

Title: Radial Artery Dilatation to Improve Access and Lower complication rates during coronary angiography (RADIAL): A Randomized Controlled Trial.

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Radial Artery Dilatation to Improve Access and Lower complication rates during coronary angiography (RADIAL): A Randomized Controlled Trial

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The authors have no conflicts of interests to declare and no relationships with industry regarding this study.

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A consultant at the Biostatistics Unit within the Division of Epidemiology and Biostatistics, Stellenbosch University assisted with the design and analysis of this study through support from the Faculty of Medicine and Health Science's Dean's Fund.

Running title: Improving radial artery access



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3-Part Abstract:

Aims: To explore the use of prolonged occlusion flow mediated dilatation (PO-FMD) to dilate the radial artery prior to cannulation to increase cannulation success, reduce puncture attempts and reduce access site complications in transradial coronary angiography.

Methods and results: 1156 patients undergoing transradial coronary angiography were randomized into PO-FMD and sham PO-FMD groups. PO-FMD was achieved by a 10 minute inflation of a blood pressure cuff on the arm to above systolic pressure, followed by deflation with resultant radial artery dilation. In the sham PO-FMD group the cuff was not inflated. Operators were blinded to the intervention.

580 patients were randomized to the sham PO-FMD group and 576 to the PO-FMD group.

Cannulation failure was reduced with PO-FMD with cannulation failure rates of 2.7% in the PO-FMD group and 5.8% in the sham PO-FMD group ($p=0.01$). The number of puncture attempts were reduced with the use of PO-FMD, with a median of 1 attempt in the PO-FMD group and 2 in the sham PO-FMD group ($p<0.001$). Radial artery pulsation loss (RAPL) was reduced with PO-FMD with 1.4% in the PO-FMD group and 3.8% in the sham PO-FMD group ($p=0.02$).

Conclusion: PO-FMD reduces cannulation failure rates, decreases puncture attempts, and decreases RAPL during transradial coronary angiography.

Key Words: Other technique; Radial; Access site; Vessel occlusion

Condensed Abstract:

Prolonged occlusion flow mediated dilatation (PO-FMD) was used to dilate the radial artery prior to cannulation for coronary angiography to increase cannulation success, reduce puncture attempts and reduce complications. Cannulation failure was reduced with PO-FMD with failure rates of 2.7% in the PO-FMD group and 5.8% in the sham PO-FMD group ($p=0.01$). The number of attempts to cannulate the radial artery were reduced by using PO-FMD ($p<0.001$). Radial artery pulsation loss (RAPL) was reduced with PO-FMD with 1.4% in the PO-FMD group and 3.8% in the sham PO-FMD group ($p=0.02$).

Abbreviations:

RAS: Radial artery spasm

RAPL: Radial artery pulsation loss

RAO: Radial artery occlusion

FMD: Flow mediated dilatation

PO-FMD: Prolonged occlusion-flow mediated dilatation

PCI: Percutaneous coronary intervention

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Introduction:

Access to the coronary arteries has traditionally been obtained via the femoral arteries, the first transfemoral coronary angiogram being performed in 1958(1). Alternative access sites have since been explored with the first transradial coronary angiogram performed in 1989(2). Access via the radial artery has now been shown to be superior to femoral access with less major bleeding and vascular complications(3–8) , to be more cost effective with decreased hospital stay, improve patient satisfaction(3,9–11) and reduce all cause mortality(12). Transradial catheterization has therefore become the accepted standard of practice.

The transradial approach is however not without challenges and complications. Cannulation of the radial artery is technically more challenging, with a steep learning curve to become proficient in the procedure and with higher cannulation failure rates compared to the transfemoral approach(8)(13). Access difficulty may result in complications with an increase in the number of radial artery puncture attempts being reported to increase the occurrence of radial artery spasm (RAS)(14), radial artery pulsation loss (RAPL), radial artery occlusion (RAO), pain and discomfort(15).

One strategy to increase access success is to dilate the radial artery prior to cannulation. Various strategies can be used to achieve dilatation including sublingual or subcutaneous nitrates, hand exercises, hand warming, and flow mediated dilatation (FMD). Flow mediated dilatation is a physiological process whereby an artery is dilated by increasing the flow through it. This is usually achieved by inflation of a blood pressure cuff above the systolic pressure for a period of time with subsequent deflation to restore flow and dilate the vessel. Occlusion of the brachial artery for 5 minutes results in nitric oxide dependant dilatation of the artery distal to the occlusion during reperfusion(16) and is commonly used as a diagnostic tool to assess endothelial function(17–19). This nitric oxide dependant dilatation is short-lived and diminished in patients with atherosclerosis. However, prolonged occlusion times prior to restoring blood flow induces nitric oxide independent

FMD resulting in prolonged vasodilatation even in patients with hypercholesterolemia(16).

Compared to other methods available to dilate the radial artery FMD is cheap, easy to perform, needs minimal equipment with negligible risk making it an ideal strategy.

We explored the impact of prolonged occlusion flow mediated dilatation (PO-FMD) in augmenting radial artery cannulation success. The primary aim was to assess its impact on transradial cannulation failure rate. Secondary aims were to assess its impact on the number of radial artery puncture attempts and to evaluate its impact on rates of RAS, RAPL and RAO.

Methods:

All patients scheduled to undergo transradial coronary angiography at a single tertiary cardiac centre (Tygerberg Hospital), as indicated by their clinical condition, were considered for inclusion. Patients who had consented for coronary angiography were asked to participate in the study and informed consent was obtained from those wishing to participate. Patients undergoing emergency primary percutaneous coronary intervention (PCI), emergency rescue PCI, or who were haemodynamically unstable precluding ultrasound assessment and 10-minute occlusion for PO-FMD were excluded from participation. Recruitment was done from 1 April 2017 to 31 July 2018. The Health Research Ethics Committee of Stellenbosch University approved the study protocol and the study was funded by the Research fund of the Division of Cardiology, Department of Medicine, Stellenbosch University.

