

Evaluation of radial artery endothelial functions in transradial coronary angiography according to different radial access sites

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ABSTRACT

Objective: Radial endothelial dysfunction may occur after transradial coronary angiography (CAG). This study aimed to make a comparative evaluation of the radial endothelial functions before and after catheterization between three different radial access sites: left radial (LR) artery, left distal radial (LDR) artery, and right radial (RR) artery.

Methods: Seventy patients scheduled for elective transradial CAG and intervention from September 6, 2017 to March 6, 2018 were consecutively enrolled. Radial artery endothelial functions of the catheterization arm were measured by flow-mediated vasodilation (FMD) upon admission, at 24 hours, and 2 months following the procedure.

Results: LR access was used in 17 patients, whereas the LDR and the RR access were used in 27 and 26 patients, respectively. Basal radial diameters and FMD median values measured on the intervention arm were found to be similar between groups (LR 3.04 ± 0.29 mm, 13.33%; LDR 2.79 ± 0.31 mm; 13.64%; RR 2.74 ± 0.29 mm; 12.52%, $p=0.952$). The radial vasodilation percentage change expressed as median decreased in all groups 24 hours after the procedure; however, the one with the LDR access was found to be significantly higher than with the LR (9.7% vs. 6.25% $p=0.013$) and the RR access (9.7% vs. 3.39 $p<0.001$). A partial recovery of endothelial functions was seen at 2 months after the procedure, approximating to basal values (11.11%; 12%; 10.62%, $p=0.079$, respectively).

Conclusion: Radial artery functions deteriorate early after transradial catheterization. The LDR access seems safer than the other conventional radial access sites in terms of preservation of radial endothelial functions.

Keywords: transradial coronary angiography, endothelial function, flow-mediated vasodilation test, left distal radial artery

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Introduction

Coronary angiography (CAG) and intervention performed through transradial access are feasible and safe, as confirmed by multiple studies (1, 2).

Although the radial arteries are patent in most patients after transradial catheterization, physical damage to the vascular endothelium can disrupt vasodilator functions of arteries, thus leading to diffuse stenosis and perhaps occlusion (3). An impaired endothelial (vasodilation) response and arterial remodeling account for the quality of the radial artery, which may limit its use as a bypass graft or for a dialysis shunt (4, 5). The most common noninvasive method for endothelial function assessment is the flow-mediated vasodilation (FMD) test, which reflects the nitric oxide-mediated endothelium-dependent pro-

cess of vasodilation response during reactive hyperemia (6). There is little knowledge about the radial endothelial functions and their course after catheterization in the left distal radial access site. Therefore, we aimed to investigate the radial endothelial functions using the FMD test following transradial catheterization and compare them between three different radial access sites, left radial (LR) artery, left distal radial (LDR) artery, and right radial (RR) artery, in a prospective observational study.

Methods

Patients admitted for elective transradial coronary angiography and intervention by September 6, 2017 were included in

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our study, whereas patients with previous transradial catheterization history and those intervened in an emergent way (acute coronary syndrome) were excluded. Enrollment continued until March 8, 2018, including a total of 70. After the explanation of the study, a written informed consent was taken from all patients. Transradial coronary angiography and intervention were made by one operator being blind of the study.

The study was designed in accordance with the principles of the Declaration of Helsinki and got approval from the Local Ethics Committee of our hospital.

Radial artery ultrasonography

The radial artery of the intervention arm was imaged 5 cm proximal to the styloid protuberance with a 4.5–12 MHz linear array probe (GE Healthcare Vivid E9 4D Cardiovascular ultrasound system device). FMD measurements were performed upon admission, 24 hours, and 2 months after the intervention. The artery was identified by color flow mapping, and then image acquisition was recorded to define the maximum diameter of the artery during end diastole concurrently tracked by the R wave in electrocardiography (ECG) (Fig. 1). All the measurements were performed by one dedicated cardiologist with experience on vascular ultrasonography. He was left unaware of the patients' coronary angiography results to prevent any possible influence on radial ultrasonography and FMD evaluation.

