

Impact of Catheter Sheath Insertion into the Radial Artery on Vascular Endothelial Function Assessed by Reactive Hyperemia Peripheral Arterial Tonometry

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SUMMARY

The transradial approach has been used for coronary procedures, but this procedure carries a risk of injury to the endothelium of the radial artery. In this study, the vascular dysfunction caused by transradial catheterization was examined using reactive hyperemia peripheral arterial tonometry (RH-PAT), a recently developed technique for assessing endothelial function in digits, and the differences in injuries were compared according to the size of sheath.

Forty-three patients undergoing transradial catheterization with 6-Fr sheaths ($n = 17$) or 4-Fr/5-Fr (non-6-Fr; $n = 26$) sheaths underwent RH-PAT using an Endo-PAT2000 before, the day after, and 6 months after catheterization. RH-PAT was assessed in the arm of sheath placement and in the other arm as a control.

RH-PAT values decreased from 2.42 ± 0.67 before catheterization to 2.08 ± 0.41 the day after catheterization in the 6-Fr group ($P = 0.031$); this was more evident in patients with a longer procedure time (> 91 minutes). In contrast, the change in the non-6-Fr group was not significant. RH-PAT of the non-catheterized arm was unchanged in both groups. At 6 months after catheterization, RH-PAT values in the 6-Fr group had not completely returned to baseline.

In conclusion, the insertion of a 6-Fr catheter sheath into the radial artery, especially with a longer procedure time, impaired vascular endothelial function assessed by RH-PAT the day after the procedure and was sustained for 6 months. Thus, the use of smaller size sheaths (< 6 -Fr) with a shorter procedure should be considered when performing transradial catheterization. (Int Heart J 2015; 56: 489-494)

Key words: Transradial catheterization, Sheath size, Procedure time

The transradial approach is widely used for coronary procedures, which is associated with fewer access site-related bleeding complications and with a lower risk of mortality following percutaneous coronary intervention (PCI) than procedures via the femoral artery.¹⁻⁵ However, some complications exist, such as spasm and occlusion of the radial artery (RA), which may be due to the insertion of the catheter sheath into the relatively small radial artery.⁶ This has a direct physical impact on the endothelial lining of the vessel wall. Removal or damage of the endothelial lining impairs arterial relaxation by decreasing NO bioavailability, and it then promotes intimal hyperplasia, thrombus formation, and the development of atherosclerotic plaques.^{7,8} Indeed, recent studies using intravascular ultrasound (IVUS) imaging^{9,10} and optical coherence tomography (OCT)¹¹ showed that transradial catheterization causes injury to the radial artery wall resulting in endothelial cell dysfunction. In addition, the radial artery is a donor graft for coronary artery bypass surgery; therefore, the structural and functional damage may affect surgical outcomes in such cases.

Assessment of brachial artery flow-mediated dilation (FMD) by ultrasound is the most established and commonly used noninvasive method for assessing endothelial function.¹²⁻¹⁴ By measuring FMD, a transradial intervention with a 6-Fr sheath was found to have negative effects on endothelial function and the size of the RA.¹⁵ However, technical problems can occur during FMD measurement.¹⁶ Kuvin, *et al*¹⁷ demonstrated a new method to evaluate endothelial dysfunction called reactive hyperemia peripheral arterial tonometry (RH-PAT), which is a noninvasive, automatic, and quantitative clinical test for digital measurement of the hyperemic response. However, few studies that assessed vascular endothelial function caused by transradial catheterization using this technique have been reported.

Because of the advantages of RH-PAT, including ease of administration and an automated analysis program that facilitates acquisition of reliable data,¹⁸ this technique was used to measure endothelial function and examine the effects of sheath insertion into the RA on vascular endothelial function.

