but recovered in long-term follow-up. Recovery of FMD was not jeopardized by repeated catheterization, which suggests the potential of the brachial artery to recover endothelial function after repeated transradial procedures.

Key Words: Endothelial dysfunction • Flow mediated dilatation • Transradial cardiac catheterization

INTRODUCTION

Coronary artery disease (CAD) is one of the major causes of death in developed countries,[1] and cardiac catheterization, specifically coronary angiography (CAG), is the standard diagnostic test for CAD. Although the femoral artery remains the most common vascular access for percutaneous coronary interventions (PCIs), a transradial approach is increasingly being used given its relatively lower risk of bleeding complications for diagnostic CAG and recently even for PCIs.[2-4] However, inserting a catheter via the radial artery for cardiac catheterization can induce vascular injury and impairment of endothelial function in radial and brachial arteries.[5,6] Of note, in radial arteries, it has been reported that 7.7% of patients undergoing transradial catheterization experience

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radial artery occlusion within 24 h.[7] In terms of brachial arteries, which are in the upstream pathway of the radial artery, previous studies have reported that endothelial function is transiently impaired immediately after transradial catheterization, and then subsequently recovers.[6,8,9] Nevertheless, controversy exists regarding the recovery of endothelial function after CAG,[10,11] and the impact of repeated catheterization on the recovery of endothelial function in brachial arteries has not been elucidated. Flow-mediated dilatation (FMD) is a non-invasive test to evaluate the endothelial function of brachial arteries, which has high reproducibility and is widely accepted.[12-14] In the present study, we investigated the effect of repeated transradial catheterization on FMD of the ipsilateral brachial artery after long-term follow-up.

MATERIALS AND METHODS

Participants

We prospectively enrolled 50 consecutive patients with suspected coronary artery disease who were referred for elective diagnostic coronary angiography based on the following inclusion criteria: age > 20 years; sinus rhythm; and those who were scheduled for transradial cardiac catheterization via the right radial artery for the first time. The exclusion criteria were: acute coronary syndrome, refusal to participate, unavailable access via the right radial artery, history of trans-brachial catheterization, renal insufficiency, those who were scheduled for ad-hoc PCIs within the same catheterization, negative Allen's test, and loss of follow-up. Allen's test was performed before the procedure to confirm the patency of the radial and ulnar arteries and palmer arch. In 30 patients (63.8%), PCIs and/or repeated follow-up diagnostic catheterization were subsequently performed via the radial artery used at the index catheterization (default access site; right radial artery). A 5Fr sheath and catheters were used for repeated diagnostic catheterization, and a 6Fr sheath and guiding catheter were used for PCIs. After excluding 3 patients with radial artery occlusion after the index catheterization, the final study group consisted of 47 patients in whom serial FMD evaluations were performed. The protocol was approved by the Institutional Review Board of our hospital, and was consistent with the principles of the Declaration of Helsinki and local regulations. All patients gave written informed consent.

Measurement of FMD

Patients were asked to avoid food for 4 h, and caffeine, vasoactive medications, smoking and alcohol for 24 h prior to the examination. All examinations were performed by an experienced technician who was blinded to the patients' history of catheterization in a quiet, temperature-controlled room, with the patients seated for 10 min before the first study measurement was made. FMD was measured before (pre-FMD) and at 24 h after catheterization (post-FMD). Follow-up FMD was performed at least 3 months after the last catheterization (follow-up FMD). The initiation of vasodilative agents was avoided after pre-FMD until post-FMD had been performed. All measurements were conducted according to previously published guidelines.[14] Brachial arteries were imaged using an instrument equipped with software to monitor the brachial artery diameter and blood flow velocity. The system was comprised of a 10.0-MHz linear array transducer and a novel stereotactic probe-holding device (UNEX EF 38G; Unex Co., Nagoya, Japan). Continuous recordings of B-mode images and A-mode waves of the brachial artery in the longitudinal plane were obtained. A segment with a clear image of near (media-adventitia) and far (intima-lumen) borders of vessel layers was manually determined. These border interfaces were identified automatically based on the A-mode waves, and the diastolic diameter of the brachial artery per beat was synchronized with the electrocardiographic R-wave and was tracked automatically. The patients lay in the supine position for 30 min in a quiet air-conditioned room (22-24 °C). The right brachial artery was scanned in longitudinal sections 1-10 cm above the elbow. The skin surface was then marked, and the arm was kept in the same position during the study. A pneumatic cuff was placed around the forearm and inflated for 5 min to at least 50 mmHg above systolic pressure. The diameter of the brachial artery was scanned and recorded at baseline before cuff inflation, and continuously from the release point to 2 min after cuff deflation to obtain the maximum diameter during reactive hyperemia. The diameter of the artery was measured from one media-adventitia interface to the other at end-diastole, coinciding with the R-wave on the continu-

