Original research

Peripheral Venous Dilation Using Flow-Mediated Dilation Response: A Randomized Crossover Study

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Competing interests

All authors declare that they have no conflict of interest.

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Author contributions

Conceptualization: Ryo Sekiguchi, Michiko Kinoshita, and Katsuya Tanaka; Methodology: Hiroya Endo, Ryo Sekiguchi, and Michiko Kinoshita; Investigation: Hiroya Endo, Ryo Sekiguchi; Analysis: Hiroya Endo, Ryo Sekiguchi, and Michiko Kinoshita; Project administration: Katsuya Tanaka; Writing – original draft preparation: Hiroya Endo; Writing – reviewing and editing: Ryo Sekiguchi, Michiko Kinoshita, and Katsuya Tanaka. All

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Abstract

Background: Venodilation is crucial in enhancing the success rate of peripheral intravenous cannulation. Flow-mediated dilation (FMD) is a vasodilatory response initiated by temporary ischemia followed by reperfusion. This crossover study aimed to test the hypothesis that FMD induces dilation of the peripheral veins of the forearm.

Methods: Fifteen healthy volunteers underwent the FMD and control conditions in a randomized order. FMD involved a 5-minute occlusion of blood flow in the brachial artery, followed by reperfusion, achieved by inflating and deflating a cuff placed on the upper arm. The control condition involved participants remaining at rest. The primary outcome measure was a change in the cross-sectional area of the cephalic vein post-intervention. The secondary outcomes included changes in venous diameter and perfusion index (PI).

Results: FMD significantly increased the cross-sectional area of the cephalic vein compared with the control condition (relative change to baseline: 37.7% [31.4] vs 2.2% [11.7]), with a mean difference of 35.4% (95% confidence interval [CI]: 16.4 to 54.5, *P*=.001). Both longitudinal and transverse diameters were significantly expanded with FMD compared to the control (relative change to baseline: 15.7% [15.4] vs 2.6% [3.6], *P*=.004; 18.9% [15.6] vs −0.0 [10.2], *P*=.003, respectively). Additionally, PI significantly increased with FMD compared with the control (relative change to baseline: 77.8% [56.9] vs 14.6% [36.0]), with a mean difference of 63.2% (95% CI: 31.2 to 95.2, *P*=.001).

Conclusion: FMD application induced dilation of the cephalic vein of the forearm. The findings suggest that FMD is an effective technique for dilating the venous area and potentially improving the success rate of peripheral intravenous cannulation.

Introduction

Peripheral intravenous cannulation (PIVC) is one of the most frequently performed invasive procedures in hospitals, with an estimated usage of approximately two billion devices annually worldwide.[1] The initial failure rate of PIVC has been reported to range from 12% to 26% in adults and from 24% to 54% in children.[2] Considering that failure of PIVC and multiple attempts cause pain to the patient, escalate costs, and increase the risk of complications, including infections, phlebitis, and extravasation, strategies to enhance the success rate are imperative.[3]

The venodilation technique improves the success rate of PIVC, as dilated veins enhance visibility and palpability.[2,4] Targeting larger-diameter vessels is beneficial in contexts where imaging technologies, such as ultrasound, are increasingly important for PIVC in clinical practice.[5,6] Numerous studies have demonstrated the effectiveness of various techniques for venodilation, including tourniquet application, warming, tapping, milking, fist clenching, topical nitrates/nitrites, negative pressure, and Valsalva maneuver.[2,7] Among these methods, warming, tapping, and topical nitrates/nitrites have been suggested to facilitate the release of nitric oxide (NO), thereby contributing to vasodilation.[2,8]

Flow-mediated dilation (FMD) is a vasodilatory response triggered by temporary ischemia, followed by reperfusion of an artery, which is mediated by the production of endothelium-dependent NO.[9,10] Clinically, FMD has been adopted as a noninvasive method to assess vascular endothelial function.[11] Moreover, previous studies have shown that applying FMD increases arterial diameter, positively affecting radial artery cannulation outcomes.[12,13] Although the impact of FMD on arterial dilation has been well-documented, its potential to dilate veins has not been explored.