Flow-mediated vasodilation test

Flow-mediated vasodilation test was applied in a quiet room with normal room temperature in accordance with international guidelines (7, 8). Patients were requested not to exercise and

drink tea or coffee for at least 4 hours before the procedure. After a 5-minute rest in the supine position, the patient's arm cuff located over the antecubital area was inflated until 220 mm Hg for total occlusion of the distal hand arteries. After 5 minutes of occlusion, the cuff was deflated, and the maximal diameter of the radial artery was obtained by measuring the distance from the anterior wall intima to the posterior wall intima layer. Radial artery diameter and vasodilation (expressed as the percentage change of baseline value) were recorded at end diastole determined by simultaneous monitoring of ECG. Percentage change measurements were made in basal, 30 seconds, and 1, 2, and 3 minutes after arm cuff deflation (Fig. 1). The highest diameter and percentage diameter change were recorded during the first minute, which were accepted as reference measurements (Fig. 2). FMD percentage change was calculated by using the following formula:

$$\text{FMD}(\%) = \frac{\text{Diameter after reactive hyperemia} - \text{Basal arterial diameter}}{\text{Basal arterial diameter}}$$

Equipment and medications used during transradial coronary angiography intervention

A radial hydrophilic sheath (6 French Prelude 170 Ease, Merit Medical) was used for all transradial CAG. Judkins 6 French catheters were used for all the procedures. To prevent vessel-related complications, 2500 units of unfractionated heparin, 200 mcg nitrate, and saline cocktail were applied to all patients. In case of intervention, heparin dose was contemplated intravenously according to the patient's body weight and dual antiplatelet therapy administered. Figure 3 shows images of different