ously recorded electrocardiogram. FMD was calculated as the maximum percentage increase in arterial diameter during continuous measurements in the 4.5 min following cuff deflation.

Cardiac catheterization

All transradial coronary angiographies and interventions were successfully performed. Each patient underwent standard selective coronary and left ventricular angiography via the right radial artery with a 5 French system at the index procedure. The patients who were scheduled to undergo a PCI after the index procedure were treated with a 6 French system via the same radial artery. Follow-up catheterization after the PCI was performed in clinically indicated patients.

Statistical analysis

Data analysis was performed with SPSS version 24.0 (SPSS, Chicago, IL). Categorical data were expressed as numbers and percentages, and were compared using the chi-squared or Fisher's exact test, as appropriate. Continuous variables are expressed as mean ± standard deviation for normally distributed variables, and as median (25th-75th percentiles) for non-normally distributed variables and compared using the Student's t-test and the Mann-Whitney U-test, respectively. Pre-, post-, and follow-up FMD values were compared using analysis of variance and paired t-tests. Follow-up FMD was compared between the patients receiving one procedure and those receiving repeated transradial procedures. Post-FMD was defined as the measurement obtained 24 h after the first catheterization in both single and multiple procedure groups. Predictors of well-recovered FMD, which was defined as having a greater change between post-FMD and follow-up FMD than the median value of this cohort, were determined using logistic regression analyses. Predictors of high follow-up FMD, which was defined as having a greater value of post-FMD than the median value, were also determined using logistic regression analyses. A p value < 0.05 was considered to be statistically significant.

RESULTS

Baseline clinical characteristics

The median duration from first catheterization to follow-up FMD was 32 (24-43) months, and was not different between the patients who underwent no catheterization procedures after the index procedure (single catheterization group) and those who underwent two or more transradial catheterizations after the index procedure via the same radial artery (multiple procedures group) [33 (25-36) months and 19 (8-32) months, respectively, p = 0.16]. The characteristics of the study population are summarized in Table 1. There were no significant differences between the single and multiple procedure groups except for age.

Measurement of FMD

Changes in FMD are shown in Figure 1. Overall, the post-FMD value was significantly lower than the pre-FMD value (3.0 ± 1.7% vs. 3.7 ± 1.6%, p < 0.001), and follow-up FMD was significantly increased from post-FMD (4.0 ± 1.6% vs. 3.0 ± 1.7%, p = 0.001), which was comparable to pre-FMD (4.0 ± 1.6% vs. 3.7 ± 1.6%, p = 0.30). The median value of the change between post-FMD and follow-up FMD was 1.04 (-0.59-2.37). There was no significant difference in follow-up FMD between the single and multiple procedure groups (3.4 ± 1.3 vs. 4.3 ± 1.7, p = 0.06) (Figure 2 and Table 2). The median value of follow-up FMD was 4.01 (3.06-4.80). When the patients were divided into two groups according to the median value of follow-up FMD, no significant difference was observed in the number of procedures (2.6 ± 1.3 vs. 2.2 ± 1.3, p = 0.32) (Figure 3). Moreover, the change in FMD from the baseline to follow-up was not correlated with the duration from the most recent catheterization to the follow-up FMD examination (R = 0.02, p = 0.910). No significant predictive factor was identified for either well-recovered FMD (greater than the median value of follow-up FMD – post-FMD) or high FMD at follow-up FMD (greater than the median value) (Table 3).

