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# Sustained Shear Stress Reveals Agreement between Flow-Mediated Dilation and Flow-Mediated Slowing

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**Key Points**

- Flow-mediated slowing (FMS) is a simpler, operator-independent alternative to flow-mediated dilation (FMD) for evaluating endothelial function.
- Traditional flow-mediated assessment uses reactive hyperemia, yet sustained shear stress is a more common physiological occurrence and can detect endothelial dysfunction undetected by transient reactive hyperemia.
- Whether the FMS technique can detect improvements in endothelial function elicited by a physiologically relevant, sustained shear stress stimulus is unknown.
- In response to a stepwise sustained shear stress protocol, sustained-shear FMS and sustained-shear FMD co-vary in the theoretically predicted direction, demonstrating convergent validity as indicators of acute endothelial function.
- FMS is a user-objective technique for assessing bidirectional changes in endothelial function, positioning it as a viable tool for assessing acute vascular responsiveness to physiological interventions and cardiovascular risk.

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**Keywords**
Endothelial function · Flow-mediated dilation · Flow-mediated slowing · Arterial stiffness · Pulse wave velocity · Shear stress

**Abstract**
***Introduction:*** Flow-mediated slowing (FMS), the decrease in pulse wave velocity (PWV) in response to elevated shear stress, is a simpler, operator-independent alternative to assessing arterial diameter (DIA) increase via flow-mediated dilation (FMD). Traditional flow-mediated assessment uses reactive hyperemia, yet sustained shear (ss) stress is a more ubiquitous in vivo physiological occurrence. This study aimed to determine the agreement between sustained-shear FMD (ssFMD) and sustained-shear FMS (ssFMS) in response to a sustained shear stress stimulus designed to enhance endothelial function. ***Methods:*** In 19 participants (12 male, 28 ± 8 years), brachial artery DIA and brachial-radial PWV were measured in experimental and control arms. Following baseline, sustained stepwise increases in shear rate were induced using upper-limb heating (10 min) at 47.5°c and 52.5°c, and handgrip exercise (4 min) at 0.33 Hz and 0.67 Hz in the experimental arm. The agreement was tested by modeling the overall association using a linear mixed-effects model. ***Results:*** The sustained shear protocol elicited a large increase in mean shear rate in the experimental arm (Δ 299 1/s, $p < 0.001$). This resulted in a significant time × condition interaction in the experimental arm, with a moderate increase in DIA (Δ 0.04 cm, ~13%; $p < 0.001$) and a moderate decrease in PWV (Δ −1.7 m/s, ~20%; $p < 0.001$). There was a significant within-person inverse association between ssFMD and ssFMS ($\beta = -0.200$, $p < 0.001$) in the experimental arm. ***Conclusion:*** ssFMS demonstrates a response consistent with ssFMD following a sustained shear stress protocol. Findings support ssFMS as a viable tool for assessing acute improvements in endothelial function.

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## Introduction

Vascular homeostasis is partly governed by the endothelium, which modulates tone, directs immune responses, and regulates blood fluidity and coagulation in response to humoral, neural, and especially hemodynamic stimuli [1, 2]. Dysfunction of the endothelium is associated with incident cardiovascular events and mortality [3, 4]. The gold-standard non-invasive approach for assessing endothelial function is the ultrasound-based flow-mediated dilation (FMD) test, which measures an artery's vasodilatory response to the hemodynamic stimulus shear stress [5–7]. But while FMD is highly valid, its operator-dependence and technical complexity have limited its widespread clinical use and driven researchers to identify simpler, user-objective alternatives; one such alternative is flow-mediated slowing (FMS).