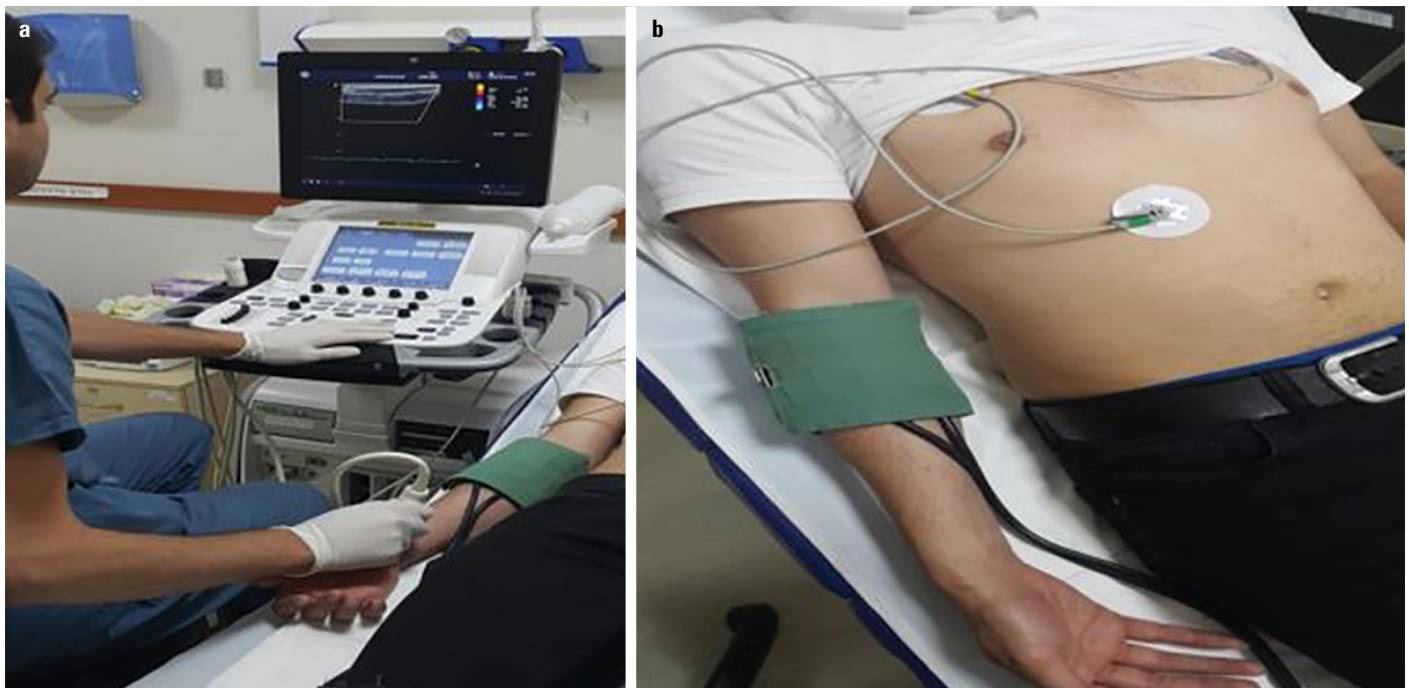


Figure 1. (a) Ultrasonography of the radial artery on the intervention arm. (b) Patient and cuff position during flow-mediated vasodilation test

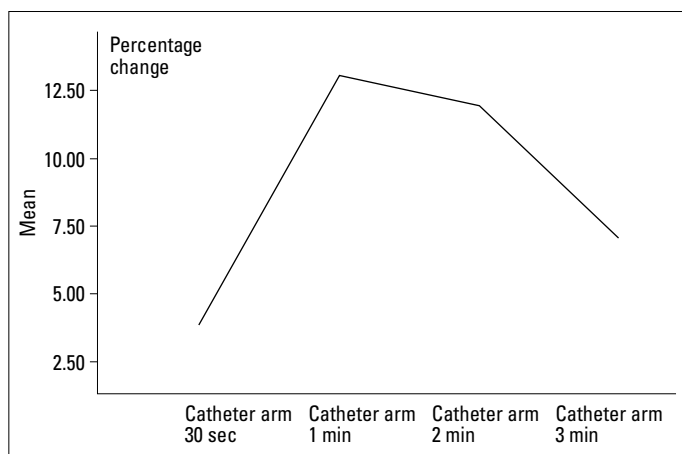


Figure 2. Flow-mediated vasodilation test performed at different time frames

access sites. Radial sheath was removed at procedure termination in both diagnostic and interventional procedures. Early hemostasis was achieved by manual compression for 15 minutes. The slightly compressing bandage remained for 12 hours for complete hemostasis.

Statistical analysis

IBM SPSS Statistics 21.0 Program was used. The sample size calculation was done with the G Power 3.0.8 program. Power analysis for one-way analysis of variance (ANOVA) was applied. The minimum sample size was found to be 66 to find the difference of FMD between different access sites, with alpha 0.05 error level, effect size=0.4, and 80% power. The suitability of numerical variables to normal distribution was examined using the Shapiro–Wilk test. If normal distribution was achieved, one-way ANOVA was used; if not, the Kruskal–Wallis test was used. Numerical variables are given as mean and standard deviation and median (min-max). The chi-square test was ap-

plied for categorical data. After the Kruskal–Wallis test, pair comparisons were made using the Dunn test with Bonferroni correction. Afterward, FMD percentage change variable was considered significant at $p < 0.05/3 = 0.016$ corrected for pairwise comparison. ANOVA and Tukey post hoc test were used. Categorical variables were shown as numbers (n) and proportions (%). The significance level was accepted as < 0.05 for all hypotheses.

Results

In nearly a 6-month period, 70 patients were included in the study and analyzed accurately. According to the operator access site decision, three groups were identified: 17 patients intervened through the LR artery, 27 patients through the LDR artery, and 26 patients through the RR artery.

Demographic features

Table 1 depicts the demographic features and basal medication usage. The study population had a relatively young age (58.8 ± 12.3 years), predominantly male (68.5%) ($p = 0.720$). Patients were in an overweight range according to their BMI (27.7 ± 5.3 m²/kg). Hypertension was the most common comorbid disease seen in 67.4% of the LR group, 77.8% of the LDR group, and 84.6% of the RR group. No significant difference was noted between the groups in terms of comorbidities. In addition, the study population had a preserved left ventricle ejection fraction ($53.6 \pm 9.4\%$), and together with other valvular pathologies, no statistically different echocardiographic feature was noted between the groups.