DISCUSSION

We investigated the effects of transradial catheterization on long-term endothelial function of the brachial artery. There were three major findings in this study. First, FMD decreased significantly after radial catheterization and recovered to a value comparable to the baseline within a median follow-up period of 2.6 years.

Table 1. Baseline clinical characteristics of the study patients

	Total (N = 47)	Single procedure group (N = 17)	Multiple procedures group (N = 30)	p value
Age, years	67 ± 10	62 ± 12	70 ± 8	0.02
Female sex (%)	14 (29.8)	4 (23.5)	10 (33.3)	0.48
Smoking (%)	27 (57.4)	10 (58.8)	17 (56.7)	0.89
Body mass index, kg/m^2	25.2 ± 4.1	25.5 ± 5.9	25.0 ± 2.8	0.75
Hypertension (%)	36 (76.6)	12 (70.6)	24 (80.0)	0.46
Diabetes mellitus (%)	19 (40.4)	6 (35.3)	13 (43.3)	0.59
Dyslipidemia (%)	25 (53.2)	9 (52.9)	16 (53.3)	0.98
Family history of CAD (%)	11 (23.4)	3 (17.6)	8 (26.7)	0.58
NT-proBNP, pg/ml	160 (69-571)	173 (62-725)	135 (77-269)	0.76
Uric acid, mg/dl	5.9 ± .16	6.7 ± 1.2	5.3 ± 1.6	0.10
Total cholesterol, mg/dl	183 ± 39	197 ± 48	176 ± 32	0.13
LDL-C, mg/dl	105 ± 35	114 ± 41	100 ± 31	0.23
HDL-C, mg/dl	48 ± 22	52 ± 21	47 ± 23	0.38
Triglycerides, mg/dl	157 ± 85	166 ± 82	153 ± 87	0.62
eGFR, ml/min/1.73 m^2	72.4 ± 19.6	76.5 ± 19.4	70.0 ± 19.6	0.29
CRP, mg/dl	0.06 (0.00-0.15)	0.07 (0.00-0.19)	0.00 (0.00-0.11)	0.18
HbA1c (%)	6.4 ± 0.8	6.3 ± 0.7	6.6 ± 0.8	0.22
LVEF (%)	60 ± 16	57 ± 19	62 ± 13	0.33
Medications at the baseline				
Beta-blockers (%)	11 (23.4)	4 (23.5)	7 (23.3)	0.99
Ca-channel blockers (%)	16 (34.0)	9 (52.9)	7 (23.3)	0.06
ACE-I or ARB (%)	24 (51.1)	6 (35.3)	18 (60.0)	0.14
Statins (%)	24 (51.1)	8 (47.1)	16 (53.3)	0.77
Oral nitrates (%)	14 (29.8)	3 (17.6)	11 (36.7)	0.20
Medications at follow-up				
Beta-blockers (%)	18 (38.3)	7 (41.2)	11 (36.7)	0.76
Ca-channel blockers (%)	24 (51.1)	11 (64.7)	13 (43.3)	0.16
ACE-I or ARB (%)	31 (66.0)	9 (52.9)	22 (73.3)	0.16
Statins (%)	34 (72.3)	11 (64.7)	23 (76.7)	0.50
Oral nitrates (%)	14 (29.8)	3 (17.6)	11 (36.7)	0.17

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide.

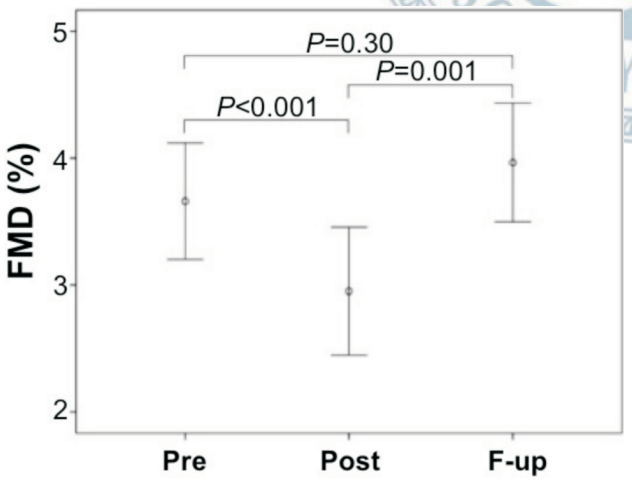

Figure 1. *The change in flow-mediated dilatation in all patients. Flow-mediated dilatation (FMD) significantly deteriorated from pre- to post-FMD measurement, and then, increased from post to follow-up measurement. However, there was no significant difference between pre- and follow-up measurements.*