Typically undertaken in the upper limb, the FMS test measures the decrease in arterial pulse wave velocity (PWV) in response to elevated shear stress [8, 9]. Given that a change in PWV is inversely proportional to a change in vessel diameter (DIA) [10], FMS is thought to be the reciprocal of FMD, with a greater reduction or lower minimum PWV representing better endothelial function [9]. It has been established that FMS and FMD demonstrate good agreement [8], and that FMS is capable of tracking acute impairment of endothelial function, including that a protocol designed to induce retrograde shear, a known cause of endothelial dysfunction [11], induces correspondingly attenuated FMD and FMS responses [12]. Despite this progress, prior work has exclusively utilized a transient, reactive hyperemia stimulus to evoke an increase in conduit artery shear stress. Reactive hyperemia is atypical in day-to-day life with a potential to differ between measurement timepoints or groups, hampering the interpretation of endothelial function evaluation [13]. An alternative approach is the use of stimuli that evoke sustained shear stress. Although infrequently employed to interrogate peripheral conduit artery endothelial function, sustained increases in shear stress are a ubiquitous in vivo physiological occurrence. Techniques used to stimulate sustained increases in shear, including forearm exercise [14–17] and heating [18–21], permit uniform stimulus control in a dose-dependent manner, without altering systemic hemodynamics. Evidence also suggests that sustained shear stress stimuli can provide unique insights into endothelial health [13], detecting endothelial dysfunction undetected by transient reactive hyperemia [22, 23].

There is a critical gap in our understanding: can a simple, user-objective sustained-shear FMS (ssFMS) technique detect improvements in endothelial function elicited by a physiologically relevant, sustained shear stress stimulus? To address the question, this study used a contralateral-arm protocol. Stepwise increases in sustained shear stress were induced in one arm (EXP), and the other arm served as a control (CON). We tested two hypotheses: (1) the protocol will induce sustained increases in shear stress (stimulus), leading to increased brachial artery DIA, sustained-shear FMD (ssFMD), and decreased brachial-radial PWV, ssFMS in EXP but not CON; (2) in the EXP arm, there will be a significant negative association between ssFMS and ssFMD.

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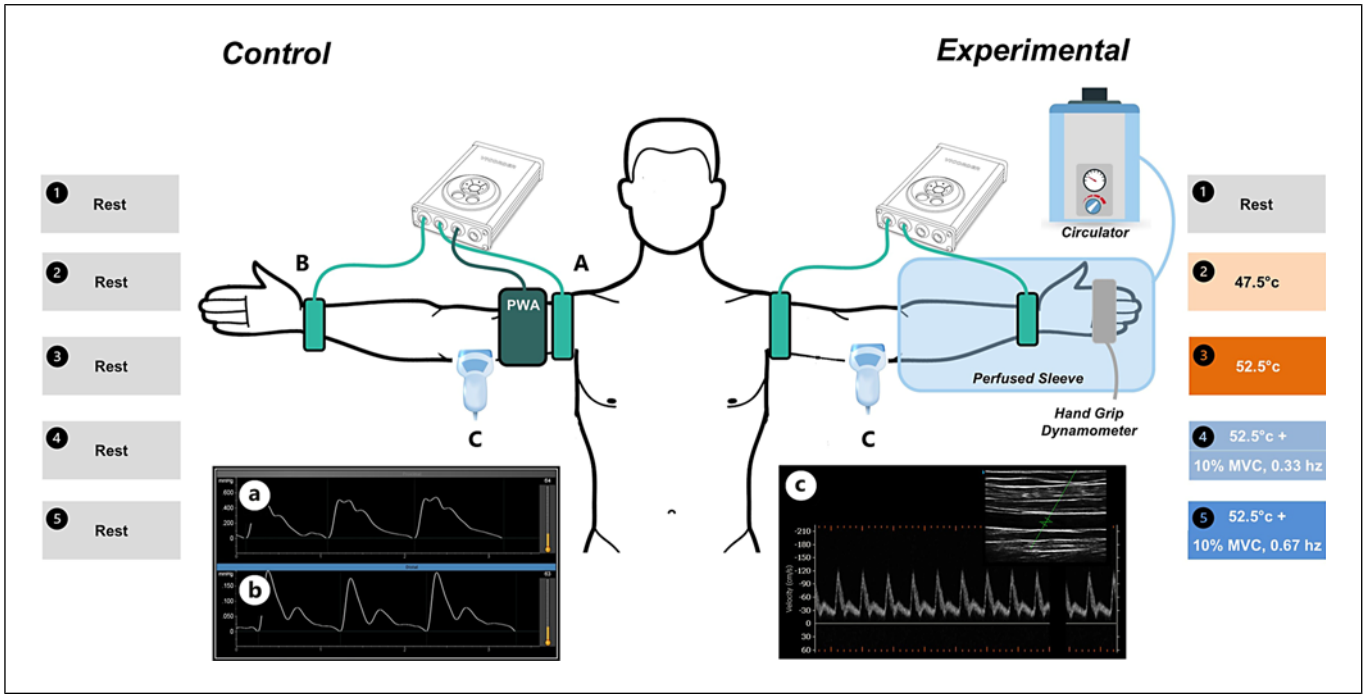