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METHODS

Patients: Forty-three patients receiving transradial cardiac catheterization with 6-Fr sheaths ($n = 17$) or 4-Fr/5-Fr (non-6-Fr; $n = 26$) sheaths who underwent RH-PAT between May 2010 and October 2011 at Nagasaki University Hospital were considered for inclusion in this prospective, non-randomized study. The non-6-Fr group was composed of 2 patients with normal coronary arteries, 2 with vasospastic angina, 8 with a significant stenosis of the coronary arteries who underwent PCI a few days later via a femoral artery, and 14 with no significant stenoses of the coronary arteries who underwent a follow-up CAG several months after PCI. All of the patients in the 6-Fr group had a significant stenosis in the coronary arteries and underwent subsequent PCI. Exclusion criteria were acute coronary syndrome, chronic inflammatory disease (ie, coeliac disease, vasculitis, lupus, and irritable bowel disease), clinically active malignancy, end-stage renal failure, abnormal Allen's test result, and Raynaud's syndrome. This study complied with the Declaration of Helsinki with regard to human investigation. All of the included patients provided written, informed consent to participate in the study before enrollment.

Measurement of RH-PAT: RH-PAT was measured using an Endo-PAT2000 system (Itamar Medical, Caesarea, Israel) before breakfast in a quiet, dimmed, temperature-controlled room. Before the examination, patients remained in the supine position for at least 15 minutes. PAT sensors were placed on the index fingers of the right and left hands. All studies were conducted strictly according to the manufacturer's instructions and in accordance with the current literature.^{17,19-21)}

First, the sheath side arm was tested, while the non-sheath side arm provided information about whole-body homeostasis and served as a control. Each measurement consisted of 5 minutes of baseline data, 5 minutes of compression of the sheath side brachial artery, and 5 minutes of reactive hyperemia measurement after release of the cuff. The pulse amplitude recordings were digitized and analyzed by an automated, proprietary algorithm. The brachial artery compression was performed using the blood pressure cuff, which was inflated to at least 60 mmHg over a patient's systolic blood pressure level. Next, after resting again in the supine position for at least 15 minutes, the non-sheath side arm was tested by the same procedure as for the sheath side.

Measurement of radial artery diameter: Two-dimensional ultrasound was performed to measure the luminal inner radial arterial diameter at 1–2 cm proximal to the styloid process before the transradial procedure using a 6-13 MHz transducer with a Vivid q (GE Healthcare Japan, Tokyo) before the initial measurement of RH-PAT.

Transradial cardiac catheterization: The radial artery was cannulated with a 17-cm-long sheath (Super Sheath, MEDIKIT Co. Ltd., Tokyo). The sizes were non-6-Fr sheaths for coronary angiography (CAG) and 6-Fr sheaths for percutaneous coronary interventions (PCI). The external diameter of the sheath was 1.88 mm/4-Fr, 2.20 mm/5-Fr, and 2.50 mm/6-Fr. After sheath insertion, 2,000-7,000 IU of unfractionated heparin was injected to prevent thrombosis through the side-arm of the sheath. At the end of the procedure, the sheath was removed immediately, and hemostasis was achieved in the catheterization laboratory by a compression device. The patients were mobilized instantly, and the compression device

was removed after 4 to 6 hours. Sheath insertion into the radial artery was performed once for each patient in this study.

Measurement of blood samples: Venous blood samples were withdrawn from the forearms of all patients, who had fasted overnight. Total LDL- and HDL-cholesterol, triglycerides, creatinine, and HbA1c (NGSP) levels were measured at our hospital using routine laboratory techniques. The estimated glomerular filtration rate (eGFR) was calculated as follows: $194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094}$ (if female, $\times 0.739$).

Study protocol: RH-PAT was measured before, the day after, and 6 months after the cardiac catheterization. As shown in Figure 1, 16 patients in the 6-Fr group and 13 patients in the non-6-Fr group underwent repeat RH-PAT 6 months after the catheterization.

Statistical analysis: Continuous variables are expressed as the mean \pm standard deviation, whereas categorical variables are given as numbers (percentages). Comparisons between groups were performed using the Mann-Whitney *U* test for continuous variables and Pearson's chi-squared test for categorical variables. Comparisons of data across the 2 time points were conducted using the Wilcoxon signed-rank test. $P < 0.05$ was considered significant. Statistical analysis was performed using SPSS version 18 (IBM Corp., Somers, NY).

RESULTS

The clinical characteristics of the patients are reported in Table I. There were no significant clinical differences between the two groups. Likewise, no significant differences in RH-PAT, radial artery diameter, and frequency of inserting the sheath were observed before the catheterization, while the procedure time of catheterization was significantly longer in the 6-Fr group than in the non-6-Fr group (Table II).