The most common drug used was beta-blocker (47.1%), which was followed by acetyl salicylic acid (45.7%), angiotensin-converting enzyme inhibitors, oral antidiabetics, statins, and



Figure 3. Different radial artery access sites. From left to right: left distal radial access, left forearm radial access, and right forearm radial access

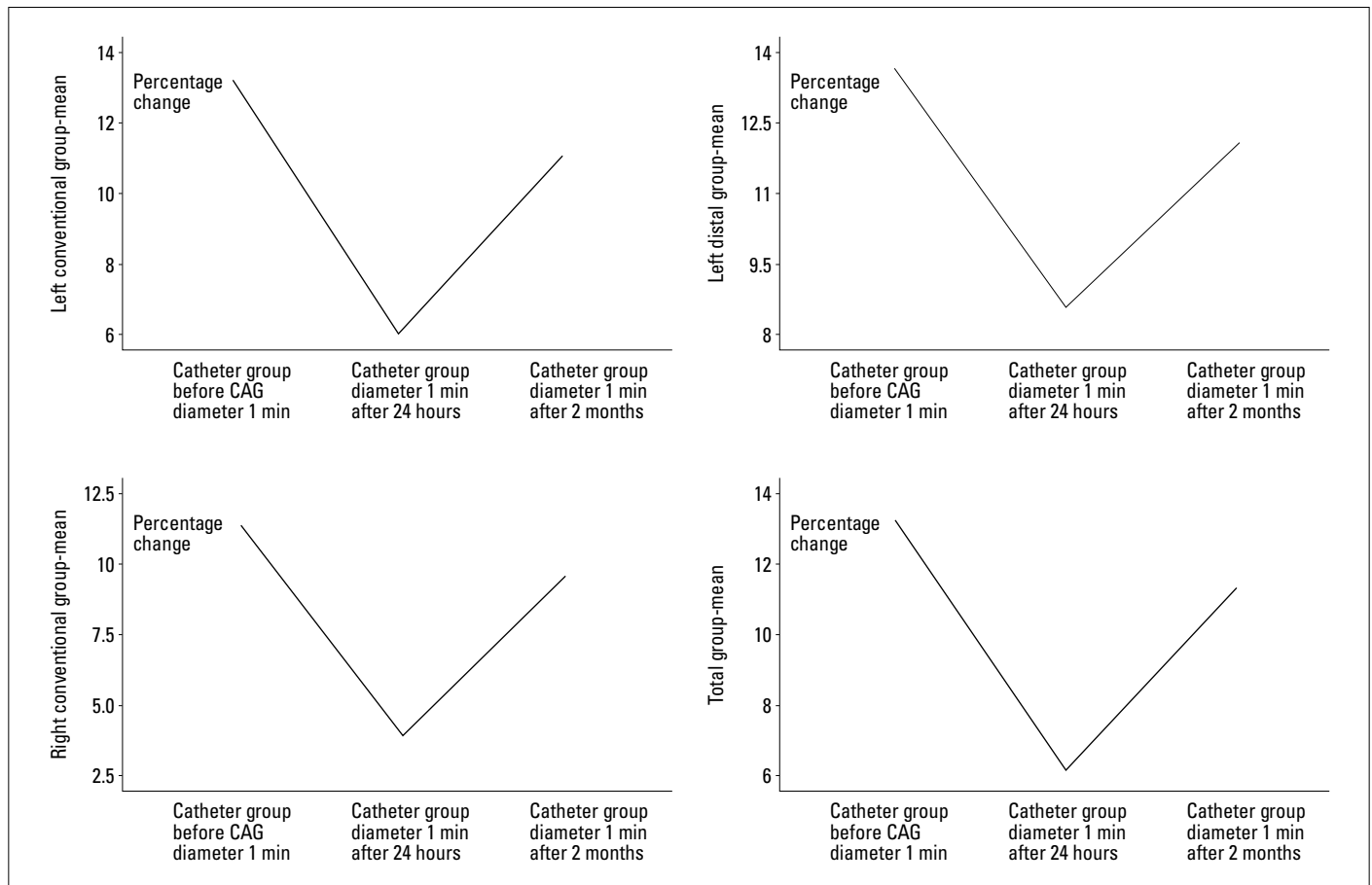


Figure 4. Percentage change of radial artery diameters on flow-mediated dilatation according to the access site

clopidogrel, respectively. All three access site groups showed similar basal medication usage ($p>0.05$) (Table 1).