The clinical hypothesis of this study was that peripheral veins dilate in response to FMD. A randomized crossover study was conducted to explore changes in the cross-sectional area of the forearm vein with and without FMD.

Methods

Study design and ethics

The Institutional Review Board approved the trial protocol in accordance with the Declaration of Helsinki, and was registered with the University Hospital Medical Information Network. This randomized, open-label crossover trial was conducted at the authors' institute from September 2023 to November 2023. Randomization was performed using the envelope method. The nature of the study prevents blinding. Written informed consent was obtained from all participants prior to their participation. This manuscript addresses the extension of randomized crossover trials of the Consolidated Standards of Reporting Trials (CONSORT) statement.

Participants

This study recruited healthy adult volunteers aged ≥ 20 years with American Society of Anesthesiologists physical status (ASA-PS) of I–II, indicating a stable health status. The exclusion criteria were as follows: ASA-PS score ≥ III, active skin disease requiring treatment, presence of wounds on the forearm, cardiovascular disease, severe diabetes mellitus, ongoing vasoactive drug therapy, pregnancy, lack of a suitable vein for intervention, and declining to participate.

Procedure

The participants were seated and rested for at least 10 minutes before the measurements. The non-dominant arm was elevated to heart level, with the elbow extended and the hand gently formed into a fist. The investigator used an ultrasound device (SonoSite

SII and L25x/13-6 linear array probe, FUJIFILM Healthcare Corp., Tokyo, Japan) to identify the target cephalic vein in the nondominant forearm. This vein was required to run straight for ≥ 30 mm, be positioned between 120 mm proximal to the radial styloid process and 30 mm distal to the antecubital fossa, and have a depth ≤ 10 mm, as stipulated by referring to previous studies.[14-16] Upon identifying the target vein, the ultrasound probe was fixed to ensure consistent imaging of the same vein segment throughout the measurements. A large amount of ultrasound gel was applied between the probe and skin during the measurements to facilitate optimal imaging conditions and avoid vein compression.

Regardless of the FMD intervention and control conditions, a blood pressure cuff was placed on the target side of the upper arm. The FMD condition temporarily halts the blood flow in the brachial artery for 5 minutes by inflating the cuff to a pressure exceeding the systolic blood pressure by at least 50 mmHg.[9] This action was followed by rapid deflation of the cuff to restore blood flow promptly. For the control condition, the cuff remained unmanipulated, and the participant was kept at rest for 5 minutes. The participants underwent the FMD and control conditions in a randomized order, with a minimum washout period of one hour between conditions to prevent carryover effects.

Measurements of the target cephalic vein, including its longitudinal and transverse diameters and their distance from the skin, were systematically recorded. Initial measurements were taken at baseline, followed by subsequent assessments every minute for a minimum of 5 minutes post-intervention. For those under FMD conditions, the measurement period was extended to 10 minutes. Additionally, the perfusion index (PI) was recorded using a pulse oximeter placed on the index finger of the target side and connected to a patient monitor (BSM-1753, NIHON KOHDEN Corp., Tokyo, Japan). The forearm

temperature on the target side was measured using an infrared radiation thermometer. Concurrently, blood pressure and heart rate were measured noninvasively on the arm opposite the target side. The study procedure is summarized in Figure 1.

Outcome measures

The primary outcome measure was the change in the cross-sectional area of the target vein after the intervention. Secondary outcomes included changes in the vein's longitudinal diameter, depth from the skin, PI, skin temperature, blood pressure, and heart rate post-intervention. The cross-sectional area of the vein was calculated using the ellipse formula: cross-sectional area (mm^2) = π × [transverse diameter (mm)/2] × [longitudinal diameter (mm)/2].

Statistical analysis

The sample size for this study was determined based on a pilot study involving five participants, in which the FMD intervention led to an average vein cross-sectional area dilation of 40% with an effect size (d) of 1.0. The calculated sample size was 13, assuming an α error of .05, power ($1-\beta$) of .90, and effect size of 1.0. The numbers were rounded up, resulting in the recruitment of 15 participants for the study.

Data are presented as mean (standard deviation [SD]) or number (percentage, %). The potential carryover and period effects of the crossover design were evaluated using repeated-measures analysis of variance (ANOVA). Paired t tests were conducted to compare paired numerical variables. All P values were calculated on a two-sided basis, with values <.05, considered to be statistically significant.

Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 4.3.1 (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R Commander that incorporates additional statistical functions commonly employed in biostatistics.[17]

Results

Fifteen participants were enrolled and completed the study; no participants were excluded. Figure 2 shows a flow diagram. Table 1 summarizes the demographic characteristics.

Table 2 shows the changes in cephalic veins pre- and post-intervention. FMD significantly dilated the cross-sectional area compared to the control condition (relative change to baseline: 37.7% [31.4] vs 2.2% [11.7]), with a mean difference of 35.4% (95% confidence interval [CI]: 16.4 to 54.5, *P*=.001). Similarly, FMD significantly enlarged the longitudinal and transverse diameters compared with the control condition (relative change to baseline: 15.7% [15.4] vs 2.6% [3.6], *P*=.004; 18.9% [15.6] vs −0.0 [10.2], *P*=.003, respectively). Regarding vein depth from the skin, there was no significant difference between the two conditions (*P*= 0.34).

PI significantly increased after the FMD intervention compared to the control condition (relative change to baseline: 77.8% [56.9] vs 14.6% [36.0]), with a mean difference of 63.2% (95% CI: 31.2 to 95.2, *P*=.001). There were no significant differences between the two conditions regarding changes in skin temperature. (Table 3) Blood pressure and heart rate remained consistent throughout the procedure in both conditions.

Figure 3 shows the temporal changes in the venous cross-sectional area and the PI during the experimental period. The peak effects of FMD on the venous area and PI were observed at various times across subjects. Maximal dilation of the venous area was observed at 3.1 minutes (95% CI: 1.7 to 4.4) following FMD, whereas the PI reached its maximum at 2.3 minutes (95% CI: 1.1 to 3.4) following FMD.

No participants reported pain or any discomfort symptoms associated with this study.

Discussion

This study tested the hypothesis that FMD could induce dilation of the peripheral veins of the forearm. In accordance with this hypothesis, the venous area significantly increased following FMD intervention. Given the absence of dilation under the control condition, which merely involved rest, the observed dilation effect can be attributed to FMD rather than the resting position over a certain period.

The underlying mechanism of the FMD phenomenon is recognized as vasodilation initiated by the production of endothelial NO and triggered by flow-associated shear stress.[11] NO, produced by endothelial NO synthase, plays a vital role in the local regulation of vascular tone in both the arteries and veins.[18] This suggests that FMD application can dilate arteries and veins, which was corroborated by this study.

Venodilation achieved with FMD resulted in an approximately 38% increase in venous area and a 15–20% increase in diameter, degrees comparable to those achieved through other venodilation methods such as tapping, massage, and warming.[14-16,19-21] Although this study did not directly evaluate PIVC outcomes, previous studies have demonstrated that venodilation techniques enhance the success of PIVC.[2,22,23] Additionally, ultrasound-guided techniques are beneficial for PIVC in both patients with normal and difficult venous access, and venodilation can enhance the efficacy of this approach.[24,25] Therefore, applying FMD will likely positively affect PIVC success by promoting venous dilation. Further research is necessary to determine whether the venodilation effect achieved with FMD can enhance the efficacy of PIVC in clinical practice.

Additionally, this study observed an elevation in PI following the application of FMD. PI, a continuous and noninvasive measure for assessing peripheral perfusion, is

determined by the ratio of pulsatile to non-pulsatile blood volume in peripheral tissues.[26,27] This index reflects the interaction between peripheral and central hemodynamic characteristics, such as vascular tone and stroke volume.[28] Anxiety and emotional stress, often induced by invasive procedures such as vascular puncture, can lead to peripheral vasoconstriction, resulting in pale and cold skin.[29,30] Although this study did not specifically explore these conditions, existing research suggests the potential of FMD to counteract vasoconstriction induced by mental stress.[31]

While the peak effects of FMD varied among individuals, the maximum elevation in PI occurred approximately 2 minutes after FMD, consistent with findings from prior studies.[11,32] Peak venodilation was observed later, approximately 3 minutes post-FMD, indicating that the effects of FMD on veins might have been succeeded by peripheral vasodilation. Although this study did not specifically focus on the duration of venodilation post-FMD, observations indicated that dilation persisted variably across participants. Some participants exhibited a return to baseline within the observation period, while others did not — the persistence of venodilation following FMD warrants further investigation.