RH-PAT values did not change significantly between be-

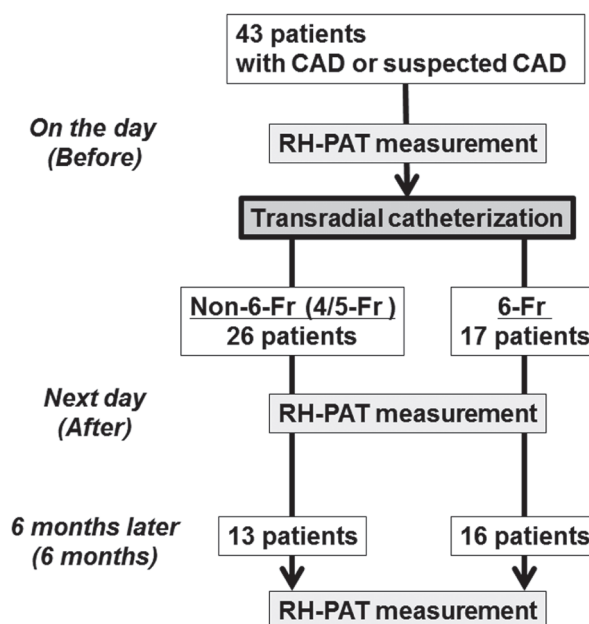


Figure 1. Study design. CAD indicates coronary artery disease; and RH-PAT, reactive hyperemia peripheral arterial tonometry.

Table I. Clinical Characteristics of the Study Population

	Non-6-Fr (n = 26)	6-Fr (n = 17)	P
Gender (male)	21 (81%)	14 (82%)	0.90
Age (years)	65 ± 11	66 ± 9	0.61
Hypertension	19 (73%)	10 (59%)	0.33
Diabetes	10 (38%)	6 (35%)	0.83
Dyslipidemia	20 (77%)	15 (88%)	0.35
Current smoking	4 (15%)	4 (24%)	0.50
Body mass index (kg/m ²)	24.8 ± 4.5	25.2 ± 2.9	0.72
eGFR (mL/minute/1.73 m ²)	64.8 ± 17.3	66.9 ± 11.7	0.65
HbA1c (%)	6.3 ± 1.0	6.1 ± 0.6	0.45
Triglycerides (mg/dL)	135 ± 79	379 ± 893	0.34
HDL cholesterol (mg/dL)	44 ± 11	40 ± 11	0.27
LDL cholesterol (mg/dL)	92 ± 26	95 ± 26	0.72

eGFR indicates estimated glomerular filtration ratio; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

Table II. Peripheral Endothelial Function and the Characteristics of Catheterization

	Non-6-Fr (n = 26)	6-Fr (n = 17)	P
RH-PAT, sheath side	2.22 ± 0.56	2.42 ± 0.67	0.47
RH-PAT, non-sheath side	2.33 ± 0.63	2.42 ± 0.45	0.70
Frequency of inserting the sheath	1.96 ± 1.87	1.59 ± 0.80	0.44
Radial artery diameter (mm)	2.9 ± 0.5	2.7 ± 0.3	0.13
Procedure time (minutes)	42.5 ± 21.0	88.2 ± 27.7	< 0.001

RH-PAT indicates reactive hyperemia peripheral arterial tonometry.

fore and the day after catheterization in the non-6-Fr group (from 2.22 ± 0.56 to 2.08 ± 0.61 ; $P = 0.133$), while the values decreased significantly from 2.42 ± 0.67 before catheterization to 2.08 ± 0.41 the day after catheterization in the 6-Fr group ($P = 0.031$) (Figure 2A and B). In both groups, the RH-PAT values of the non-sheath side arm were unchanged (Figure 2A and B). The patients in the 6-Fr group were divided into two groups according to the procedure time, using 91 minutes (the median value in this study) as the cut-off. RH-PAT values decreased significantly after catheterization in the group with procedure time > 91 minutes, while there was no significant difference in the group with procedure time ≤ 91 minutes (Figure 2C).