Radial artery flow-mediated vasodilation test on the catheterization arm

Table 2 and Figure 4 depict the FMD test results on the catheterization arm. Due to abnormal distribution, FMD values were presented as median with percentiles (Q1–Q3). Basal radial artery diameter and percentage change according to access site were as follows: the LR group 3.04 ± 0.29 mm with median 13.33 (11.7–14.84), the LDR group 2.79 ± 0.31 mm with median 13.64 (12–15), and the RR group 2.74 ± 0.29 mm with median 12.52 (11.24–15.38). No statistically significant difference was noted between the groups ($p=0.952$).

The radial artery diameter was increased in all three groups at 24 hours following transradial catheterization. However, the vasodilation response expressed as percentage of baseline was decreased in all groups: 6.25 (3.23–8.13) in the LR group, 9.37 (6.90–10.71) in the LDR group, and 3.33 (2.99–3.48) in the RR group, respectively. Interestingly we found that this vascular response measured by FMD test was significantly higher in the LDR group than in the LR ($p=0.013$) and RR groups, respectively ($p<0.001$).

Radial vascular functions showed recovery at 2 months following transradial coronary angiography, approximating the pre-

catheterization basal values. The radial artery diameter percentage change was increased in all groups: LR, 11.1 (9.12–13.33); LDR, 12 (11.11–13.64); and RR, 10.62 (7.69–11.65), respectively. No statistically significant difference seen between the intervention groups ($p=0.079$) indicated the possible time period needed for healing of endothelium of the radial artery tree independent of access site.

Procedural angiographic features

A total of 19 patients (5 in LR group, 7 in LDR, and 7 in RR) underwent coronary stent procedure with no significant difference between them ($p=0.968$). The stent implantation procedure being an indirect finding of the atherosclerotic burden was higher in the LDR group than in the LR and similar to the RR access site. In contrast to this finding, the basal FMD percentage changes were similar between the groups (Table 2), showing no influence by the extensive atherosclerotic burden. The fluoroscopy time was higher in the LDR group (13.04 minutes), no statistical significance was seen between the other groups ($p=0.367$) (Table 3).

Complications

Complications that patients developed after transradial CAG were evaluated (Table 3). The most common vascular complications were thrombosed areas inside the radial artery detected

Table 1. Baseline patient characteristics and physical examination findings according to access sites upon admission

Parameters	Left radial (n=17)	Left distal radial (n=27)	Right radial (n=26)	Total (n=70)	P-value
Age	58.5±14.56	57.6±12.5	60.3±10.8	58.8±12.3	0.720
Male, n (%)	15 (88.2)	17 (63)	16 (61.5)	48 (68.5)	0.133
BMI	26.7±3.9	27.9±7.1	28.1±3.9	27.7±5.3	0.487
Hypertension	11 (67.4)	21 (77.8)	22 (84.6)	54 (77.1)	0.313
DM	7 (41.2)	11 (40.7)	10 (38.5)	28 (40)	0.979
CAD	6 (35.3)	12 (44.4)	9 (34.6)	27 (38.6)	0.725
HLP	7 (41.2)	13 (48.1)	6 (23.1)	26 (37.1)	0.155
TC	168.3±42	172.9±36.9	176±49	173±42.5	0.852
HDL	40.8±10.7	44.8±11.7	46.3±10.9	44.4±11.2	0.293
LDL	96.6±27.7	97.2±37.6	105.5±42.2	99.8±37.9	0.665
Uric acid	6±1.9	5.4±1.5	5.3±1.3	5.5±1.5	0.364
Anemia	1 (5.9)	2 (7.4)	3 (11.5)	6 (8.6)	0.781
Smoking	6 (35.3)	9 (33.3)	6 (23.1)	21 (30)	0.840
LVEF	51.7±11.8	53.7±10.7	55.2±6.6	53.6±9.4	0.440
Moderate-to-severe MV disease	5 (29.4)	3 (11.1)	3 (11.5)	11 (15.7)	0.478
Moderate-to-severe AV disease	1 (5.8)	2 (7.4)	4 (15.3)	7 (10)	0.155
Moderate-to-severe TV disease	4 (23.5)	6 (22.2)	4 (15.3)	14 (20)	0.234
Beta-blockers	8 (47.1)	12 (44.4)	13 (50)	33 (47.1)	0.921
ASA	5 (29.4)	14 (51.9)	13 (50)	32 (45.7)	0.298
ACEi	5 (29.4)	5 (18.5)	10 (38.5)	20 (28.6)	0.274
Oral antidiabetic	5 (29.4)	8 (29.6)	5 (19.2)	18 (25.7)	0.634
Statin	4 (23.5)	8 (29.6)	3 (11.5)	15 (21.4)	0.268
Clopidogrel	3 (17.6)	5 (18.5)	4 (15.4)	12 (17.1)	0.953
CCB	2 (11.8)	3 (11.1)	1 (3.8)	6 (8.6)	0.553