Baseline demographics were recorded on an anonymized case report form (age, sex, smoking habits, dyslipidaemia, hypertension, diabetes, weight, height and serum creatinine). The indication for coronary angiography and whether or not previous transradial coronary angiography had been performed was recorded. This data was captured by the cardiac technologists involved with the case.

Participants were allocated a study number in numerical order during recruitment and were randomly allocated into two groups, those in whom PO-FMD would be performed and those receiving sham PO-FMD (blood pressure cuff placed over the right brachial artery but the cuff was not inflated). Randomization was accomplished by a computer generated randomization scheme using the participant study numbers. Allocation was recorded on a confidential study log available only to the cardiac technologists, blinding patient and operator to group allocation. The computer generated randomization scheme allocated patients to groups in a random manner, minimizing bias, but blocked randomization into groups of 100, with an allocation ratio of 1:1, to ensure balanced numbers throughout the recruitment process.

Participants had an ultrasound of the radial artery to be cannulated performed prior to angiography. All ultrasound assessments were performed using a Logiq E ultrasound machine (General Electric, Boston, United States of America) with a 22 MHz probe. The radial artery internal diameter was measured 2-5 cm proximal to the styloid process. Cardiology fellows doing the assessments were blinded to group allocation.

In the PO-FMD group a blood pressure cuff was placed above the antecubital fossa of the arm to be cannulated. It was inflated to 50 mmHg above the patient's systolic blood pressure for 10 minutes after which the cuff was deflated and cannulation commenced. In the sham PO-FMD group a blood pressure cuff was placed above the antecubital fossa of the arm to be cannulated but not inflated. The PO-FMD/sham PO-FMD protocol was performed by the cardiac technologist involved with the case. The interventional cardiologists performing the radial artery puncture and subsequent angiogram were blinded from group allocation.

All study investigators were proficient in transradial coronary angiography. Investigators included cardiology trainees who had completed ≥ 50 radial cannulations. A palpation guided transradial cannulation was performed according to a strict protocol (addendum A). The number of puncture attempts, success or failure of cannulation, time to cannulation and occurrence of RAS was

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recorded. Number of radial artery puncture attempts was defined as the number of forward movements of the cannula in an attempt to cannulate the radial artery. A “patent haemostasis” protocol was followed after completion of the angiogram (addendum B)

After achieving haemostasis, and once the TR band had been removed, the radial artery was assessed again. The radial artery was palpated to determine whether RAPL had occurred (RAPL was defined as the inability to palpate the radial pulse). Ultrasound was then performed and the vessel diameter and the occurrence of RAO were recorded (RAO defined as the loss of radial artery pulsation on Doppler ultrasonography of the artery post procedure). If RAO occurred the mechanism of the occlusion was determined by ultrasound. The timing of this assessment could not be standardized but needed to occur prior to discharge.

Statistical analysis:

Sample size estimation was based on the assumption of a cannulation failure rate of 10% with a 50% reduction with the use of PO-FMD with beta error set at 20%, power at 80% and two-sided significance level of 0.05. The estimated sample size under these assumptions was n=864. Our sample size calculation was anticipated to be potentially unreliable. Cannulation failure rates are highly variable between centres with rates of <1% to >10% reported (8, 20, 21, 22). Local cannulation failure rates had not been previously studied in our centre but was estimated at 10% based on operator experience. Secondly the impact of PO-FMD could only be speculated on as it had not been used for this purpose previously. An interim analysis was performed to assess the need to adjust sample size. Due to lower than expected failure rates sample size was increased after the interim analysis with an assumption of a cannulation failure rate of 6% with a 50% reduction with the use of PO-FMD. Beta error and power was left unchanged. A one-sided 0.05 significance level was used after confirmation of the beneficial direction of the intervention effect following interim analysis. The estimated total sample size under these assumptions was n=1131 using a Z test with

unpooled variance. IBM SPSS version 25 was used to analyse the data. Non-parametric Mann-
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Whitney tests were used to compare non-normally distributed outcomes between the two treatment groups while independent samples t-tests were used to compare normally distributed variables between the two treatment groups. Pearson's chi square tests were used to compare categorical variables between treatment groups. Spearman's correlation analysis was used to investigate linear relationships between continuous variables that were not normally distributed.

Results:

1156 participants were enrolled into the study. 576 participants were randomized to the PO-FMD group and 580 into the sham PO-FMD group. 26 patients were excluded from the data analysis, 16 from the PO-FMD group and 10 from the sham PO-FMD group. Analysis was performed on 560 patients in the PO-FMD group and 570 patients in the sham PO-FMD group (figure 1). 6 were excluded due to a lack of clarity on which intervention (PO-FMD or sham PO-FMD) was performed on the patient as there was a discrepancy between the patients' group allocation according to the randomization plan and the group recorded on the case report form. 12 patients had femoral access performed from the start. 2 patients were excluded as there was a possible delay between performing PO-FMD and attempting cannulation. 4 patients had PO-FMD performed on the right arm but the left arm was cannulated. 2 patient's procedures were cancelled after randomization. The baseline demographics, cardiovascular risk profile and pre-procedural radial artery diameters were comparable between the sham PO-FMD and PO-FMD groups (table 1). Higher rates of smoking were noted in the PO-FMD group, otherwise there were no significant differences between the groups. 6 French sheaths were routinely used. 5 French sheaths were used in 27 cases, 13 in the PO-FMD group and 14 in the sham PO-FMD group.

Cannulation failure rates:

A reduction in cannulation failure was demonstrated with the use of PO-FMD with cannulation failure rates of 2.7% in the PO-FMD group and 5.8% in the sham PO-FMD group ($p=0.01$) (figure 2). These patients required crossover to the left radial or femoral approach. Cannulation failures were associated with smaller preprocedural radial artery diameters when compared to those in whom cannulation was successful ($p<0.001$).

Number of radial artery puncture attempts:

With the use of PO-FMD a reduction in the number of radial artery puncture attempts was demonstrated with a median number of puncture attempts of 1 in the PO-FMD group and 2 in the sham PO-FMD group (figure 3) ($p<0.001$).