**Fig. 1.** Experimental setup. Brachial-to-radial pulse wave velocity (PWV) was measured bilaterally using the Vicorder device, whereby PWV is determined by simultaneously capturing arterial pressure waveforms at proximal (**a**) and distal (**b**) sites using oscillometry. **c** Duplex Doppler ultrasound was used to simultaneously capture pulse Doppler waveforms and DIA of the brachial artery bilaterally. Peripheral and central hemodynamics were determined using the Vicorder device on the right, control arm only.

## Methods

This study is reported in accordance with TREND (Improving the Reporting Quality of Nonrandomized Evaluations of Behavioral and Public Health Interventions) guidelines [24]. Study procedures were approved by the Cardiff School of Sport and Health Sciences Ethics Committee (STA-9009) and conformed to the ethical standards established by the Declaration of Helsinki (2013), excluding prior registration in a database. All participants provided written informed consent prior to participating in the study. The corresponding author had complete access to the study's data and was responsible for the integrity of the dataset and data analyses.

*Participants*

A healthy population sample was recruited to mitigate the risk of age or disease-related influences on the primary outcomes. Participants were included if they were free of overt cardiovascular disease and aged >18 years. Participants were excluded if they reported any known cardiometabolic disorders, were taking medications known to affect cardiovascular function, reported cigarette smoking or vaping, or were pregnant.

*Experimental Design and Overview*

The experimental design and setup are depicted in Figure 1. The experimental design consisted of repeated measures on an experimental arm (left) and a contralateral control arm (right). In a supine position using the experimental arm, participants first completed three repetitions of isometric rhythmic handgrip exercise at maximal voluntary contraction (MVC). Following 15 min of quiet rest and baseline measures, the experimental arm was exposed to the endothelial function enhancement protocol [13]. The protocol was designed to increase sustained shear stress in four stages:

- (i) HEAT 1: hand/forearm heating at 47.5°C.
- (ii) HEAT 2: hand/forearm heating at 52.5°C.
- (iii) EXERCISE 1: rhythmic handgrip exercise at 0.33 Hz and hand/forearm heating at 52.5°C.
- (iv) EXERCISE 2: rhythmic handgrip exercise at 0.67 Hz and hand/forearm heating at 52.5°C.



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The five experimental stages were immediately consecutive except for Exercise 1 and Exercise 2, between which participants were permitted 2 min of rest from rhythmic handgrip exercise, although the heat exposure was maintained. Primary outcomes (DIA and PWV) were recorded on both arms, and descriptive outcomes (peripheral and central hemodynamics) on the control arm only. Each outcome was measured at baseline and during each stage, resulting in 10 primary outcome data points for each participant (5 per arm) and five data points for descriptive outcomes. The order of measurements comprised alternating DIA and subsequently simultaneous PWV on the experimental and control arms, followed by descriptive outcomes on the control arm only. Exposures for each stage were maintained until all measurements were complete. For 24 h preceding experimentation, participants were asked to avoid strenuous physical activity, alcohol consumption, and supplement intake. For at least 6 h preceding experimentation, participants were asked to consume water ad-lib, but otherwise fast. All measurements were collected on a single occasion in an environmentally controlled laboratory (average: 21°C, 50% humidity).

