Endothelial dysfunction and the occurrence of radial artery spasm during transradial coronary procedures: the ACRA-Spasm study

Dirk J. van der Heijden[1], MD; Maarten A.H. van Leeuwen[1], MD;
Gladys N. Janssens[1], MD, MSc; Jailen Hermie[1], MD; Mattie J. Lenzen[2], PhD;
Marco J.P.F. Ritt[3], MD, PhD; Peter M. van de Ven[4], PhD, MSc, MA;
Ferdinand Kiemeneij[1], MD, PhD; Niels van Royen[1]*, MD, PhD

1. Department of Cardiology, VU University Medical Center, Amsterdam, The Netherlands; 2. Department of Cardiology, Erasmus MC, Thoraxcenter, Rotterdam, The Netherlands; 3. Department of Plastic, Reconstructive Surgery and Hand Surgery, VU University Medical Center, Amsterdam, The Netherlands; 4. Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

D.J. van der Heijden and M.A.H. van Leeuwen contributed equally to this manuscript.

KEYWORDS

• endothelial dysfunction
• peripheral artery tone
• radial artery spasm

Abstract

Aims: The aim of this study was to analyse the relation between endothelial dysfunction (ED) and the occurrence of radial artery spasm (RAS) during transradial coronary procedures.

Methods and results: From May 2014 to June 2015, endothelial function was assessed by EndoPAT and FMD before the procedure in 165 patients referred for coronary angiography or intervention. The primary endpoint was RAS, defined by patient's symptoms and procedural characteristics. The mean age of the study population was 63 years and 71% were male. In total 16% of the patients experienced RAS. The incidence of RAS did not differ between patients with and without ED (13.8% vs. 20.2%, OR 0.63, 95% CI: 0.25-1.58, p=0.32). The strongest predictors of RAS were a ratio of radial artery inner diameter and sheath outer diameter smaller than 1 (OR 4.7, 95% CI: 1.35-16.5, p=0.009) and a combination of clinical characteristics presented as an RAS risk score of at least 4 (p=0.007, OR 3.7, 95% CI: 1.37-9.89).

Conclusions: Endothelial dysfunction was not found to be a predictor of the occurrence of radial artery spasm in a cohort of patients undergoing elective heart catheterisation. Radial artery-sheath mismatch is the strongest pre-procedural predictor of RAS.

*Corresponding author: Department of Cardiology, Room ZH-5F003, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: n.vanroyen@vumc.nl

Abbreviations

BMI	body mass index
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
DM	diabetes mellitus
ED	endothelial dysfunction
eNOS	endothelial derived nitric oxide synthase
NO	nitric oxide
OR	odds ratio
PAD	peripheral artery disease
PAT	peripheral arterial tonometry
PCI	percutaneous coronary intervention
PORH	post-occlusive reactive hyperaemia
RA	radial artery
RAID/SOD ratio	radial artery internal diameter/sheath outer diameter ratio
RAS	radial artery spasm
RHI	reactive hyperaemia index
SD	standard deviation
TFA	transfemoral approach
TRA	transradial approach
VAS	visual analogue scale

Introduction

Radial artery (RA) access has been used for coronary angiography and interventions since the late 1980s[1,2]. As a result of superior haemostasis of the superficially located artery, introduction of the transradial approach (TRA) has led to a reduction in access-site bleeding compared to the femoral approach[3,4]. One of the drawbacks of this technique is the occurrence of radial artery spasm (RAS). This often leads to patient discomfort, procedural failure and catheter friction which may lead to intimal wall injury of the radial artery[5-7]. The latter can lead to chronic changes of the vessel wall (intimal thickening) and even radial artery occlusion, hampering future procedures[8]. Some efforts have been made to identify predictors of RAS to prevent this complication[9-12]; however, the incidence of RAS is still high, varying between 4% and 20%[13].

The endothelium has a strong paracrine function and influences smooth muscle cell contraction in the vessel wall. The main characteristic of endothelial dysfunction (ED) is reduced production of nitric oxide (NO) by NO synthase (eNOS) and increased NO breakdown by reactive oxygen species[14]. This situation can result in paradoxical vasoconstriction to several stimuli. Endothelial dysfunction can be measured non-invasively and predicts future adverse cardiovascular events[15,16]. Several diagnostic tests are available: most of them are based on increased shear stress after post-occlusive reactive hyperaemia (PORH)[17]. One of these methods measures reactive hyperaemia in the fingertips by peripheral arterial tonometry (PAT) through the EndoPAT system (Endo-PAT2000; Itamar Medical Ltd., Caesarea, Israel), which has become widely recognised as a reliable method for endothelial function assessment and is a validated predictor of cardiovascular adverse events[18,19]. Because of an elevated vascular tone,

ED might be related to arterial spasm. Indeed, post-TRA transient endothelial dysfunction is detectable[20-23], but only one study has described ED before TRA as a predictor of RAS[24]. In this single study, only one type of endothelial function test was used and the RAS endpoint was defined as a combination of angiographic and clinical features.