Table III shows the changes in the lipid profile, HbA1c, and smoking status for 6 months. There were no significant differences between baseline and 6 months, as well as between the non-6-Fr and 6-Fr sheath groups at baseline and 6 months after the procedure. RH-PAT values in the non-6-Fr sheath group were not significantly different among the measurements at baseline, the day after, and 6 months after catheterization (2.17 ± 0.33 , 2.02 ± 0.46 , and 2.27 ± 0.63 , respectively; Figure 3A). In contrast, the decreased RH-PAT values the day after the procedure in the 6-Fr sheath group tended to be sustained until 6 months after catheterization (2.47 ± 0.68 , 2.12 ± 0.41 , and 2.18 ± 0.45 at baseline, the day after, and 6 months after catheterization, respectively; Figure 3B), although the difference between baseline and 6 months was not significant. This change was more evident in patients with procedure time > 91 minutes, but the difference in RH-PAT values between baseline and 6 months was not significant (Figure 3C).

DISCUSSION

In the present study, it was found that 6-Fr sheath insertion into the RA caused vascular endothelial dysfunction as assessed by RH-PAT, which occurred the day after the procedure and did not completely recover for 6 months. In addition, the dysfunction was more evident in patients with a longer procedure time (> 91 minutes).

The RA approach for coronary procedures has gained increasing acceptance and has become a standard because of easy hemostasis, fewer access site complications, and improved patient convenience, with earlier ambulation than with the transfemoral approach.²² Nevertheless, the insertion of the radial sheath induces vascular endothelial damage.

Vascular endothelium plays a key role in the regulation of vascular tone, angiogenesis, and vascular remodeling through the release of vasoactive mediators.^{23,24} The dysfunction may contribute to intimal hyperplasia and subsequent lumen occlusion. Measurement of FMD by ultrasound is an established and widely used noninvasive method for assessing endothelial function. Previous reports have demonstrated endothelial dysfunction caused by the transradial approach using FMD measurement. Heiss, *et al*²⁵ showed that significant decreases of FMD in both the RA and brachial artery were observed 6 hours after transradial approach coronary angiography even with a 5-Fr sheath, which was sustained after 24 hours in smokers, but not non-smokers. Regarding the duration of the endovascular dysfunction, a significant impairment of FMD ($5.4\% \pm 4.0\%$ at baseline versus $2.8\% \pm 2.1\%$ at 2 days) was sustained at 1 month, but it had recovered by 4 months.²⁶ Another report showed that FMD decreased significantly the day after transradial catheterization with a 6-Fr sheath and recov-

ered within 3 months.⁶⁾ The present results the day after catheterization agree with these previous reports, but vascular function in the present patients was not completely recovered after 6 months. This might be due to the difference in the method of evaluating vascular function (FMD versus RH-PAT) and/or patients' background characteristics, such as race, physical constitution, and subclinical atherosclerotic conditions.

The associations between FMD and RH-PAT reported have been varied, from no significant correlation to significant weak/moderate correlations.^{17,27-30)} FMD measures the hyperemic response in a large conduit vessel with stimulus of the release of the occlusion cuff, which increases shear stress.³¹⁾ Therefore, this dilatation has been shown to be predominantly nitric oxide (NO)-mediated.³²⁾ In contrast, RH-PAT measures