A weak negative correlation was found between the preprocedural radial artery diameter and the number of puncture attempts needed to cannulate the radial artery (Spearman's rho -0.173, $p<0.001$ in the PO-FMD group and Spearman's rho -0.220, $p<0.001$ in the sham PO-FMD group) (figure 4).

Time to cannulation:

A reduction in cannulation time was demonstrated with the use of PO-FMD with a median time to cannulation of 61 seconds in the PO-FMD group and 66 seconds in the sham PO-FMD group ($p<0.008$) (table 2).

Complications:

When assessing for complications of radial artery cannulation in terms of RAS, RAPL and RAO we found that complication rates were low (table 3). No difference was found in RAS rates in the groups, 4.6% in the PO-FMD group and 4.3% in the sham PO-FMD group ($p=0.546$). PO-FMD reduced RAPL rates being, 1.4% in the PO-FMD group and 3.8% in the sham PO-FMD group ($p=0.02$). RAO occurred in 3.9% of patients in the PO-FMD group and 5.7% in the sham PO-FMD group. This did not

reach significance ($p=0.2$). When assessing the mechanism underlying the RAO all were found to be due to radial artery thrombosis.

Additional factors impacting on radial artery diameter, number of puncture attempts and cannulation failures:

Females were found to have a significantly smaller radial artery diameter than males with a mean of 2.05mm (SD 0.39mm) in females compared to 2.41mm (SD 0.46mm) in the males ($p<0.001$). There were also significantly more radial artery puncture attempts in females compared to males ($p=0.001$) with the median attempts in females being 2 compared to that of 1 attempt in males (figure 5) as well as higher cannulation failure rates in females (7.3%) as compared to males (2.6%) ($p<0.001$) (figure 6).

Hypertension had no effect on radial artery diameter or cannulation failure rates. Those with hypertension did however have significantly more radial artery puncture attempts than those without hypertension ($p=0.047$) with the median number of attempts 2 in those with hypertension and 1 in those without hypertension.

Diabetes had no effect on radial artery diameter or cannulation failure rates. Diabetes mellitus was associated with more radial artery puncture attempts ($p=0.038$).

Dyslipidaemia had no effect on radial artery diameter or cannulation failure rates. Dyslipidaemia was associated with more radial artery puncture attempts with a median number of attempts of 2 in those with dyslipidaemia and 1 in those without dyslipidaemia ($p=0.025$).

Age, serum creatinine, smoking and body mass index had no effect on radial artery diameter, number of puncture attempts or cannulation failure rates. 23 percent of patients had undergone a previous angiogram. This was not associated with a difference in radial artery diameter, number of puncture attempts or cannulation failure rates.

Discussion:

Transradial coronary angiography has become the standard access route in many centres throughout the world. Gaining access is however more challenging than the transfemoral approach.

The use of PO-FMD to dilate the radial artery prior to cannulation has proved to be an easily performed technique that improves access success with a reduction in the number of radial artery puncture attempts, decreased cannulation failure rates and reduced cannulation times. PO-FMD reduced the local complication of radial artery pulsation loss post cannulation.

The technique is non-invasive and needs no specialized equipment. PO-FMD cuff inflation can be started prior to the patient entering the catheterization laboratory and released as draping is completed and need not delay procedural start times, making it a feasible option in a busy cardiac catheterization laboratory. The use of PO-FMD is therefore an important consideration to augment radial artery access. While we were concerned about patient discomfort due to cuff inflation PO-FMD was remarkably well tolerated with no patients asking for the cuff to be removed. We don't foresee this being a limiting factor to its use if the technique is explained to patients.

Access success in transradial coronary angiography was high in this study with failure rates of 2.7% and 5.8% in PO-FMD and sham PO-FMD groups respectively. Access failure is however highly variable between centres with rates from <1% to >10% reported in different centres(8,20–22). We foresee PO-FMD's greatest utility to be in those patients with a high risk profile for access difficulty and with inexperienced operators, assisting in the steep learning curve of perfecting the technique. The risk factors for access difficulty identified in this trial were female gender, smaller radial arteries, hypertension, diabetes mellitus and dyslipidaemia.

The difficulty in cannulation in females may be related to their smaller radial arteries. Why hypertension, diabetes mellitus and dyslipidaemia lead to more puncture attempts is less clear. A possible explanation may be that the radial arteries of these patients are more sensitive to

developing spasm induced by the surrounding tissue trauma or that underlying atherosclerosis makes these vessels more difficult to cannulate.

PO-FMD should also be effective in augmenting radial artery access or puncture in other settings such as arterial line placement for invasive blood pressure monitoring or arterial blood gas sampling but that will need to be investigated in those settings.

PO-FMD did not prevent RAS. This may be due to the fact that the majority of spasm occurs, not while cannulating the vessel, but after completing cannulation of the vessel when the guidewire is being passed. By the time the guidewire is being passed the dilatation induced by PO-FMD may have worn off.

A reduction in RAPL was demonstrated. This finding is important in this group of patients where an absent radial pulse or occluded radial artery would prevent future transradial coronary angiograms and may prevent the vessels use for coronary artery bypass graft (CABG) or fistula creation in future. None of our patients had any ischaemic complications from the RAPL or RAO.

Although not demonstrated in our data, an association between the number of puncture attempts and RAO and RAPL has been found in another study (15).

Local access site complications were lower than expected from rates reported in the literature (8,23,24). RAPL occurred in 1.4% in the PO-FMD group and 3.8% in sham PO-FMD group. RAO occurred in 3.9% in the PO-FMD group 5.7% in the sham PO-FMD group. All RAO were caused by thrombus formation. These low rates were probably achieved due to few cannulation attempts, the use of intravenous heparin after cannulation, as well as a strict patent haemostasis protocol.