We conducted a prospective study to explore the association between ED and a clinical definition of RAS in patients undergoing a transradial coronary procedure.

Methods

STUDY DESIGN AND POPULATION

We conducted this study in a high-volume academic PCI centre. Patients undergoing transradial heart catheterisation were selected for the study. Exclusion criteria were: a) inability to give informed consent; b) acute myocardial infarction; c) haemodynamic instability; d) TR approach within the last 30 days; e) expected transfemoral approach (previous coronary artery bypass grafting, chronic total occlusion, patient preference); f) renal failure with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m². A total of 796 patients referred for elective intervention were screened from May 2014 to June 2015. One hundred and sixty-five patients were eligible; most patients were not included because of logistic reasons (ambulance transport schedules to referral centres), exclusion criteria and competing studies. After informed consent was obtained, baseline characteristics were noted and pre-procedural flow-mediated dilatation (FMD) of the radial artery and EndoPAT measurements were performed. EndoPAT measurements of 23 patients were not analysable because of noisy signal quality.

The interventionalist was blinded to all study-related tests. The study protocol was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

ENDOPAT MEASUREMENTS

The EndoPAT device was used to measure the arterial pulse wave amplitude with pneumatic probes placed on the index finger of each hand, capable of sensing volume changes in the digit with each arterial pulsation. The contralateral hand was used as a reference to correct for potential systemic changes. Volume changes in the fingertip were recorded digitally as pulse amplitude and tracked over time. Brachial occlusion for a period of five minutes was achieved by inflating a blood pressure cuff at the brachium. The reactive hyperaemia index (RHI) was measured: this is the post-to-pre-occlusion PAT signal ratio on the occluded side, divided by the same ratio of the control arm, and further corrected for baseline vascular tone. An RHI with an outcome of <1.68 was considered as endothelial dysfunction[25].

FMD MEASUREMENTS

Measurements for achieving FMD were performed with a dedicated ultrasound machine (Sparq; Philips Medical Systems, Andover, MA, USA), using a broadband linear array L12-4

transducer. Ultrasound recordings were made in a cross-sectional view at 5 cm from the styloid process. After baseline measurement of the RA diameter, recordings of the radial artery were made for two to three minutes after occlusion by the pressure cuff, simultaneously with EndoPAT measurements. The maximal diameter at any time following the first few minutes after blood flow restoration was recorded. FMD was expressed as percentage change in radial artery diameter after cuff deflation, compared with the pre-inflation measurement. Measurements were performed by a single operator who was blinded to procedural outcomes.

TRANSRADIAL CORONARY PROCEDURE

All patients received local subcutaneous anaesthesia with 1% lidocaine in the relevant arm. TRA was achieved with a venous cannula technique, and a 6 Fr 10 cm long sheath (Terumo Corp., Tokyo, Japan) was positioned in the radial artery. A standard cocktail of 0.1 mg nitroglycerine and 2.5 mg verapamil was given intra-arterially to reduce spasm. In case of coronary angiography a standard dose of 5,000 IU of unfractionated heparin was given intra-arterially for thrombosis prevention. When a PCI was performed, the amount of unfractionated heparin was adapted to the patient's body weight. At the end of the procedure, the sheath was removed and a TR band haemostatic device (18 mL TR Band®; Terumo Corp.) was applied, according to the advised protocol of the manufacturer. Procedure characteristics were scored. After each procedure the operator was asked if there was resistance at catheter manipulation or at removal of the catheter or sheath. Patients were asked whether they felt pain in the forearm during the procedure. The amount of self-reported pain was measured on a visual analogue scale (VAS) from 0-10 ("no pain at all" was scored as 0 and "unbearable pain" as 10) at the end of the procedure and before discharge.

After sheath insertion and injection of 200 mg nitroglycerine and 5 mg verapamil the radial artery was used to perform heart catheterisation. To assess the presence of angiographic RAS, angiography was repeated just before sheath removal.