*Endothelial Function Enhancement Protocol*

Forearm Heating

The hand and forearm, up to the cubital fossa, were wrapped in a custom-made water-perfused sleeve. The sleeve was lined with silicone tubes (radius width of tube 8 mm; wall width 2 mm each; intermittent space of 20 mm between rows) connected to a water circulator (Julabo F12; Labortechnik GmbH, Seelbach, Germany). Before the heating protocol was initiated, the water-perfused sleeve was prewarmed to 47.5°C. After baseline measurements, the preheated arm sleeve was wrapped around the hand and arm and secured with Velcro® strips, while avoiding excessive pressure and discomfort to the participant. To minimize heat loss, thermo foil (emergency blanket; Trespass, Glasgow, UK) was additionally wrapped around the outside of the arm sleeve. Perfusate temperature was set to 47.5°C for the stage of the heating protocol, increased to 52.5°C for the second stage, and then maintained throughout the subsequent forearm exercise protocol. At each stage, primary outcome and descriptive outcome measures were commenced following 10 min of exposure. Localized warming of the skin is expected to increase blood flow locally without systemic autonomic influence [13, 25–27]. Forearm skin temperature was continuously monitored using a skin temperature probe via PowerLab 8/30 and using LabChart (ADInstruments, Oxford, UK).

Forearm Exercise

For the experimental arm, two stages of isometric rhythmic handgrip exercise, while heated to 52.5°C, were completed using an isometric handgrip transducer (ADInstruments, Oxford, UK). For each stage, the participant was asked to squeeze to 10% of their MVC. Exercise was undertaken for 4 min prior to the collection of hemodynamic measurements and maintained until all measurements were complete. For stage 1, the subject contracted once every 3 s (0.33 Hz). For stage 2, the subject contracted twice every 3 s (0.67 Hz). The DIA (~30 s) and PWV (~20 s) measurements were recorded during brief pauses of the isometric rhythmic handgrip exercise, with a resumption of exercise of at least 60 s prior to subsequent measures. Low-intensity handgrip exercise of a small muscle group was chosen to minimize systemic autonomic responses [14, 16, 25]. Subjects were encouraged to perform the exercise with minimal biceps activity. Contraction timing was controlled using an electronic metronome. Force output was captured continuously via PowerLab 8/30 using LabChart, with live visual feedback of effort (% MVC) being provided to the subject.

*Primary Outcomes*

PWV and ssFMS

At each of the five experimental stages, PWV (Vicorder, 80 Beats Medical GmbH, Kantstraβe, Berlin) was measured 3 times. Each recording consisted of at least 8 consecutive cardiac cycles. The average of the closest two measures was used in analyses. PWV (m/s) is calculated by dividing the arterial path length by the pulse transit time between proximal (upper arm) and distal (wrist) arterial sites [28, 29]. Path length was directly measured using a custom body-length measuring caliper to bypass body contours between the midpoint of the two cuffs. To measure pulse transit time, the cuffs were simultaneously inflated to a low (~50 mm Hg) pressure, and a proprietary algorithm was used to automatically calculate the time between the foot of the proximal pressure waveform and the foot of the distal pressure waveform.