Study limitations:

It is a strength of this study that the cardiologists performing angiography were blinded to the radial artery size measured by ultrasound and to the pre-procedural intervention (PO-FMD vs sham PO-

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FMD) prior to gaining radial artery access. However, patients were aware if the blood pressure cuff was inflated or not prior to radial artery cannulation. It is possible that some of the patients could have made comments during the procedure about the inflation of the blood pressure cuff, alerting the cardiologist to fact that the patient was in the one group or the other. Patients undergoing coronary angiography in our unit routinely receive pre-medication and none of the investigators could recall a case where the patient provided information that could have unblinded the investigator. The post procedural assessment of the radial artery for RAPL and RAO was not blinded. To minimize bias all ultrasound assessments were recorded and cases of RAO were reviewed and confirmed by a second observer.

The degree of dilatation induced after PO-FMD was not evaluated in this study. This would have delayed the time from dilatation to trans-radial access and as the dilatation achieved is transient this delay could not be accommodated in the protocol. The study was based on the known phenomenon of nitric oxide independent dilatation of the arteries in the forearm following prolonged occlusion and hence quantifying its presence in this study was not considered essential. This limitation would have been important in a negative trial, but given the beneficial effect of PO-FMD on the number of puncture attempts, cannulation success and RAPL the concern about this potential limitation has been minimized.

Conclusion:

This study demonstrates that in units proficient in a transradial approach to coronary angiography, access success can be improved with decreased cannulation failures, puncture attempts and complications reduced with less RAPL by a simple and practical measure inducing PO-FMD of the radial artery prior to radial artery puncture. Overall success of transradial coronary angiography is however high and we foresee the most benefit for the use of PO-FMD in patients at risk of access failure.

Impact on daily practice:

Use of PO-FMD prior to radial artery puncture in patients undergoing transradial coronary angiography can be implemented without prolonging the procedure and will result in less cannulation failures, less puncture attempts and reduce RAPL. Overall success of transradial coronary angiography is however high and we foresee the most benefit for the use of PO-FMD in patients at risk of access failure.

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Tables:

Table 1: Patient demographics, cardiovascular risk profile and pre-procedural radial artery diameter.

	Sham PO-FMD (n = 570)	PO-FMD (n=560)	p-value
Demographics			
Age (mean, SD)	58.1 (11.3)	57.3 (11.8)	0.225
Male (n)	357 (62.6%)	361 (64.5%)	0.496
Female (n)	213 (37.4%)	199 (35.5%)	0.496
Cardiovascular Risk factors			
Smoking (n)	304 (53.3%)	334 (59.6%)	0.018
Hypertension (n)	368 (64.6%)	381 (66.8%)	0.314
Diabetes Mellitus (n)	181 (31.8%)	176 (32.5%)	0.977
Dyslipidaemia (n)	195 (34.2%)	174 (31.8%)	0.299
Body Mass Index (mean, SD)	29.6 (7.1)	29.2 (7.0)	0.426
Creatinine (mean, SD)	83.6 (23.6)	81.9 (24.5)	0.230
Radial artery diameter			
(mean, SD)	2.25mm (0.46)	2.30mm (0.47)	0.086
Previous transradial angiogram			
(n, percentage)	122 (21.4%)	109 (19.5%)	0.503

PO-FMD: Prolonged occlusion – flow mediated dilatation

Table 2: Time to cannulation success

		Sham PO-FMD	PO-FMD
Time to access (seconds)	Median	66	61
	Percentile 25	45	42
	Percentile 75	130	104

PO-FMD: Prolonged occlusion – flow mediated dilatation. p=0.008

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Table 3: Complication rates of radial artery access during coronary angiography

	Sham PO-FMD	PO-FMD	p-value
RAS	26 (4.6%)	24 (4.3%)	0.546
RAPL	19 (3.8%)	7 (1.4%)	0.020
RAO	28 (5.7%)	19 (3.9%)	0.200

PO-FMD: Prolonged occlusion – flow mediated dilatation, RAO: radial artery occlusion, RAPL: radial artery pulsation loss, RAS: radial artery spasm.

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Figures: Titles and legends

Figure 1: Flow chart illustrating the randomization and exclusion of participants in the trial

Figure 2: Cannulation failure rates

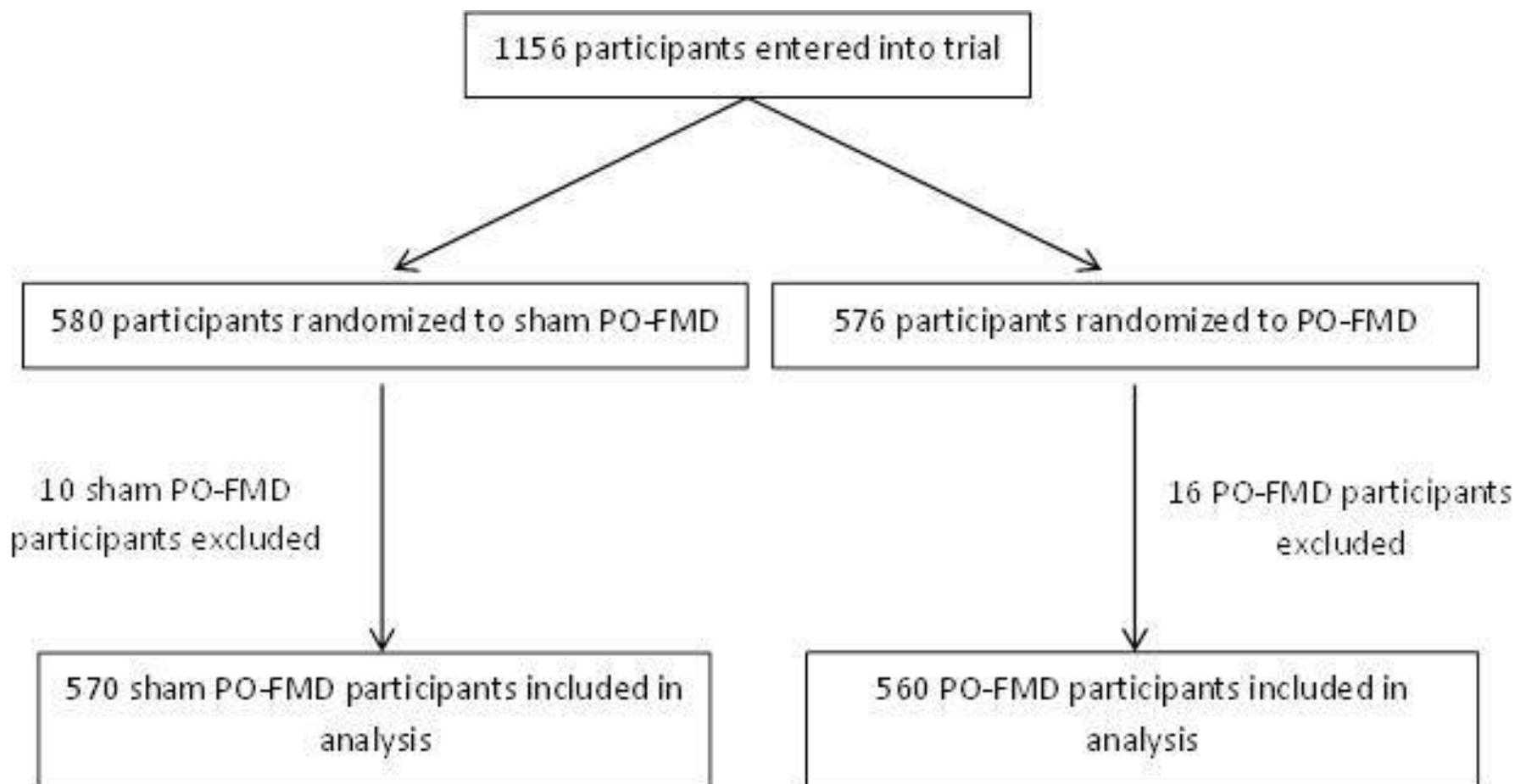
Figure 2: Number of radial artery puncture attempts to cannulate the radial artery.