An access-site complication was defined as: vessel dissection and rupture, a haematoma more than 5 cm, pseudoaneurysm, arteriovenous fistula and localised infection. Radial artery occlusion was defined as a reverse Barbeau test type 3 or 4. The procedure was considered successful if the target lesion was treated with or without access-site conversion.

DEFINITIONS OF RADIAL ARTERY SPASM

Clinical RAS was defined as follows: persistent forearm pain (extending beyond the period of catheter manipulation), pain response to catheter manipulation (manoeuvres of the catheter other than withdrawal, such as rotation or small movements to obtain optimal catheter position), pain response to catheter withdrawal, difficult catheter manipulation after being "trapped" by the radial artery and considerable resistance on withdrawal of the sheath. Clinical RAS was present if there were two of the five

parameters. Angiographic RAS was defined as follows: the smallest diameter of the radial artery was measured, using the edge detection method by catheter calibration (Philips Xcelera 3.2; Philips Medical Systems, Eindhoven, The Netherlands), and compared to the same segment in the reference angiography. A reduction in diameter of more than 25% compared to the pre-procedural reference diameter was considered as angiographic radial artery spasm[26]. Combined RAS was defined as RAS with angiographic confirmation.

RADIAL ARTERY SPASM RISK SCORE

An RAS risk score was calculated for all patients. This score was recently published. It consists of five weighted risk factors for radial artery spasm: BMI less than 25 kg/m² (1 point), height less than 170 cm (1 point), current smoking (2 points), hypertension (2 points), PAD (3 points). A predefined score of 4 or more is related to a high risk of RAS[10].

RADIAL INTERNAL DIAMETER-SHEATH OUTER DIAMETER RATIO (RAID/SOD RATIO)

The radial artery internal diameter/sheath outer diameter ratio (RAID/SOD ratio) was considered abnormal when smaller than 1.0[27]. The baseline FMD radial artery diameter measurement was used as RAID, and SODs for 5, 6 and 7 Fr sheaths (Radifocus® Introducer II Transradial Kit; Terumo Europe, Leuven, Belgium) were, respectively, 2.29, 2.62 and 2.95 mm.

ENDPOINTS

The difference in clinical RAS occurrence between patients with and without endothelial dysfunction (measured with EndoPAT and FMD) was considered as the primary endpoint. Secondary endpoints were the difference in occurrence of combined RAS in patients with and without endothelial dysfunction (measured with EndoPAT and FMD).

STATISTICAL ANALYSIS

Baseline characteristics are tabulated separately for groups with and without clinical RAS. Continuous variables are presented as mean±standard deviation (SD) in case of a normal distribution and median (interquartile range [IQR]) otherwise. Categorical variables are expressed as frequencies (percentages). Continuous baseline characteristics were compared between groups using an independent samples t-test for normally distributed random variables and the Mann-Whitney test for variables that were not normally distributed. Normality was assessed using histograms and using estimates for skewness and kurtosis. Categorical variables were compared between groups using the chi-square test. All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant. A multivariable prediction model for occurrence of RAS was built using stepwise logistic regression with forward selection. Candidate predictors were defined as having a p-value <0.20 in univariate logistic regression analysis. To adhere to the rule of thumb of 10 events per variable, we restricted

the number of predictors to be included in the model to a maximum of three. The predictive value of RHI and FMD (as continuous variables) was tested using a ROC analysis. RHI was also tested in a chi-square test using the validated cut-off of 1.68. All statistical analyses were performed with SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

The mean age of the study population was 63±11 years and 71% were male. Sixteen percent of the patients experienced clinical radial artery spasm, and 27% had angiographic spasm. Clinical spasm confirmed by angiography (combined spasm) occurred in 5% of the patients. Clinical characteristics stratified into clinical RAS or no clinical RAS are presented in **Table 1**. There were no

differences in cardiovascular history, cardiovascular risk factors or medication between the two groups except for patient height.

PROCEDURAL CHARACTERISTICS

The procedure was successful in 98% of the cases. In three cases the access site had to be converted to the femoral artery; all conversions were related to radial artery spasm. Before catheter advancement, 99% of the patients received a radial artery cocktail and at least 5,000 IU heparin. Two patients had an access-site complication and two other patients experienced a procedural complication. Clinical RAS was not related to previous radial artery access, number of punctures, procedural time, contrast use or number of catheter changes. Patients in the clinical RAS group experienced significantly more pain during the procedure using the VAS pain scale **(Table 2)**.