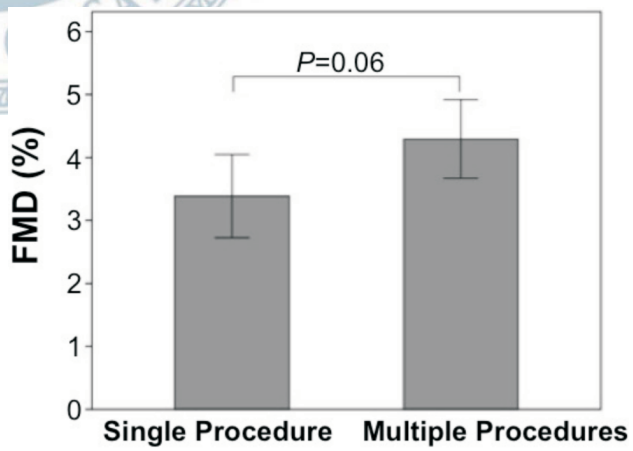

Figure 2. *Follow-up flow-mediated dilatation in the single and multiple procedure groups. Follow-up flow-mediated dilatation (FMD) values in the single and multiple procedure group were compared. Follow-up FMD was slightly higher in the multiple procedures group but the difference did not reach statistical significance.*

Table 2. Pre-, post-, and follow-up flow-mediated dilatation in the single and repeated procedure groups

	Total (N = 47)	Single procedure group (N = 17)	Multiple procedures group (N = 30)	p value
Pre-FMD, %	3.66 ± 1.56	3.64 ± 1.49	3.67 ± 1.62	0.96
Post-FMD, %	2.95 ± 1.71	2.91 ± 1.42	2.98 ± 1.89	0.89
Follow-up FMD, %	3.97 ± 1.59	3.39 ± 1.28	4.29 ± 1.67	0.06

FMD, flow-mediated dilatation.

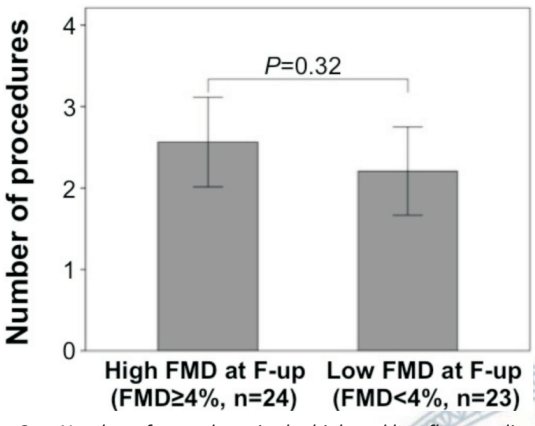

Figure 3. *Number of procedures in the high and low flow-mediated dilatation groups at follow-up. The number of procedures performed in patients with high or low flow-mediated dilatation values at follow-up was compared. Patients differed by a median value of 4%. The number of procedures performed was not different between the two groups.*

Second, no significant differences in follow-up FMD were detected between the single and repeated procedure groups. Third, no significant difference was observed in the final follow-up FMD with respect to the number of procedures. These findings suggest the potential recovery of FMD in the brachial artery after repeated transradial catheterization in long-term follow-up.