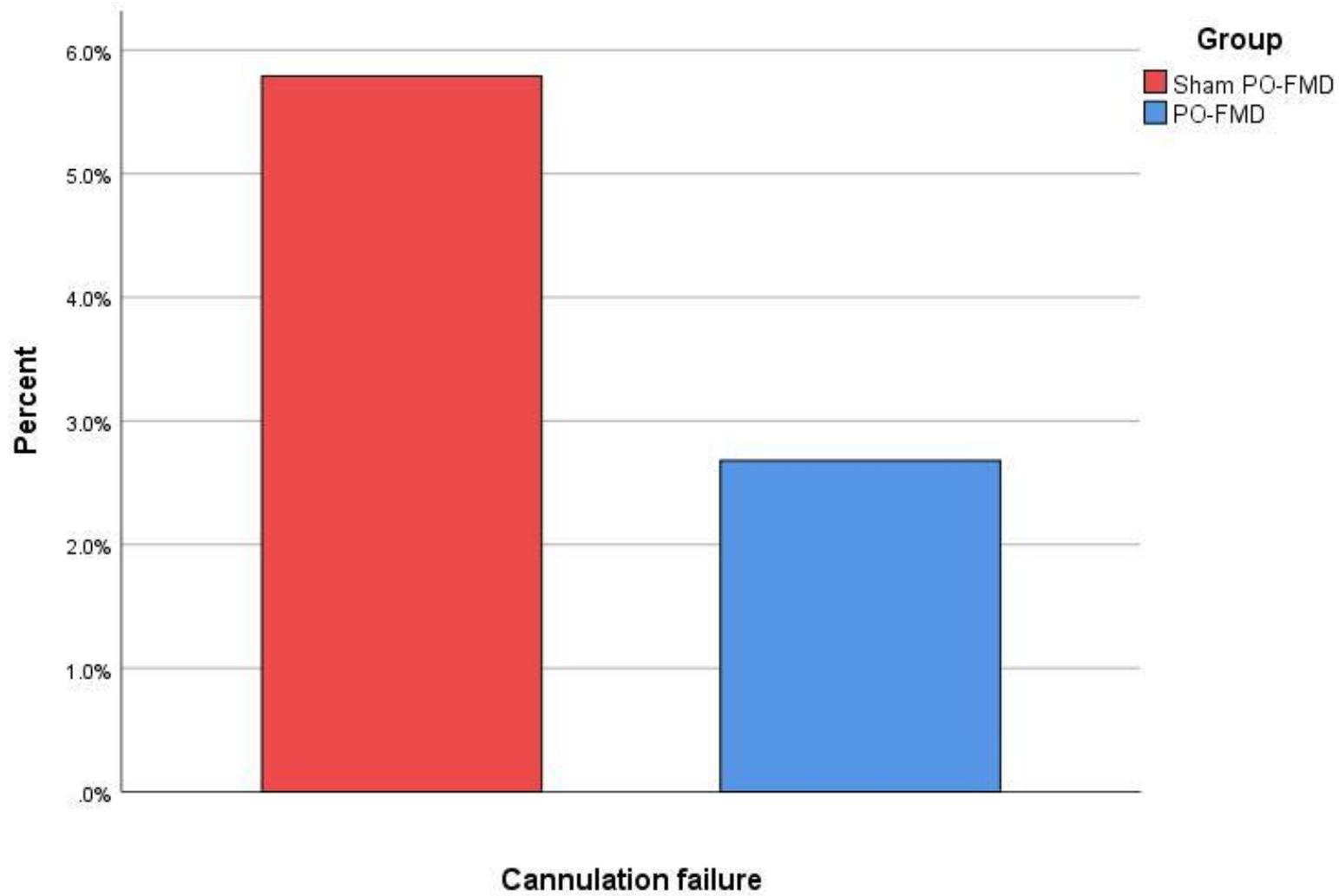
Figure 4: Correlation between the number of radial artery puncture attempts and radial artery diameter