MEASUREMENTS OF ENDOTHELIAL FUNCTION

The median RHI was 2.01 (IQR 1.48-2.28) in patients with clinical RAS and 1.75 (IQR 1.44-2.34) in those without clinical RAS (p=0.56). In univariate logistic regression analysis, RHI was not found to be associated with the presence of clinical RAS (OR 0.82, 95% CI: 0.71-2.10, p=0.46). The association was still not significant when the validated cut-off of RHI of 1.68 was used to define the presence of ED (OR 0.63, 95% CI: 0.25-1.58, p=0.32) **(Figure 1)**. The mean FMD in patients with clinical RAS was 12.9±13.8% compared to 13.8±11.2% in patients without clinical RAS (p=0.72). Using a previously proposed cut-off value for FMD of 2.95% found in a comparable study[24], no difference in clinical RAS was detected either (OR 1.88, 95% CI: 0.67-5.29, p=0.24). Also, a ROC analysis of FMD and continuous RHI values showed poor predictive performance of both tests for the occurrence of RAS (AUC=0.47 and AUC=0.55, respectively).
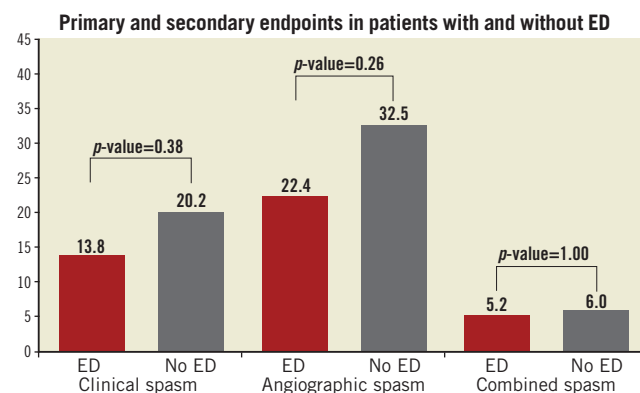
Table 1. Baseline characteristics stratified by occurrence of clinical radial artery spasm.

	No RAS (n=139)	RAS (n=26)	p-value
Mean age (years)	63±11	61±10	0.31
Male, n (%)	102 (73)	15 (58)	0.16
Height (cm)	176±9.2	171±9.0	0.036*
Weight (kg)	84±17.6	81±15.8	0.46
Cardiovascular history			
Previous MI, n (%)	27 (19)	4 (15)	0.79
Previous CABG, n (%)	1 (0.7)	0 (0)	1.00
Previous PCI, n (%)	35 (25)	8 (31)	0.63
Peripheral artery disease, n (%)	4 (3)	2 (8)	0.24
Cardiovascular risk factors			
Current smoking, n (%)	19 (14)	6 (23)	0.24
Hypertension, n (%)	59 (42)	13 (50)	0.52
Hypercholesterolaemia, n (%)	49 (36)	10 (39)	0.83
Family history, n (%)	54 (39)	15 (58)	0.09
DM, n (%)	24 (17)	5 (19)	0.78
BMI (kg/m²)	27.2±4.5	27.4±4.7	0.99
Medication			
Aspirin, n (%)	107 (77)	21 (81)	0.80
P2Y$_{12}$ inhibitor, n (%)	39 (28)	5 (19)	0.47
Oral anticoagulant, n (%)	19 (14)	7 (27)	0.14
ACE-I/ARB, n (%)	74 (53)	18 (69)	0.20
Beta-blocker, n (%)	103 (74)	17 (65)	0.35
Statin, n (%)	108 (78)	20 (77)	1.00
Nitrate, n (%)	32 (23)	2 (8)	0.11
Diuretic, n (%)	33 (24)	5 (19)	0.80
Calcium channel blocker, n (%)	37 (27)	11 (42)	0.16

Complicated procedure was defined and reported by the operator. *Statistically significant. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; DM: diabetes mellitus; IQR: interquartile range; MI: myocardial infarction; PCI: percutaneous coronary intervention; RAS: radial artery spasm

Primary and secondary endpoints in patients with and without ED

Figure 1. *Primary and secondary endpoints in patients with and without ED. The Y-axis represents the percentage of patients with radial artery spasm (RAS). The three different definitions of radial artery spasm are represented on the X-axis using three sets of bars. The red bar represents patients with endothelial dysfunction (ED); the grey bar represents patients without ED. ED is defined as an RHI value <1.68.*

Table 2. Procedural characteristics stratified by occurrence of clinical radial artery spasm.