Limitations

This study had some limitations. First, it was conducted as an open-label crossover trial without blinding participants or researchers, which can induce the risk of bias, such as the Hawthorne effect. However, given the unlikely possibility that participants intentionally influence vein size, these potential biases are considered to have a minimal impact on the results. Second, as this small-scale study was conducted at a single center in Japan, the results may not be broadly applicable because of possible regional and demographic biases. Third,

the age range of the participants was confined to 20–64 years, limiting the generalizability of the findings to other age demographics. Moreover, solely recruiting healthy adult participants may not accurately reflect the outcomes for individuals with various health conditions, particularly diabetes and cardiovascular diseases. Fourth, although standardized FMD assessments typically require ≥ 6 h of fasting for accurate endothelial function evaluation,[11] this study did not enforce specific fasting restrictions before the intervention, potentially leading to variations in the FMD effect. Nevertheless, the primary focus was on assessing the impact of FMD on the veins, rather than on detailed endothelial function, an objective successfully achieved. Fifth, this research focused on the cephalic vein in the forearm, indicating that the effects on other veins warrant further exploration. Finally, 5-min occlusion-induced FMD. Although previous studies have shown that FMD effects are discernible within shorter periods, albeit with a potential reduction in potency,[33] future research is necessary to determine whether similar venous dilation effects can be achieved with abbreviated application durations.

Conclusion

The application of FMD induced dilation of the cephalic vein in the forearm. As FMD is a noninvasive and simple technique that requires no special tools, it may be a useful method for facilitating PIVC. However, further research is necessary to determine whether the venodilation effect achieved with FMD can improve the success rate of PIVC in clinical practice.

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Figure legends

Figure 1: Study procedure

FMD, flow-mediated dilation.

Red A, cross-sectional area; purple D, depth; yellow L, longitudinal diameter; green T, transverse diameter.

Figure 2: Flow diagram

Figure 3: Temporal changes in the venous area and perfusion index during the experimental periods

FMD, flow-mediated dilation.

Table 1: Participants' demographics

Age, y	31.9 (5.7)
Height, cm	166.3 (8.2)
Weight, kg	64.8 (14.7)
BMI, kg/m^2	23.2 (3.7)
Sex, male/female, n (%)	9 (60.0)/6 (40.0)
ASA-PS, I/II, n (%)	11 (73.3)/4 (26.7)
Current smoker, n (%)	3 (20.0)

Data are expressed as mean (standard deviation) or number (percent, %).

ASA-PS, the American Society of Anesthesiologists physical status; BMI, body mass index, n, number.

Table 2: Change in cephalic veins between pre- and post-intervention

	FMD	Control	Mean difference (95% CI)	*P* value
Cross-sectional area				
Baseline, mm^2	6.7 (2.9)	7.7 (3.7)		
Maximum post-intervention, mm^2	9.0 (4.1)	7.9 (3.9)		
ΔChange, %	37.7 (31.4)	2.2 (11.7)	35.4 (16.4 to 54.5)	.001
Longitudinal diameter				
Baseline, mm	3.5 (0.8)	3.8 (0.9)		
Maximum post-intervention, mm	4.0 (0.8)	3.9 (0.9)		
ΔChange, %	15.7 (15.4)	2.6 (3.6)	13.1 (4.9 to 21.4)	.004
Transverse diameter				
Baseline, mm	2.4 (0.6)	2.5 (0.7)		
Maximum post-intervention, mm	2.8 (0.7)	2.5 (0.7)		
ΔChange, %	18.9 (15.6)	−0.0 (10.2)	18.9 (7.8 to 30.1)	.003
Depth from the skin				
Baseline, mm	3.2 (1.7)	3.1 (1.5)		
Minimum post-intervention, mm	3.1 (1.7)	3.0 (1.5)		

ΔChange, %	−3.7 (9.9)	−1.2 (6.0)	−2.47 (−7.8 to 2.9)	.34

Data are expressed as mean (standard deviation).