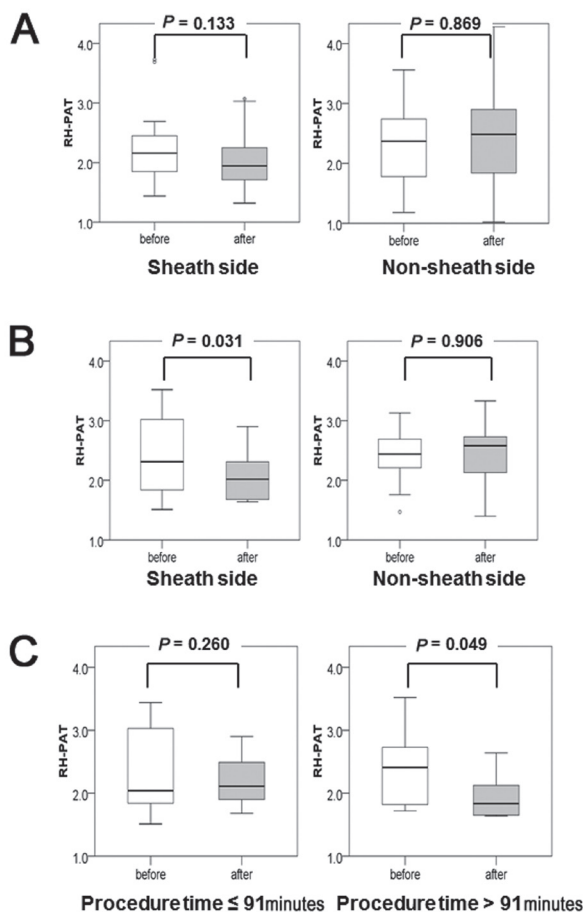


Figure 2. Comparisons of the values of reactive hyperemia peripheral arterial tonometry (RH-PAT) between before and the day after catheterization. RH-PAT values are comparable between the two measurements in the non-6-Fr group ($n = 26$) (A), while they are significantly decreased on the day after catheterization in the 6-Fr group ($n = 17$) (B). In the 6-Fr group, a significant decrease is seen in the patients who underwent the procedure for more than 91 minutes ($n = 9$). Before indicates before the transradial procedure; and after, the day after the transradial procedure.

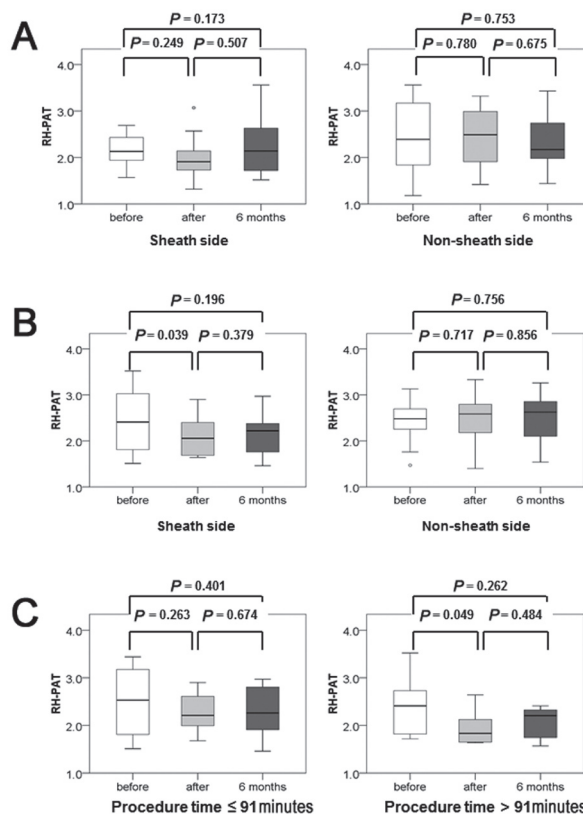


Figure 3. Comparisons of the values of reactive hyperemia peripheral arterial tonometry (RH-PAT) among before, the day after, and 6 months after catheterization. RH-PAT values are comparable among the three measurements in the non-6-Fr group ($n = 13$) (A). In the 6-Fr group, RH-PAT values decrease significantly on the day after catheterization and do not recover after 6 months ($n = 16$) (B). This change is more evident in the patients with procedure time > 91 minutes, but the values do not differ significantly between baseline and 6 months (C) (8 patients in each group). Before indicates before the transradial procedure; after, the day after the transradial procedure; and 6 months, 6 months after the procedure.

Table III. Changes in the Lipid Profile, HbA1c, and Smoking Status From Baseline to 6 Months After Transradial Catheterization

	Non-6-Fr ($n = 13$)			6-Fr ($n = 16$)			Non-6-Fr versus 6-Fr (P)	
	baseline	6 months	P	baseline	6 months	P	baseline	6 months
Triglycerides (mg/dL)	188 ± 134	188 ± 134	0.32	377 ± 918	180 ± 134	0.72	0.48	0.51
HDL cholesterol (mg/dL)	41 ± 10	41 ± 9	0.66	43 ± 13	43 ± 12	1.00	0.95	0.81
LDL cholesterol (mg/dL)	87 ± 32	82 ± 25	0.18	91 ± 30	90 ± 29	0.59	0.57	0.35
HbA1c (%)	6.4 ± 0.8	6.3 ± 0.7	0.32	6.1 ± 0.8	6.1 ± 0.8	1.00	0.34	0.38
Current smoking	2 (15%)	1 (8%)	0.54	3 (19%)	1 (6%)	0.60	0.29	0.70