Numerical variables are given as mean and standard deviation.

AV - aortic valve; BMI - body mass index; CAD - coronary artery disease; CCB - calcium channel blockers; DM - diabetes mellitus; HDL - high-density lipoprotein; LVEF - left ventricular ejection fraction; LDL - low-density lipoprotein; MV - mitral valve; TC - total cholesterol; TV - tricuspid valve

Table 2. Comparison of the radial artery diameter and percentage change of the catheter group measured by flow-mediated vasodilation test according to access sites

Flow-mediated vasodilation	Left radial (n=17)		Left distal (n=27)		Right radial (n=26)		P-value
	Diameter	Median	Diameter	Median	Diameter	Median	
Basal	3.04±0.29	13.33 (11.7-14.84)	2.79±0.31	13.64 (12-15)	2.74±0.29	12.52 (11.24-15.38)	0.952
After 24 hours	3.23±0.27	6.25 (3.23-8.13)	3.14±0.29	9.7 (6.90-10.71)	3.09±0.28	3.39 (2.99-3.48)	Left distal- Left 0.013 Left distal- Right <0.001
After 2 months	3.09±0.33	11.11 (9.12-13.33)	2.85±0.25	12 (11.11-13.64)	2.95±0.26	10.62 (7.69-11.65)	0.079

The diameter is shown as mean±standard deviation; the percentage diameter change is shown as median with percentiles Q1-Q3 in parenthesis

by radial artery ultrasonography performed at 24 hours after the procedure, which were similar among groups ($p=0.184$). Radial thrombosis areas detected by ultrasonography were observed in

7.1% of patients. Radial artery occlusion was seen in one patient in the LR group and one patient in the RR group, and no occlusion was seen in the LDR group.

Table 3. Procedural angiography features and vascular complications according to access sites

Features	Left radial (n=17)	Left distal (n=27)	Right radial (n=26)	Total (n=70)	P-value
Stent procedure	5 (29.4)	7 (25.9)	7 (26.9)	19 (27.1)	0.968
Fluoroscopy time (minutes)	9.9	13.04	6.46	8.807	0.367
Complication					
Radial thrombosis areas	2 (11.8)	0 (0)	3 (11.5)	5 (7.1)	0.184
Occlusion	1(5.9)	0 (0)	1 (3.8)	2 (2.9)	0.485