Figure 5: Number of puncture attempts in females and males

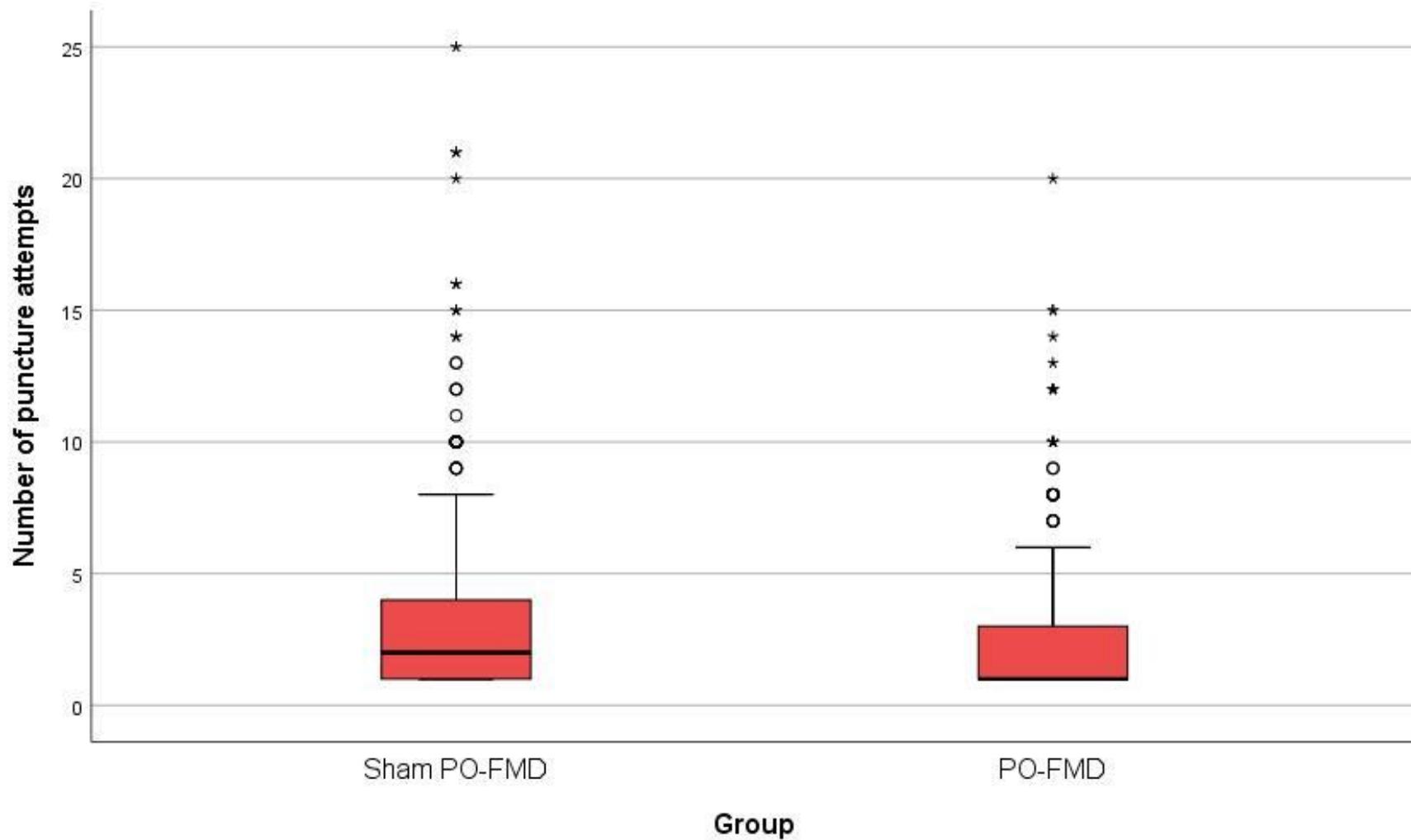
Figure 6: Cannulation failure rates in females and males

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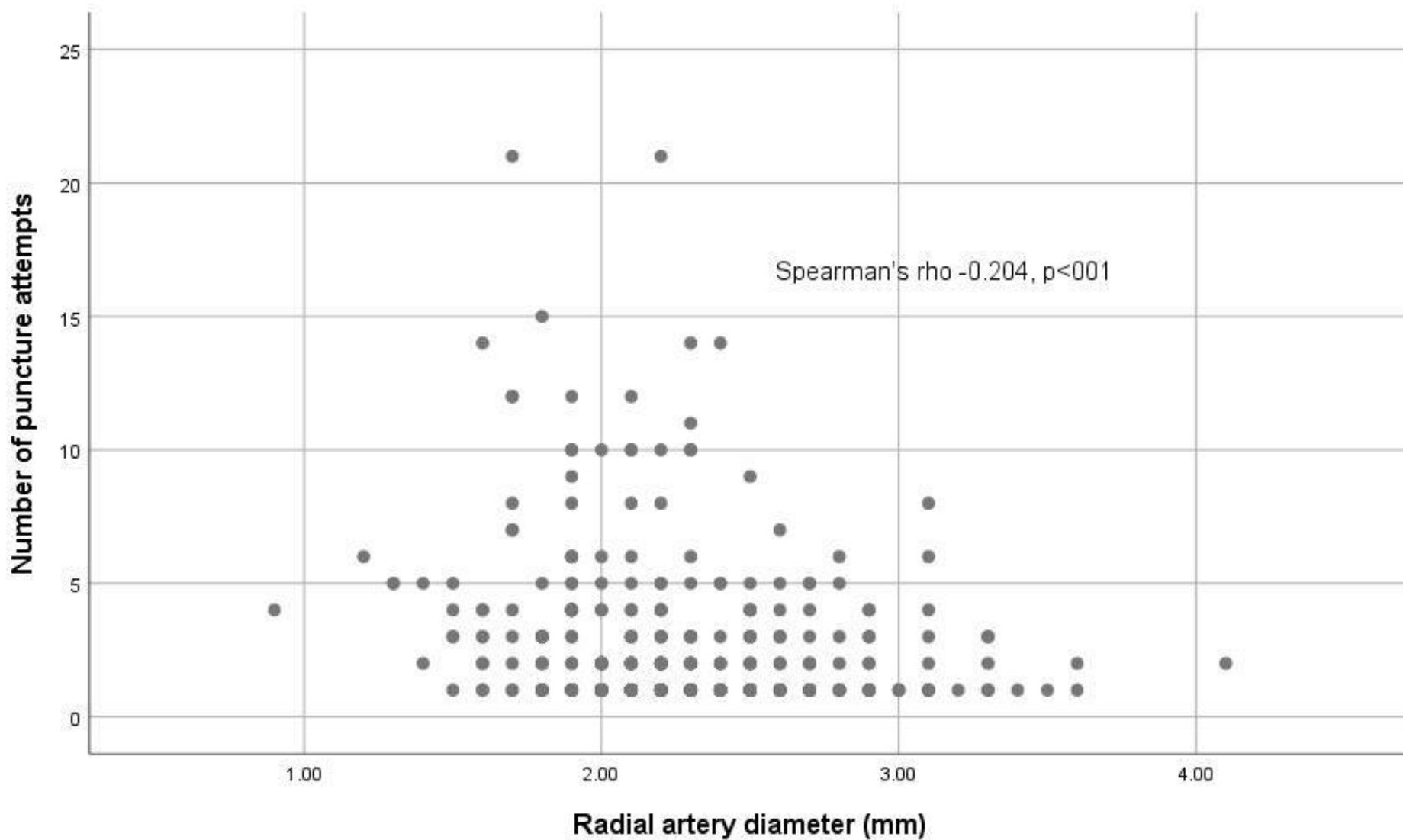