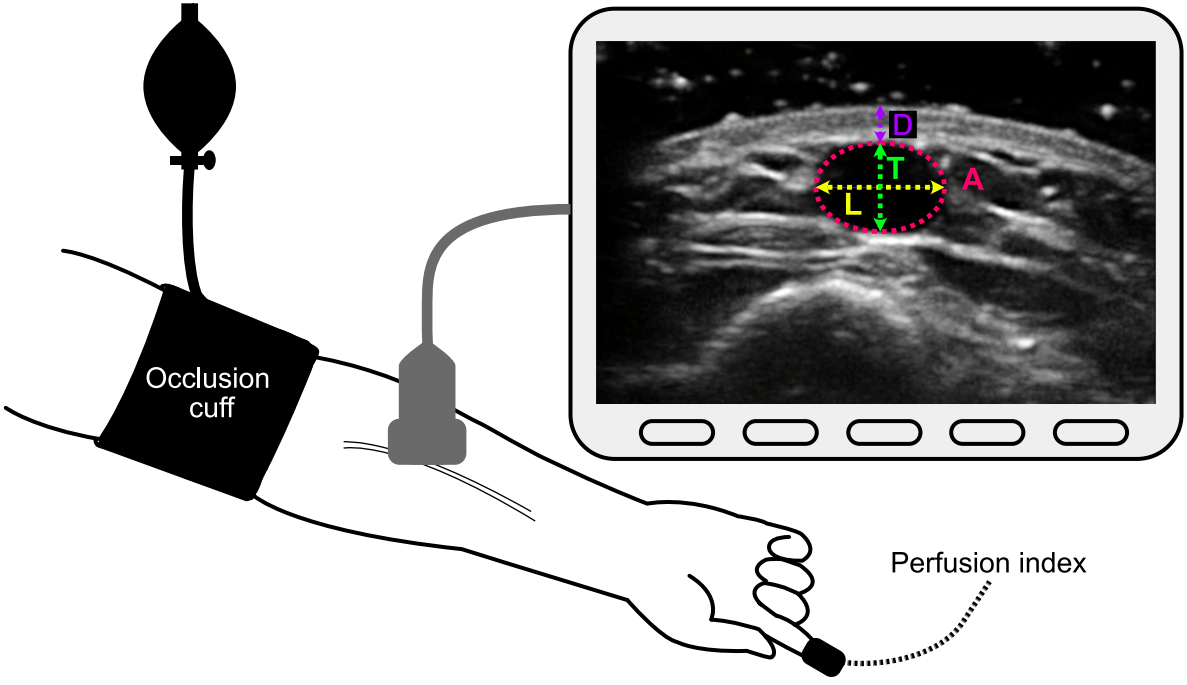
CI, confidence interval; FMD, flow-mediated dilation.

Table 3: Change in the perfusion index and the skin temperature between pre- and post-intervention

	FMD	Control	Mean difference (95% CI)	*P* value
Perfusion index				
Baseline	4.5 (1.5)	5.8 (2.3)		
Maximum post-intervention	6.2 (2.0)	7.4 (1.5)		
ΔChange, %	77.8 (56.9)	14.6 (36.0)	63.2 (31.2 to 95.2)	.001
Skin temperature				
Baseline, ℃	30.5 (2.0)	31.1 (1.5)		
Maximum post-intervention, ℃	30.7 (2.1)	31.4 (1.4)		
ΔChange, %	0.2 (0.8)	0.3 (0.7)	−0.1 (−0.7 to 0.5)	.73

Data are expressed as mean (standard deviation).