		No RAS (n=139)	RAS (n=26)	*p*-value
Previous radial access, n (%)		40 (29)	4 (15)	0.23
PCI, n (%)		57 (41)	14 (54)	0.28
Number of punctions, median (IQR)		1 (1-2)	1 (1-2)	0.32
Access-site conversion		0 (0)	3 (12)	<0.001*
Catheter change, median (IQR)		1 (1-2)	2 (1-3)	0.21
Procedural time (min), median (IQR)		32 (20-49)	39 (25-50)	0.35
Procedural success, n (%)		135 (98)	26 (96)	0.50
Complicated procedure, n (%)		1 (1)	1 (4)	0.28
Complication access site		1 (1)	1 (4)	0.28
Contrast amount (ml), median (IQR)		120 (90-200)	150 (90-200)	0.54
VAS pain score, median (IQR)		0 (0-2)	4.5 (0-7)	<0.001*
Radial artery occlusion, n (%)		23 (19)	6 (30)	0.37
Angiographic data radial artery	Mean reference diameter (mm)	2.64±0.35	2.28±0.40	<0.001
	Mean minimal luminal diameter (mm)	2.01±0.56	1.67±0.53	0.008
	Mean diameter stenosis (%)	31.0±15.7	35.1±17.2	0.26

*Statistically significant. IQR: interquartile range; PCI: percutaneous coronary intervention; RAID/SOD ratio: radial artery internal diameter–sheath outer diameter ratio; VAS: visual analogue scale

ANATOMICAL MEASUREMENTS

There was a strong relation between mean RAID/SOD ratio and clinical RAS (no clinical RAS 0.96±0.20 compared to 0.84±0.17 with clinical RAS, p-value 0.003), and RAID/SOD ratio was a strong predictor when dichotomising the values using a validated cut-off <1.0 (OR 4.7, 95% CI: 1.3-16.5, p=0.01)[27].

RAS RISK SCORE

The mean RAS risk score was significantly higher in the clinical spasm group (2.5±1.8 versus 1.8±1.4 in the group without clinical RAS, p=0.03). When using the predefined cut-off (four or more points), there was a good clinical RAS prediction (OR 3.6, 95% CI: 1.4-9.9, p=0.01).

MULTIVARIATE ANALYSIS

Candidate predictors were determined by univariate analysis with p-values <0.2 (female gender, height, family history of CAD, RAS risk score and RAID/SOD ratio). In a forward selection of these candidate predictors for logistic multivariate analysis, only RAID/SOD ratio and the RAS risk score were found to be significant predictors of spasm. When analysed in a multivariate binary regression model, the RAID/SOD ratio <1 was found be the strongest predictor of RAS (OR 5.6, 95% CI: 1.5-21.2, p-value 0.01), followed by the RAS risk score (OR 3.0, 95% CI: 1.0-8.9, p-value 0.051) **(Figure 2)**.

SECONDARY ENDPOINTS

The secondary endpoints are shown in **Figure 1**. Endothelial dysfunction could not predict angiographic RAS or angiographic RAS combined with clinical RAS. We tested RHI, FMD, RAID/SOD ratio and RAS risk score for prediction of these two
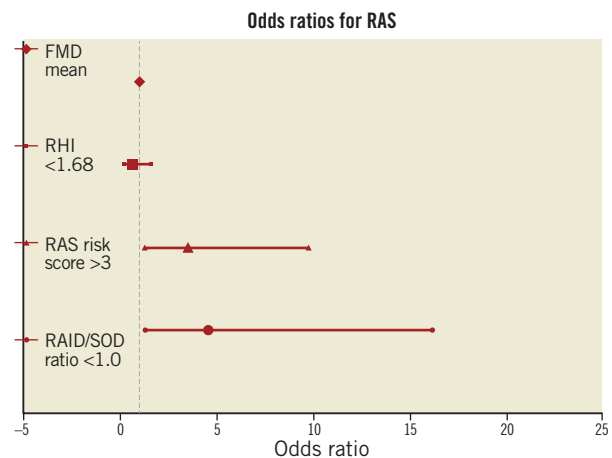
Figure 2. *Odds ratios for RAS. The X-axis resembles the odds ratios and 95% confidence intervals. FMD: flow-mediated dilation; RAID/SOD: radial internal diameter/sheath outer diameter; RAS: radial artery spasm; RHI: reactive hyperaemia index*

alternative definitions of RAS in a univariate and a multivariate analysis, but none of the candidate risk factors was found to be significantly associated with these outcomes. Also, the baseline and procedural variables **(Table 1, Table 2)** were not significantly different except for gender (more female patients with combined spasm).