Percentage values were expressed in parentheses

Discussion

Radial artery access in coronary angiography has been increasingly used in recent years and has become the standard approach in many centers (9). However, complications such as intervention-related occlusion and vasodilator dysfunction can still occur (10). Transient impairment has been described in endothelium-dependent and independent vasodilation function of the radial artery, thus supporting the endothelial layer damage caused by sheath introduction and catheter advancement (11). Likewise, our study has demonstrated that the radial vascular mechanistic injury can easily be assessed by noninvasive tests such as the FMD. By using this test, we showed early deprivation of the radial artery vasomotor functions independent of access site, which is greatly important, because the endothelial layer is very delicate and can be harmed even by the introduction of the sheath into the very distal branch of the radial artery (left distal branch). On the other hand, the LDR access site showed higher preservation of endothelial function, implying that the distal radial artery is one of the distal branches of the main radial artery and the influence of the insertion of the sheath could be not as high as the introduction of it into the main radial artery. Being a branch of the deep palmar arch and the wealthy collateral between the superficial and deep palmar arch makes the LDR artery advantageous against hand blood perfusion, consequently posing possible preservation of radial endothelial functions (12). Although we found a higher fluoroscopy time in the LDR group, indicating a longer time of sheath inside the relevant artery, the abovementioned anatomic characteristics could be the possible explanations why radial vasomotor functions have less influence on the LDR access. Post-catheterization radial artery occlusion is one of the most common complications during transradial coronary angiography, estimated to be 1%–10% (13). Although there is no large head-to-head comparison, vascular complications such as radial artery occlusion have a low incidence rate in the LDR access, an important sign indicating less shear stress directly into the main radial artery and as a result more preservation of endothelial functions (14, 15). These anatomic and physiologic features supported our study findings where no radial occlusions were noted in the LDR group compared with the RR and LR access, having one recorded case each. The same sheath (6 French) was used in all patients, and as the study population was homogeneous in relation to demographic and comorbid

diseases, endothelial function measurement through FMD was highly accurate, implying that the LDR access site could be more reliable in terms of endothelial function preservation and consequently protective against vascular complications. The extensive atherosclerotic burden indirectly presented as stent implantation procedure was higher in the LDR group than in the LR and was similar to the RR access site. In contrast to this finding, FMD percentage changes were similar between the groups (Table 2), showing no influence by the extensive atherosclerotic burden. Regarding the protocol of the FMD test, we recorded the percentage change of vasodilation response during different time frames (30 seconds; 1, 2, 3 minutes after cuff deflation). The standard protocol for the time frame of artery diameter has been a point of discussion for a long time. Although the usual time frame is 60 seconds after cuff deflation, some studies have shown that at this time maximal vasodilation response can be underestimated (16). However, to overcome this issue, we made multiple recordings in different time frames and accepted the maximum diameter recorded during the first minute after cuff deflation as a reference value. The time course of endothelial function recovery shows heterogeneity. Some relevant studies have reported irreversible vasomotor impairment (4). However, other studies have confirmed complete recovery of the radial vasomotor functions with different time periods (17, 18). Our study adds two important key points as new knowledge:

- 1) The LDR is more protective in terms of radial artery endothelial functions than other radial access sites.
- 2) Recovery of radial endothelial function can be seen early at 2 months post-catheterization irrespective of the access site.

Restoration of radial vasomotor functions is supported by another study evaluating the radial artery endothelial functions, which shows an improvement of FMD at 3 months post-catheterization (19). As a result, the radial vascular injury mechanism and its course following catheterization are of paramount importance, in which its thorough characterization will accurately define future radial artery selection as a suitable conduit for bypass grafting, shunt for arterio-venous fistula formation, and possible reuse for transradial catheterization.

Study limitations

Although the relatively small sample size was in a single center, the LDR artery group reached a statistical value, sug-

gesting that the left distal intervention site was more reliable than other access sites in terms endothelial function influence. The lack of association between endothelial function preservation and a biochemical value and the inability to evaluate endothelial functions with nitroglycerin-mediated vasodilation test may be one of the possible limitations of our study. However, tests based on drug delivery (nitrate-mediated vasodilation) or other invasive procedures were not performed due to their possible side effects, which are not ethically accepted. It would have been better if an intravascular imaging such as intravascular ultrasound or optical coherence tomography was performed to further characterize this new finding of endothelial function course in the LDR access. This method can be used for future studies to further define the injury mechanism in the radial artery. The sample size was not big enough to accurately link the vasomotor response with the vascular complications. Randomized trials with a higher number of patients will be needed to evaluate the relationship between vascular complications and endothelial function.

Conclusion

Radial artery functions deteriorate early after transradial catheterization independent of access site. The LDR access seems safer than the other conventional radial access sites in terms of preservation of radial endothelial functions. The recovery of radial endothelial functions is seen after a 2-month period irrespective of access site.

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Peer-review: Externally peer-reviewed.

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