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein, and HbA1c, hemoglobin A1c.

the response to reactive hyperemia in a vasculature bed of the digits, which is a combination of macro and micro-circulations.¹⁸⁾ This response was blunted by infusion of an endothelial NO synthase inhibitor, suggesting that the increase in digital pulse amplitude is partly dependent on flow-mediated release of NO.³³⁾ Thus, there are some differences between them, such as vascular size/site measured and dependency on a NO-mediated mechanism. Using RH-PAT, Serafino, *et al* demonstrated that peripheral endothelial function decreased at 24 hours and was restored at 30 days after 6-Fr transradial catheterization.³⁴⁾ The patients in their study also showed an early recovery of vascular function compared to the patients in the 6-Fr group of the present study. The difference might be due to the procedure time. Because the present patients in the 6-Fr group mainly underwent PCI, the procedure time with the 6-Fr sheath was approximately 2 times longer than that of Serafino's report (88.2 ± 27.7 versus 44 ± 12 minutes, respectively). The adverse structural remodeling with the transradial approach is considered to be related to sheath indwelling time, repeated sheath insertion, and sheath size. A longer procedure time may impair vascular endothelial function. However, few reports about the relationship between the procedure time of transradial catheterization and endothelial function were found.

The size of the sheath is also an important factor related to radial artery damage. A study using two-dimensional ultrasound showed that radial artery occlusion was associated with coronary intervention using a larger size sheath (≥ 6 -Fr) than diagnostic angiography using a 5-Fr sheath.⁴⁾ Abe, *et al*³⁵⁾ showed that placement of a 6-Fr system during transradial interventions resulted in a decreased RA diameter at 3-month follow-up. In contrast, the use of 5-Fr sheaths for transradial access significantly decreased the rate of radial arterial occlusion by 55%, compared with 6-Fr sheaths.³⁶⁾ Furthermore, a report using IVUS showed a reduced lumen diameter due to intima-media thickening after transradial intervention with 6-Fr sheaths, and repeated access enhanced this phenomenon.¹⁰⁾ These results suggest that smaller size is better for reducing vascular injury. The present results also showed that a non-6-Fr size sheath had no significant effect on vascular function assessed by RH-PAT with a similar frequency of sheath insertion compared to a 6-Fr size sheath.

This study had a number of limitations. There was a small number of patients in each group from a single center, and not all patients were evaluated at 6 months. The reason was that the catheterization was only for CAG in the non-6-Fr group, while coronary intervention was done in the 6-Fr group. Therefore, half of the patients in the non-6-Fr group were not required to undergo repeat CAG after 6 months when they did not have a significant stenosis in their coronary arteries. There were some differences in the severity of coronary artery stenosis between the two groups, and the possibility of differences in subclinical atherosclerotic lesions and risks cannot be excluded. However, the patient characteristics, ankle-brachial index, and cardio-ankle vascular index (data not shown) at baseline were comparable between the non-6-Fr and 6-Fr groups. In addition, RH-PAT values in the non-sheath side (control side) were not significantly different for 6 months, which means that clinical factors other than the sheath insertion may have a smaller contribution to RH-PAT measurement. A small number of patients in the 6-Fr group might contribute to the lack of significant differences between baseline and after 6

months (Figure 3B and C) and make it difficult to identify which factor, sheath size or procedure time, had a more harmful effect on endothelial function. The mechanical and functional localized effects, such as hematoma and arterial spasm, that were not clinically relevant may also have affected the measurement of RH-PAT. The patients were divided into two groups according to the median value of procedure time, indicating that the length of procedure required to damage endothelial function was not determined. Future longitudinal, prospective, randomized studies involving a large cohort are needed to address these issues.

Conclusions: Transradial catheterization with a 6-Fr sheath results in depressed vascular endothelial function as assessed by RH-PAT in the catheterized arm, and it was present the day after the procedure and was sustained for 6 months. The effect was more evident in patients with a longer procedure time (> 91 minutes). It is important to pay attention to the size of the sheath and the procedure time to avoid damaging vascular function when performing transradial catheterization.

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