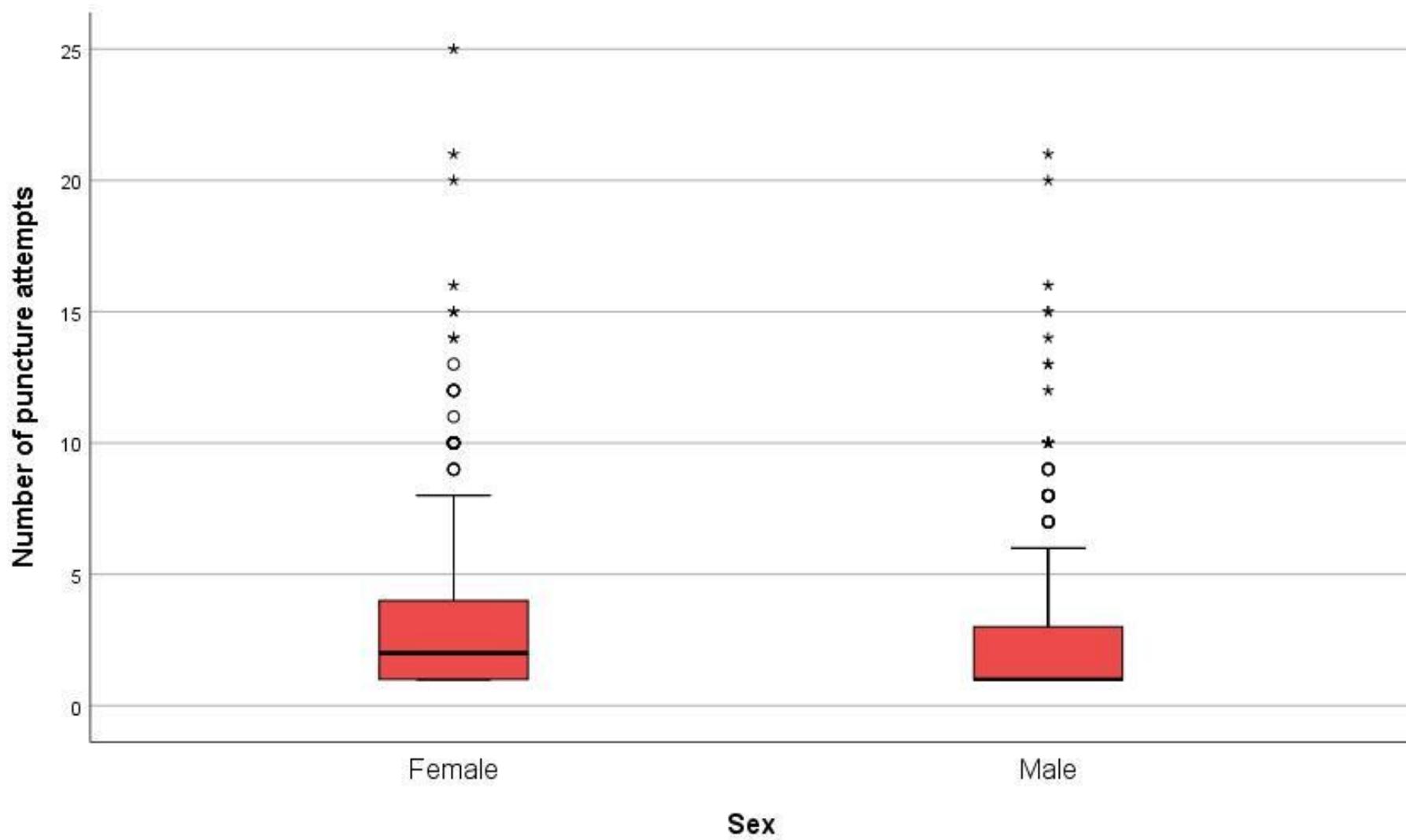
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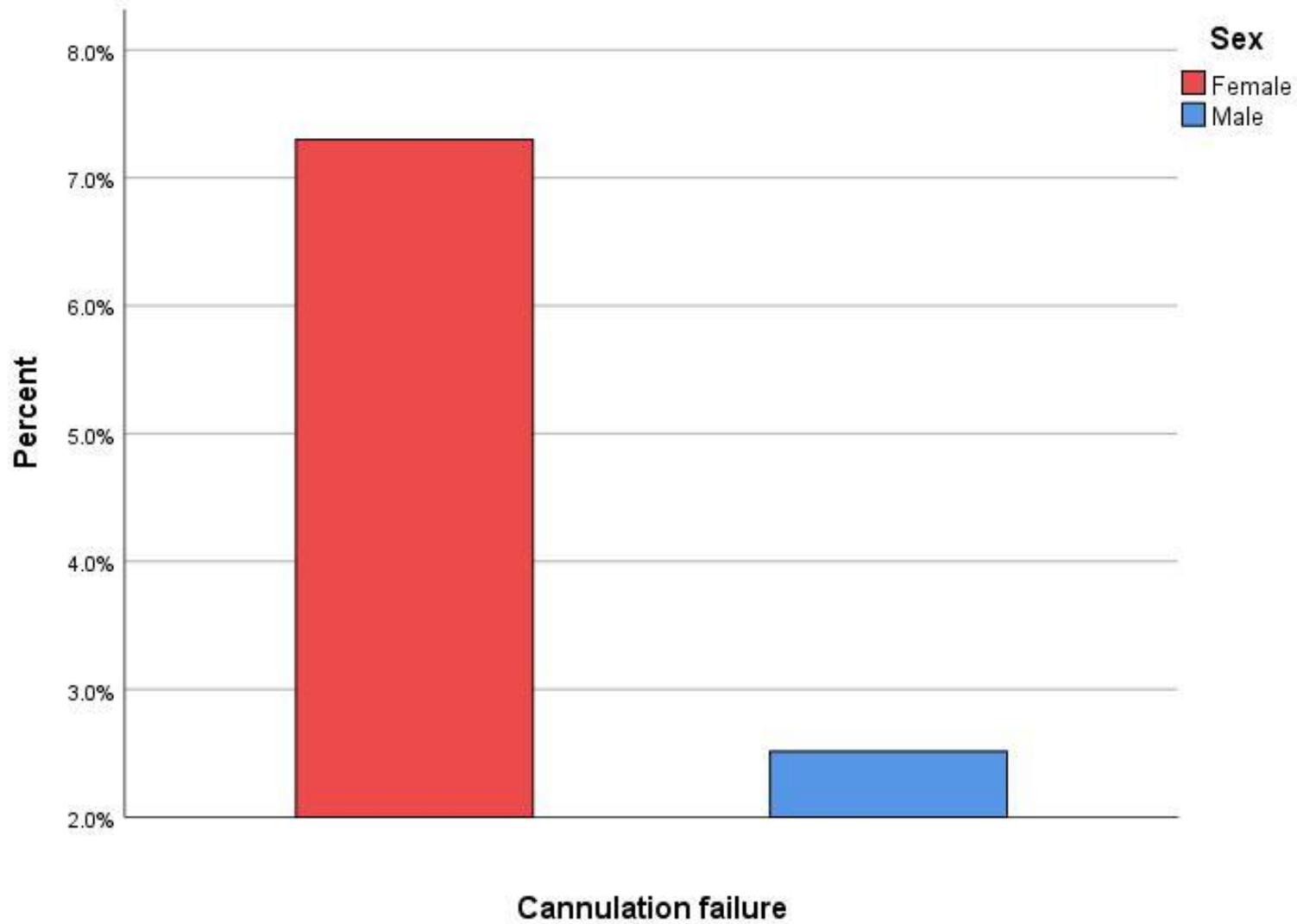
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APPENDIX