Arterial DIA and ssFMD

A high-resolution ultrasound device (Terason 3300, Teratech, Burlington, MA) fitted with a linear array probe (15-4 MHz) was used to record brachial artery brightness-mode images and pulsed Doppler waveforms for the measurement of DIA and shear rate, respectively. The ultrasound was positioned ~4 cm above the antecubital fossa, with the probe placement being marked following baseline to permit repeated measurements. The isonation angle was kept constant at 60°, and the

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sample volume included the majority of the vessel lumen. The ultrasound images were recorded for 30 s and were captured at 20 Hz using screen recording software (Camtasia, TechSmith, Okemos, MI) inherent to the ultrasound device. The recording was split into three 10 s sequences and analyzed offline using a custom-designed edge-detection and wall-tracking software (FMD/BloodFlow Software v1.1, Reed Electronics, Perth, WA, Australia), the precision and accuracy of which have been previously reported [30]. Arterial DIA (cm) was determined automatically along the highest quality portion of the B-mode image. Doppler flow velocity waveform envelopes were automatically traced, and mean blood flow velocity (cm/s) was subsequently calculated as half of this time-averaged peak envelope velocity. DIA and blood flow velocity recording were used to calculate the blood flow and total, antegrade, and retrograde shear rates. Blood flow (mL/min) was calculated as the product of mean blood flow velocity and blood vessel cross-sectional area. Shear rate ($s^{-1}$) was calculated as 4 × mean blood flow velocity/blood vessel DIA. The average of the closest two measures from the three 10 s recorded sequences was used in the analyses. To minimize the risk of operator bias, a single operator collected all measurements (T.G.) and completed all measurement analyses (K.S.).

*Descriptive Outcomes*

Peripheral and Central Hemodynamics

The Vicorder device was used to measure systemic hemodynamic variables that help explain the study findings. This includes qualitatively interpreting whether the intervention induced a systemic response, as opposed to local-only. An appropriately sized cuff was placed around the upper portion of the control (right) arm. Each measurement cycle lasts ~60 s. This includes inflating the cuff to measure brachial systolic, diastolic, and mean arterial blood pressure and then reinflating to 70 mm Hg to acquire a volumetric displacement signal. Using a previously described brachial-to-aortic transfer function [31], the Vicorder measures hemodynamic variables, including heart rate (HR), stroke volume (SV), cardiac output (CO), mean arterial pressure (MAP), and total peripheral resistance (TPR) using pulse contour analysis of the brachial waveform [32].

*Data Management and Statistical Considerations*

Sample Size

Power calculations (GPower 3.1) were made to detect at least a small effect size ($\rho^2 = 0.10$) association between ssFMS (PWV) and ssFMD (DIA), with one additional predictor (arm) and up to two adjustment covariates. For $n = 20$ and 200 data points (5 per arm per subject), with 90% power and a 5% chance of a type 1 error, we calculated that we would be able to detect $\rho^2 = 0.085$. The critical $\rho^2$ increases to 0.094 for $n = 18$ (10% drop out).

Statistical Analysis

Statistical analyses were performed using Python 3.10 (Google Colaboratory; Google LLC, Mountain View, CA) with the statsmodels, scipy, numpy, and pandas libraries. Raw data are presented as the arithmetic mean (standard deviation), and mixed model data are presented as unstandardized betas [95% confidence interval (95% CI)]. The significance level was set a priori at $\alpha = 0.05$ for the main effects. A lower threshold of $\alpha = 0.10$ was applied for interaction effects, consistent with established recommendations for repeated-measures designs with small samples in which interaction terms carry substantially reduced statistical power relative to main effects, and in which a type II error (missing a true interaction) represents a greater practical concern than a liberal type I threshold at this proof-of-concept stage [33].

*AIM 1.* The effects of time (baseline, heating 1, heating 2, exercise 1, and exercise 2) and condition (CON vs. EXP) on ssFMD (~DIA) and ssFMS (~PWV) outcomes were independently tested using linear mixed-effects models. Participant was (intercept) specified as a random effect and time (slope) and condition as fixed effects. Models were adjusted for baseline values to reduce within-participant variance. Model assumptions were verified by plotting residuals against fitted values and examining Q-Q plots. Effect sizes were calculated as Cohen's d by dividing the condition-by-time interaction coefficient by the pooled baseline standard deviation. Effect sizes were interpreted as small (d = 0.2), moderate (d = 0.5), or large (d = 0.8) [34].