CI, confidence interval; FMD, flow-mediated dilation.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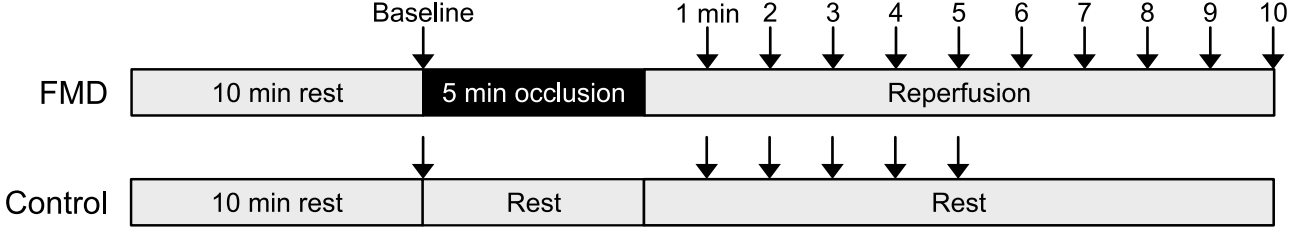
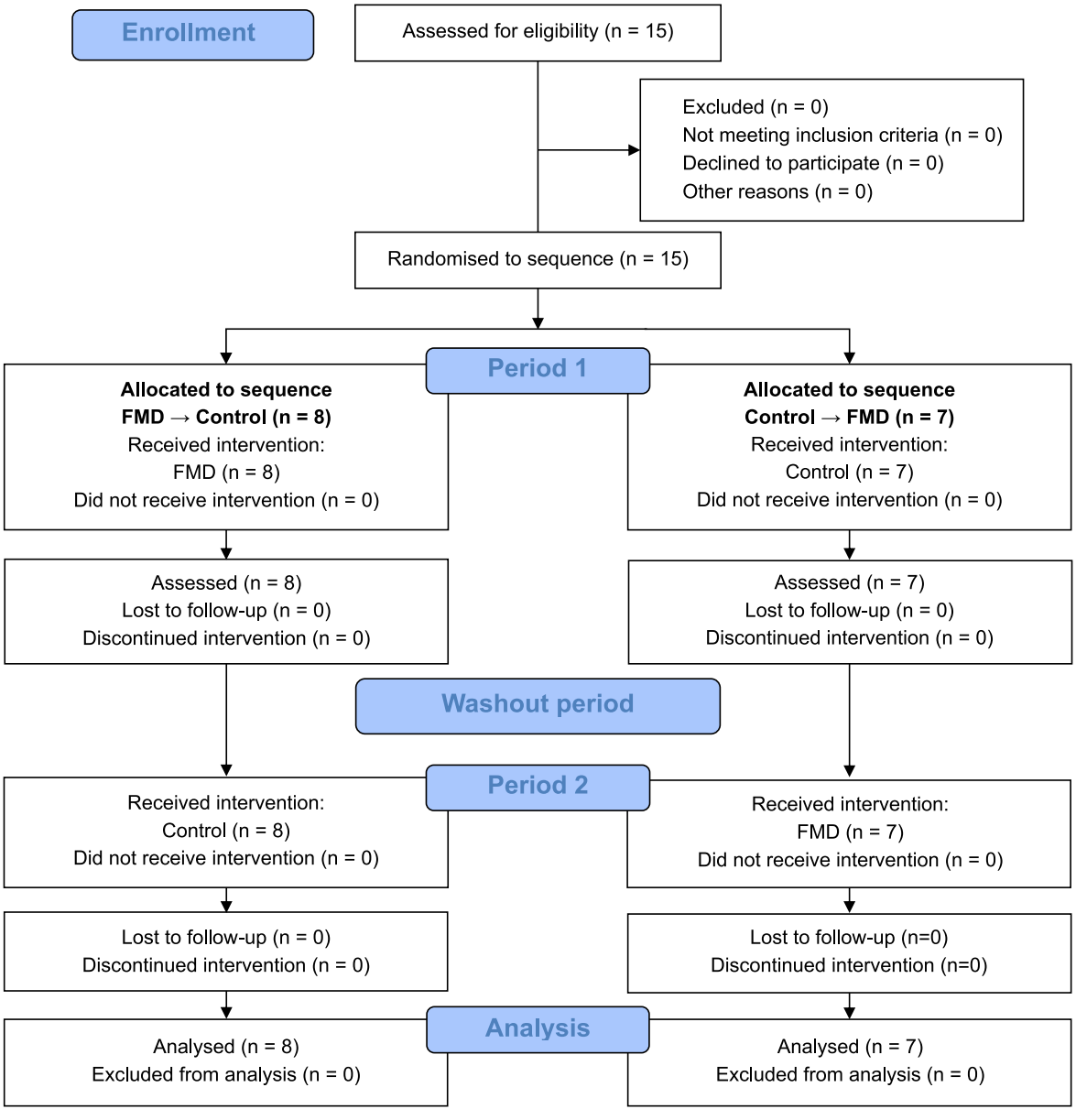
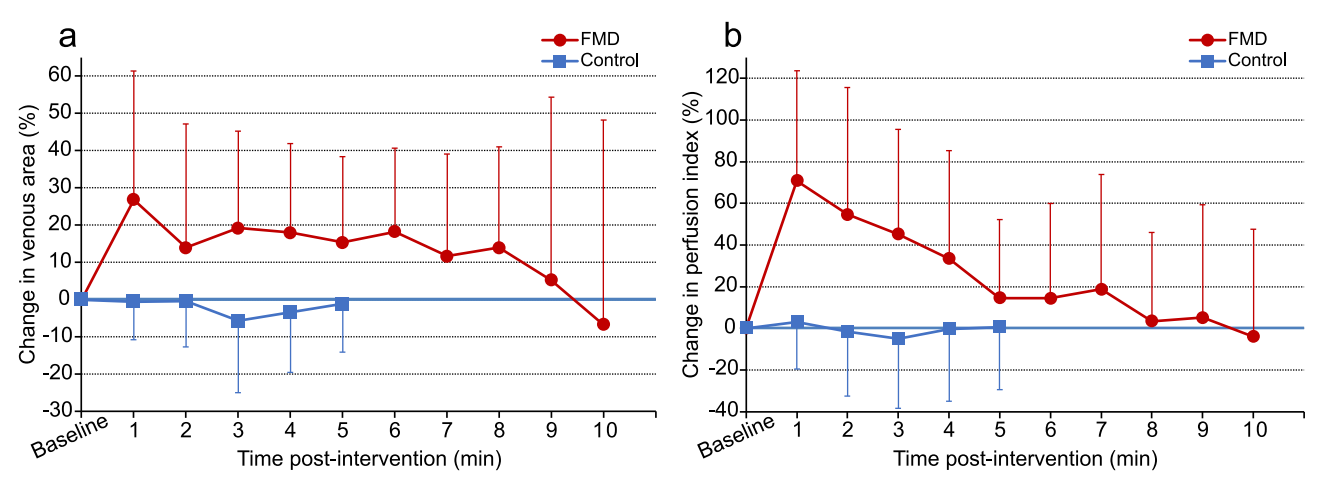
Occlusion cuff
Perfusion index