Addendum A:

The right (or left when this site was to be used) arm was placed on a custom designed radial artery angiography support (STARBoard, Adept Medical, Auckland, New Zealand) with the palm facing upward and the wrist in extension. Sterile drapes were placed for potential access to the right radial artery and right femoral artery. The radial artery was palpated to identify a puncture site 2- 5cm from the styloid process. The puncture site was infiltrated with 2% lignocaine (0.5 to 1ml) delivered as a subcutaneous bleb with a 2 ml syringe and 25-gauge needle). Radial artery access was gained with the Radifocus Introducer II KIT (Terumo Corporation, New York, United States of America). This includes a 20-gauge sheathed needle for the puncture. The needle is advanced at 45° until a flush of blood is noted via the needle. The needle is then advanced through the artery, the needle removed and the sheath carefully pulled back into the vessel to initiate pulsatile flow. A 0.025 hydrophilic guide-wire (45 cm length) is then carefully advanced into the vessel ensuring that there is no resistance. A small incision is made in the skin at the point of entry. The needle sheath is then removed, and a 6*-French hydrophilic dilator and sheath advanced into the radial artery over the guidewire. The dilator is removed and an anti-vasospastic cocktail, of 5mg verapamil and 200µg nitroglycerine diluted to 10 ml with 0.9% sodium chloride, is then injected into the vessel via the side-port. A standard J-tipped 0.032 guidewire is then inserted and the relevant catheter is guided into the aortic root. Prior to engaging the coronary arteries 5000IU unfractionated heparin was administered intravenously.

*Operators could use 5 French sheaths according to their discretion.

Addendum B:

A “patent haemostasis” protocol was followed. On completion of the procedure the sheath was withdrawn 4–5 cm and an inflatable plastic band (TR band, Terumo Corporation, New York, United States of America) was placed around the forearm at the site of entry. The TR band was then inflated with 15 ml of air as the sheath was removed. Air was slowly aspirated at 1ml increments from the TR band bladder until a spot of bleeding was noted at the puncture site. Two ml of air were then added and haemostasis confirmed. Once haemostasis was achieved, the band was left in place for 1 hour. At one hour and again at two hours an additional 2ml of air were removed from the TR band and the puncture site inspected to confirm that there was no bleeding. At three hours this was repeated with 4 ml of air being removed. If no bleeding occurred the TR band was removed.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	7
Methods Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7,8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7,8,9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8,9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9

	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8,9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9,10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	7,9

Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10,11,12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10,11,12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14,15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12,13,14,15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12,13,14,15
Other information			
Registration	23	Registration number and name of trial registry	S16/10/189 The Health Research Ethics Committee of Stellenbosch University
Protocol	24	Where the full trial protocol can be accessed, if available	The Health Research

Funding 25 Sources of funding and other support (such as supply of drugs), role of funders

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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