*AIM 2.* To maximize statistical power while accounting for correlated error variance, the within-person association between ssFMS (z-scored PWV; znpwv) and ssFMD (z-scored brachial artery DIA; zdia) in the experimental arm was modeled using linear mixed-effects regression (LME; statsmodels MixedLM, REML estimation). Analyses were restricted to the experimental arm, in which the sustained shear stress protocol was applied and progressive variation in endothelial vasodilatory tone was systematically induced; the control arm, which received no shear stress stimulus and exhibited no systematic change in either primary outcome (AIM 1 results), was excluded, as including resting observations would conflate stimulated and unstimulated physiological states and attenuate the within-person signal of interest [33, 35].

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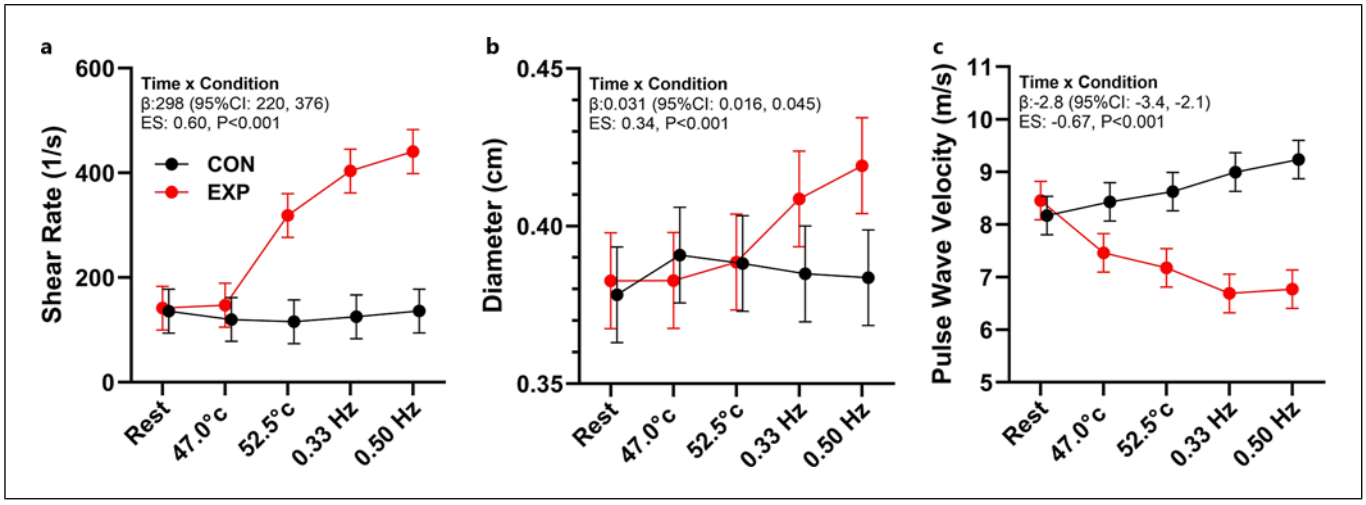



**Fig. 2.** Mean shear rate (**a**), brachial artery DIA (**b**), and brachial-to-radial PWV (**c**) for control and experimental arms across the sustained shear stress experimental protocol.

*Explanatory Outcomes*. The effects of time and condition on hemodynamic variables (HR, SV, CO, MAP, TPR) were independently tested using linear mixed-effects models, using the procedures outlined for Aim 1. Linear mixed-effects regression models, as outlined in Aim 2, tested the associations between shear rate and ssFMD and ssFMS, respectively.

## Results

*Participants*

Twenty-participants were successfully recruited, with complete data being collected on 19 participants (12 male, 7 female), with a mean age of 28.2 (±7.7) years and a mean body mass index of 27.6 (±1.4) kg/m$^2$. Participants completed an average of 3.9 (±1.8) physical activity sessions per week for an average of 55 (±19) minutes. One participant did not attend the experimental visit for a non-specified reason. All participants conformed to pretest guidelines before the experimental visit.