Sheath insertion into the radial artery may cause direct endothelial damage, while mechanical injuries rarely occur in the brachial artery during sheath insertion. Instead, insertion and exchange of guidewires and catheters may cause endothelial damage to the brachial artery, which may result in susceptibility to thrombosis, increased inflammation, and intimal hyperplasia.[15-17] Although deterioration of endothelial function certainly occurs, it is still controversial whether the function re-

Table 3. Univariate logistic regression analyses for the association with well-recovered FMD and high FMD value at follow-up

	Well-recovered FMD		High FMD at follow-up	
	Univariate analysis Odds ratio (95% CI)	p value	Univariate analysis Odds ratio (95% CI)	p value
Age, years	1.06 (0.99-1.12)	0.096	1.02 (0.96-1.08)	0.608
Female sex (%)	1.42 (0.40-4.99)	0.588	0.63 (0.18-2.21)	0.465
Smoking (%)	0.76 (0.24-2.42)	0.642	1.08 (0.34-3.42)	0.900
Body mass index, kg/m^2	0.85 (0.71-1.02)	0.085	0.83 (0.69-1.01)	0.059
Hypertension (%)	2.19 (0.54-8.81)	0.271	0.83 (0.22-3.23)	0.792
Diabetes mellitus (%)	1.11 (0.35-3.57)	0.859	0.55 (0.17-1.77)	0.314
Dyslipidemia (%)	0.77 (0.24-2.43)	0.654	1.08 (0.34-3.41)	0.891
Family history of CAD (%)	0.69 (0.18-2.73)	0.602	0.69 (0.18-2.73)	0.602
NT-proBNP, pg/ml	1.00 (0.99-1.00)	0.511	1.00 (0.99-1.00)	0.748
Uric acid, mg/dl	0.43 (0.16-1.18)	0.102	0.67 (0.32-1.42)	0.298
Total cholesterol, mg/dl	1.00 (0.99-1.02)	0.817	1.01 (0.99-1.02)	0.375
LDL-C, mg/dl	1.01 (0.99-1.03)	0.326	1.01 (1.00-1.03)	0.130
HDL-C, mg/dl	1.00 (0.97-1.02)	0.844	1.00 (0.97-1.03)	0.951
Triglycerides, mg/dl	1.00 (0.99-1.00)	0.287	1.00 (0.99-1.00)	0.438
eGFR, ml/min/1.73 m^2	1.01 (0.98-1.04)	0.629	1.00 (0.97-1.03)	0.906
CRP, mg/dl	1.95 (0.09-42.3)	0.671	1.17 (0.06-24.6)	0.920
HbA1c (%)	1.33 (0.64-2.78)	0.444	1.10 (0.53-2.26)	0.797
LVEF (%)	0.99 (0.96-1.03)	0.740	0.97 (0.93-1.01)	0.178
Beta-blockers (%)	0.93 (0.29-3.03)	0.908	0.93 (0.29-3.03)	0.908
Ca-channel blockers (%)	0.92 (0.29-2.88)	0.882	0.65 (0.21-2.06)	0.465
ACE-I or ARB (%)	2.31 (0.67-7.96)	0.186	1.07 (0.32-3.57)	0.917
Statins (%)	1.31 (0.36-4.73)	0.678	0.86 (0.24-3.09)	0.814
Oral nitrates (%)	0.94 (0.27-3.29)	0.924	2.16 (0.59-7.85)	0.242

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide.

covers after a period of time. Heiss et al. demonstrated that transradial catheterization significantly decreased FMD in the radial and brachial arteries at 6 h after transradial catheterization, and that the FMD in nonsmokers fully recovered at 24 h.[6] Likewise, Yan et al.[18] demonstrated early injury and luminal diameter reduction in the exposed radial artery, which eventually healed and returned to baseline 1 month after the catheterization. Furthermore, Mario G et al.[19] reported a positive correlation between radial artery FMD and the period from transradial catheterization. In contrast, Burstein et al.[5] demonstrated a persistent decrease in radial artery FMD following transradial catheterization at 9 weeks of follow-up. Buturak et al.[10] found a blunted FMD response and nitroglycerin-mediated dilatation, an index of arterial vasodilatation response which reflects endothelium-independent and muscle cell-mediated vasodilatation responses, 6 months after transradial catheterization. These equivocal findings mean that it is still controversial whether the endothelium can recover from functional and structural damage.