Discussion

To our knowledge, this is the first study evaluating the relation between RAS and endothelial dysfunction, measured by EndoPAT. Endothelial dysfunction was not associated with the occurrence

of RAS and could not serve as a pre-procedural predictor. A RAID/SOD ratio <1 was the strongest predictor of RAS, followed by the RAS risk score.

Recently, one study evaluating patients with proven coronary artery disease reported a significant difference in pre-procedural FMD when RAS occurred[24], but we could not confirm this in our cohort, even when using different outcome definitions of radial artery spasm. Compared to this study, our population also consisted of patients without coronary artery disease and the percentage of diabetic patients was considerably lower. So, the high mean flow-mediated dilatation may reflect less endothelial dysfunction in our cohort and this may have influenced the outcome. Furthermore, our vasodilator cocktail consisted of nitroglycerine that was not given in the aforementioned study. Nevertheless, 40% of our patients had ED according to the validated EndoPAT cut-off value.

There are reports about varying correlations between FMD and RHI measurements in several populations[28-30], and there is an indication that EndoPAT and FMD are indicators of different vascular phenomena[31], but both tests seem to be indicative of cardiovascular outcome[33,34]. Nevertheless, in our heterogeneous population, pre-procedural endothelial function measured by either one of the two tests did not predict radial artery spasm.

The incidence of RAS reported in studies is highly variable and strongly influenced by the definition of RAS. We opted for clinical RAS as the primary endpoint, which is patient- and operator-dependent. Though this is a subjective endpoint, patient discomfort and procedural failure are of most clinical importance when RAS occurs. Although evaluating RAS by angiography may appear to be a more objective measurement, angiographic spasm is a very common finding (up to 75% of the cases), and there is a weak relation between angiographic spasm and procedural outcome[23]. One of the reasons could be the occurrence of diffuse spasm. Although we calculated the maximal diameter stenosis from the minimal luminal post-procedural radial artery diameter and the pre-procedural mean radial artery diameter, pre-procedural radial artery spasm (after sheath insertion) could have influenced our findings.

In our population, RAID/SOD mismatch and RAS risk score were the strongest predictors of clinical RAS. The correlation between known predictors of spasm (gender, height, weight) and radial artery diameter may indicate that mismatch of sheath size is a more important factor in the occurrence of RAS than subtle changes in smooth muscle cell function caused by endothelial dysfunction. Mechanical injury of the vessel inner wall through sheath insertion and catheter friction due to radial artery-sheath mismatch is very common in transradial coronary procedures[34]. The small impact of endothelial dysfunction compared to mechanical factors to predict RAS is reflected by the odds ratios of the different predictors **(Figure 2)**. Operator experience with TRA and volume load will minimise catheter manipulation and are known to prevent TRA failure due to RAS[35]. Downsizing coronary catheters and sheaths may further reduce radial artery spasm[36]. If large bore catheters are mandatory for a procedure, pre-procedural risk assessment by the RAS risk score and determination of sheath mismatch by ultrasound may identify patients at risk and help to choose the most favourable access approach. Such a strategy to prevent TRA procedural failure and patient discomfort has to be validated in future studies.

Conclusion

Endothelial dysfunction was not associated with the occurrence of RAS and could not serve as a pre-procedural predictor. However, RAS could be predicted by the validated RAS risk score and by radial artery/sheath mismatch.

Impact on daily practice

Endothelial dysfunction cannot be used as a predictor of RAS; however, other parameters can predict RAS (RAID/SOD ratio and RAS risk score).

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Campeau L. Percutaneous radial artery approach for coronary angiography. *Cathet Cardiovasc Diagn.* 1989;16:3-7.

2. Kiemeneij F, Laarman GJ, de Melker E. Transradial artery coronary angioplasty. *Am Heart J.* 1995;129:1-7.

3. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, Budaj A, Niemelä M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD, Chrolavicius S, Mehta SR; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet.* 2011;377:1409-20.

4. Bertrand OF, Rao SV, Pancholy S, Jolly SS, Rodés-Cabau J, Larose E, Costerousse O, Hamon M, Mann T. Transradial approach for coronary angiography and interventions: results of the first international transradial practice survey. *JACC Cardiovasc Interv.* 2010;3:1022-31.