*Primary Outcomes*

*AIM 1*: The endothelial enhancement protocol induced significant time × condition interactions for mean shear rate ($p < 0.001$), DIA ($p < 0.001$), and PWV ($p < 0.001$). Mean shear rate increased by 298 (95% CI: 221–377, ES: 1.19) in EXP relative to CON (Fig. 2). DIA increased by 0.031 cm (95% CI: 0.016–0.045, ES: 0.34) in EXP relative to CON. PWV decreased by −2.8 m/s (95% CI: −3.4 to −2.1, ES: 0.67) in EXP relative to CON. There was a large negative association between mean shear rate and DIA (ES: −1.10, $p < 0.001$) and PWV (ES: −0.71, $p < 0.001$). *AIM 2*: The LME converged normally (N = 95; 19 participants; 5 observations/participant). Residuals were normally distributed (Shapiro-Wilk: W = 0.988, $p = 0.566$). There was a significant within-person inverse association between znpwv and zdia: β = −0.200 (SE = 0.051, 95% CI: [−0.302, −0.098]), F (1, 78.8) = 15.2, $p < 0.001$, Fig. 3). The ICC of 0.888 ($\sigma^2_s = 0.964$, $\sigma^2_r = 0.121$) indicates that 88.8% of total variance reflects stable between-subject differences in resting vascular caliber. EFA of person-centered scores yielded equal factor loadings for both indicators ($\lambda = 0.844$; $h^2 = 0.712$; 71.2% variance explained; df = 0, descriptive). A complete summary and exploratory analysis of the statistical outcomes for aim 1 and aim 2 are provided in Data online supplementary Table S1-S5 (for all online suppl. material, see https://doi.org/10.1159/pls/aeoag002).

*Peripheral and Central Hemodynamics*

The was a moderate significant increase in HR (Δ 8 beats/min, ES 0.61, $p < 0.001$), MAP (Δ 8 mm Hg, ES 0.58, $p < 0.001$), and CO (Δ 1.5 L/min, ES 0.58, $p < 0.001$) but no change in SV (Δ 8 mL, ES 0.21, $p < 0.112$), TPR (Δ −0.03, ES −0.07, $p = 0.703$), or AIx (Δ −2.50%, ES −0.23, $p < 0.333$) across the sustained shear stress experimental protocol (Table 1). In the EXP condition, none of the hemodynamic variables (MAP, HR, SV, or TPR) were significantly associated with either DIA or PWV (all $p > 0.05$).

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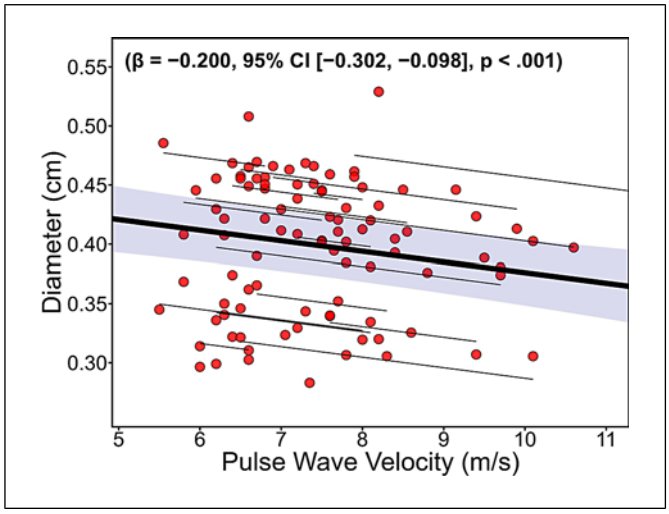



**Fig. 3.** Within-person association between brachial artery DIA (ssFMD) and PWV (ssFMS) across the five sustained shear stress stages in the experimental arm ($N$ = 95 observations; 19 participants). Lines connect observations within each participant. The fixed effect of z-scored PWV on z-scored DIA (β = −0.200, 95% CI: [−0.302, −0.098], $p$ < 0.001) reflects the within-person signal after accounting for stable between-subject differences in resting vascular caliber (ICC = 0.888, model diagnostic).