Recently, physicians have increasingly used the radial artery for repeated catheterization, and the technical feasibility and safety of repeated catheterization have been reported.[20] However, several studies have shown that repeated catheterization increasingly damages vessel walls of the radial artery. Yonetsu et al.[21] demonstrated with optical coherence tomography that repeated transradial catheterization induced intimal thickening, and Sansone et al.[22] reported that intima-media thickness after transradial catheterization was correlated with radial artery FMD. These findings suggest that repeated transradial catheterization may damage endothelial function and structure. In contrast with the number of studies on radial arterial function after a single catheterization procedure, the effects of repeated transradial catheterization on radial and brachial arterial function remains unclear. Heiss et al.[6] reported that the number of catheters used in the procedure was an independent predictor of poor recovery from brachial artery FMD, and that using 4 to 5 catheters during a single procedure caused more severe and sustained impairment endothelial function at 24 h. However, in the present study, there was no significant correlation between the number of procedures and the recovery from decreased FMD in long-term follow-up. Our results may indicate that brachial arterial dysfunction caused by multiple transradial catheterization procedures may be severe, but that it can recover after a certain period of time. In the present study, FMD in the brachial artery recovered to the baseline at follow-up. Of interest, in the repeated catheterization group, FMD was even numerically better during follow-up than at baseline, which may be attributable to medical therapy initiated after CAG for ischemic heart disease. In this study, only half of patients were prescribed with statins at baseline. In other words, nearly half of the patients were naïve to medical therapy and subsequently initiated medical therapies, some of which have been shown to be beneficial to improve endothelial function.[23]

The sheath diameter during transradial catheterization is one of the most important factors in endothelial damage, and the ratio of sheath to artery diameter has been shown to be a predictor of radial artery occlusion.[24,25] Saito et al.[26] reported severe flow reduction in patients with an artery to sheath ratio < 1. Uhlemann et al.[27] demonstrated that the use of 5F sheaths for transradial access significantly decreased the rate of radial arterial occlusion by 55% compared with 6F sheaths. In the present study, the single procedure group used 5 French sheaths and catheters while the multiple procedure group used 6 French sheaths and catheters. However, there were no significant differences between these two groups. These findings suggest that repeated transradial catheterization may be performed safely without fear of damaging brachial artery endothelial function.

Limitations

There may be several limitations to this study. First, this is a single center observational study which consisted of a small number of cases, which may have led to selection bias. Second, we did not control for age, exercise, medical treatment, or genetic background, which may have affected FMD.[28-31] Third, we did not examine other indicators of vascular function. Although FMD is a widely accepted noninvasive method to assess endothelial function, several studies have recommended adjunctive measurements in addition to conventional FMD.[14] Fourth, although we evaluated vascular function, structural changes in the vasculature need to be assessed by other modalities such as optical coherence tomography,

intravascular ultrasound, or pathological examinations. Fifth, in the present study, medications were left to the physician's discretion. Although medication regimens were not statistically different between the single procedure group and multiple procedure group, a weak trend could not be cancelled, which may have affected the results. Moreover, detailed information regarding PCI procedures and procedure time in the patients who underwent subsequent catheterization, which may have impacted the follow-up FMD values, was lacking. Sixth, the present study excluded patients who presented with radial artery occlusion at the time of follow-up examination of FMD, because occluded radial arteries may have a large influence on FMD measurements in the brachial artery, which would preclude a fair assessment of endothelial function of the brachial artery. Seventh, the handedness of the patients, which may have been association with FMD and arterial diameters, was not assessed in the present study. Further studies are needed to take into account the handedness of patients. Lastly, measurements of FMD, ultrasound, and assessments of patency were not performed in the radial artery, which may have been associated with FMD in the brachial artery. Dawson et al.[29] demonstrated that transradial catheterization decreased low-flow mediated constriction in the radial artery. Madssen et al.[30] reported that the radial artery diameter was diminished 1 year after transradial coronary angiography while vasodilatory properties were preserved. In addition, some reports have indicated that the coating of the sheaths may induce vascular inflammation,[32-34] which may influence radial artery function. These findings could not be assessed in our study because of a lack of radial artery assessments.

CONCLUSIONS

After transradial catheterization, FMD in the ipsilateral brachial artery was decreased at 24 h after catheterization and recovered during the median follow-up period of 2.6 years. Recovery of FMD was not influenced by repeated catheterization, which suggests that vascular endothelium of the brachial artery may either tolerate or have the ability to functionally recover even after repeated transradial catheterization.

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None.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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