5. Abdelaal E, Brousseau-Provencher C, Montminy S, Plourde G, MacHaalany J, Bataille Y, Molin P, Déry JP, Barbeau G, Roy L, Larose É, De Larochellière R, Nguyen CM, Proulx G, Costerousse O, Bertrand OF: Interventional Cardiologists at Quebec Heart-Lung Institute. Risk score, causes, and clinical impact of failure of transradial approach for percutaneous coronary interventions. *JACC Cardiovasc Interv.* 2013;6:1129-37.

6. Goldsmit A, Kiemeneij F, Gilchrist IC, Kantor P, Kedev S, Kwan T, Dharma S, Valdivieso L, Wenstemberg B, Patel T. Radial artery spasm associated with transradial cardiovascular proce-

dures: results from the RAS registry. *Catheter Cardiovasc Interv.* 2014;83:E32-6.

7. Mamas MA, Fraser DG, Ratib K, Fath-Ordoubadi F, El-Omar M, Nolan J, Neyses L. Minimising radial injury: prevention is better than cure. *EuroIntervention.* 2014;10:824-32.

8. Sakai H, Ikeda S, Harada T, Yonashiro S, Ozumi K, Ohe H, Ochiai M, Miyahara Y, Kohno S. Limitations of successive transradial approach in the same arm: the Japanese experience. *Catheter Cardiovasc Interv.* 2001;54:204-8.

9. Koga S, Ikeda S, Futagawa K, Sonoda K, Yoshitake T, Miyahara Y, Kohno S. The use of a hydrophilic-coated catheter during transradial cardiac catheterization is associated with a low incidence of radial artery spasm. *Int J Cardiol.* 2004;96:255-8.

10. Giannopoulos G, Raisakis K, Synetos A, Davlouros P, Hahalis G, Alexopoulos D, Tousoulis D, Lekakis J, Stefanadis C, Cleman MW, Deftereos S. A predictive score of radial artery spasm in patients undergoing transradial percutaneous coronary intervention. *Int J Cardiol.* 2015;188:76-80.

11. Rosencher J, Chaïb A, Barbou F, Arnould MA, Huber A, Salengro E, Jégou A, Allouch P, Zuily S, Mihoub F, Varenne O. How to limit radial artery spasm during percutaneous coronary interventions: The spasmolytic agents to avoid spasm during transradial percutaneous coronary interventions (SPASM3) study. *Catheter Cardiovasc Interv.* 2014;84:766-71.

12. Ruiz-Salmerón RJ, Mora R, Vélez-Gimón M, Ortiz J, Fernández C, Vidal B, Masotti M, Betriu A. [Radial artery spasm in transradial cardiac catheterization. Assessment of factors related to its occurrence, and of its consequences during follow-up]. *Rev Esp Cardiol.* 2005;58:504-11.

13. Ho HH, Jafary FH, Ong PJ. Radial artery spasm during transradial cardiac catheterization and percutaneous coronary intervention: incidence, predisposing factors, prevention, and management. *Cardiovasc Revasc Med.* 2012;13:193-5.

14. Arrebola-Moreno AL, Laclaustra M, Kaski JC. Noninvasive assessment of endothelial function in clinical practice. *Rev Esp Cardiol (English Ed).* 2012;65:80-90.

15. Suessenbacher A, Dörler J, Wanitschek M, F Alber H, Pachinger O, Frick M. Prognostic value of peripheral arterial tonometry in patients with coronary artery disease and a high cardiovascular risk profile. *J Atheroscler Thromb.* 2014;21:230-8.

16. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, Rigatto C, Komenda P, Sood MM, Tangri N. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging.* 2014;15:736-46.

17. Roustit M, Cracowski JL. Assessment of endothelial and neurovascular function in human skin microcirculation. *Trends Pharmacol Sci.* 2013;34:373-84.

18. Hamburg NM, Benjamin EJ. Assessment of endothelial function using digital pulse amplitude tonometry. *Trends Cardiovasc Med.* 2009;19:6-11.

19. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, Pumper GM, Lerman LO, Lerman A. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J.* 2010;31:1142-8.

20. Di Serafino L, Pyxaras SA, Mangiacapra F, Dierickx K, Toth G, Bartunek J, De Bruyne B, Van Mieghem C, Wijns W, Barbato E. Influence of transradial versus transfemoral diagnostic heart catheterisation on peripheral vascular endothelial function. *EuroIntervention.* 2013;8:1252-8.

21. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, Karas RH, Udelson JE. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J.* 2003;146:168-74.