Baseline
1 min
2
3
4
5
6
7
8
9
10
FMD
10 min rest
5 min occlusion
Reperfusion
Control
10 min rest
Rest
Rest


Enrollment
Assessed for eligibility (n = 15)
Excluded (n = 0)
Not meeting inclusion criteria (n = 0)
Declined to participate (n = 0)
Other reasons (n = 0)
Randomised to sequence (n = 15)
Period 1
Allocated to sequence
FMD → Control (n = 8)
Received intervention:
FMD (n = 8)
Did not receive intervention (n = 0)
Allocated to sequence
Control → FMD (n = 7)
Received intervention:
Control (n = 7)
Did not receive intervention (n = 0)
Assessed (n = 8)
Lost to follow-up (n = 0)
Discontinued intervention (n = 0)
Assessed (n = 7)
Lost to follow-up (n = 0)
Discontinued intervention (n = 0)
Washout period
Period 2
Received intervention:
Control (n = 8)
Did not receive intervention (n = 0)
Received intervention:
FMD (n = 7)
Did not receive intervention (n = 0)
Lost to follow-up (n = 0)
Discontinued intervention (n = 0)
Lost to follow-up (n=0)
Discontinued intervention (n=0)
Analysis
Analysed (n = 8)
Excluded from analysis (n = 0)
Analysed (n = 7)
Excluded from analysis (n = 0)


a
FMD
Control
Change in venous area (%)
60
50
40
30
20
10
0
-10
-20
-30
Baseline
1
2
3
4
5
6
7
8
9
10
Time post-intervention (min)
b
FMD
Control
Change in perfusion index (%)
120
100
80
60
40
20
0
-20
-40
Baseline
1
2
3
4
5
6
7
8
9
10
Time post-intervention (min)