22. Park KH, Park DW, Kim MK, Kim HS, Park WJ, Cho GY, Choi YJ. Effects of sheath injury and trimetazidine on endothelial dysfunction of radial artery after transradial catheterization. *J Interv Cardiol.* 2012;25:411-7.

23. Fukuda N, Iwahara S, Harada A, Yokoyama S, Akutsu K, Takano M, Kobayashi A, Kurokawa S, Izumi T. Vasospasms of the radial artery after the transradial approach for coronary angiography and angioplasty. *Jpn Heart J.* 2004;45:723-31.

24. Deftereos S, Giannopoulos G, Kossyvakis C, Driva M, Kaoukis A, Raisakis K, Theodorakis A, Panagopoulou V, Lappos S, Tampaki E, Pyrgakis V, Stefanadis C. Radial artery flow-mediated dilation predicts arterial spasm during transradial coronary interventions. *Catheter Cardiovasc Interv.* 2011;77:649-54.

25. Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *J Am Coll Cardiol.* 2004;44:2137-41.

26. Gorgulu S, Norgaz T, Karaahmet T, Dagdelen S. Incidence and predictors of radial artery spasm at the beginning of a transradial coronary procedure. *J Interv Cardiol.* 2013;26:208-13.

27. Saito S, Ikei H, Hosokawa G, Tanaka S. Influence of the ratio between radial artery inner diameter and sheath outer diameter on radial artery flow after transradial coronary intervention. *Catheter Cardiovasc Interv.* 1999;46:173-8.

28. Onkelinx S, Cornelissen V, Goetschalckx K, Thomaes T, Verhamme P, Vanhees L. Reproducibility of different methods to measure the endothelial function. *Vasc Med.* 2012;17:79-84.

29. Wilk G, Osmenda G, Matusik P, Nowakowski D, Jasiewicz-Honkisz B, Ignacak A, Cześnikiewicz-Guzik M, Guzik TJ. Endothelial function assessment in atherosclerosis: comparison of brachial artery flow-mediated vasodilation and peripheral arterial tonometry. *Pol Arch Med Wewn.* 2013;123:443-52.

30. Woo JS, Jang WS, Kim HS, Lee JH, Choi EY, Kim JB, Kim WS, Kim KS, Kim W. Comparison of peripheral arterial tonometry and flow-mediated vasodilation for assessment of the severity and complexity of coronary artery disease. *Coron Artery Dis.* 2014;25:421-6.

31. Lee CR, Bass A, Ellis K, Tran B, Steele S, Caughey M, Stouffer GA, Hinderliter AL. Relation between digital peripheral arterial tonometry and brachial artery ultrasound measures of vascular function in patients with coronary artery disease and in healthy volunteers. *Am J Cardiol.* 2012;109:651-7.

32. Charakida M, Masi S, Lüscher TF, Kastelein JJ, Deanfield JE. Assessment of atherosclerosis: the role of flow-mediated dilatation. *Eur Heart J.* 2010;31:2854–61.

33. Selamet Tierney ES, Newburger JW, Gauvreau K, Geva J, Coogan E, Colan SD, de Ferranti SD. Endothelial pulse amplitude testing: feasibility and reproducibility in adolescents. *J Pediatr.* 2009;154:901-5.

34. Yonetsu T, Kakuta T, Lee T, Takayama K, Kakita K, Iwamoto T, Kawaguchi N, Takahashi K, Yamamoto G, Iesaka Y, Fujiwara H, Isobe M. Assessment of acute injuries and chronic intimal thickening of the radial artery after transradial coronary intervention by optical coherence tomography. *Eur Heart J.* 2010;31:1608-15.

35. Pristipino C, Roncella A, Trani C, Nazzaro MS, Berni A, Di Sciascio G, Sciahbasi A, Musarò SD, Mazzarotto P, Gioffrè G, Speciale G; Prospective Registry of Vascular Access in Interventions in Lazio region (PREVAIL) study group. Identifying factors that predict the choice and success rate of radial artery catheterisation in contemporary real world cardiology practice: a sub-analysis of the PREVAIL study data. *EuroIntervention.* 2010;6:240-6.

36. Cheaito R, Benamer H, Hovasse T, Tritar A, Hage F, Garot P, Lefèvre T, Unterseeh T, Chevalier B, Morice MC, Louvard Y. Feasibility and safety of transradial coronary interventions using a 6.5-F sheathless guiding catheter in patients with small radial arteries. *Catheter Cardiovasc Interv.* 2015;86:51-8.