**Table 1.** Peripheral blood pressure and central hemodynamic responses to the sustained shear stress experimental protocol

| | HR | SV | CO | MAP | TPR |
|---|---|---|---|---|---|
| | bpm | ml | L/min | mm Hg | mm Hg/min/L |
| Mean | | | | | |
| BASE | 59.8 | 120 | 7.2 | 78.9 | 0.69 |
| TEMP 1 | 58.2 | 120 | 7.2 | 78.0 | 0.69 |
| TEMP 2 | 61.3 | 116 | 7.1 | 79.1 | 0.72 |
| EXE 1 | 66.7 | 123 | 8.3 | 83.0 | 0.66 |
| EXE 2 | 67.7 | 128 | 8.7 | 86.6 | 0.66 |
| Standard deviations | | | | | |
| BASE | 8.3 | 16 | 1.6 | 7.9 | 0.1 |
| TEMP 1 | 8.2 | 25 | 1.6 | 7.6 | 0.2 |
| TEMP 2 | 8.7 | 21 | 2.0 | 10.1 | 0.3 |
| EXE 1 | 11.1 | 25 | 2.2 | 10.2 | 0.2 |
| EXE 2 | 9.9 | 27 | 2.4 | 11.0 | 0.3 |
| Time effects | | | | | |
| B | 7.84 | 8.34 | 1.50 | 7.76 | −0.03 |
| $p$ | <0.001 | 0.112 | <0.001 | <0.001 | 0.703 |
| ES | 0.66 | 0.21 | 0.58 | 0.79 | −0.07 |

## Discussion

This study investigated the agreement between ssFMD and ssFMS in response to a sustained, stepwise shear stress protocol designed to enhance endothelial function. The primary findings support our hypothesis: the protocol successfully increased shear rate, which led to a concomitant increase in brachial artery DIA (~ssFMD) and a decrease in PWV (~ssFMS). Furthermore, a significant inverse association between these two measures was observed, suggesting that ssFMS is a viable, user-objective tool for tracking acute vascular responsiveness to a sustained shear stress stimulus, consistent with endothelium-mediated vasodilation.

### *Limitations and Strengths*

The known limitations and strengths of this study should be addressed to facilitate a balanced review of the Explanation of Findings in the next section. First, the recruitment of a young, healthy population, while providing an ideal mechanistic environment for demonstrating ssFMD–ssFMS agreement, limits the generalizability of findings to older or clinically compromised populations. Future work must establish whether ssFMS retains sensitivity and agreement with ssFMD in populations with hypertension, cardiometabolic disease, or endothelial dysfunction, in whom the clinical utility of the technique would be greatest. Second, our sample size was not powered to investigate potential sex-based differences in the FMD-FMS relationship. Third, shear rate was computed as 4 × mean blood flow velocity/brachial artery DIA – a formula that incorporates DIA, which is also a primary outcome of this study. This mathematical dependency introduces a degree of circularity into the shear rate-DIA associations reported in the explanatory outcomes analyses; those associations should be interpreted with appropriate caution. The primary AIM 2 analysis, which does not include shear rate as a covariate, is unaffected by this limitation. However, the study possesses significant strengths that we believe outweigh these limitations. The primary strength is the use of a repeated-measures design with a contralateral control arm, which provides a robust internal control for any systemic changes over time. Additionally, the use of a sustained, physiologically relevant stimulus (heating and exercise) to probe endothelial function provides novel insight compared to studies relying solely on transient reactive hyperemia.

### *Explanation of the Findings*

The significant within-person fixed effect (β = −0.200, $p$ < 0.001) confirms that ssFMD and ssFMS co-vary in the theoretically predicted direction across sustained shear stress levels, consistent with the Moens-Korteweg

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relationship between vessel DIA and PWV. The marginal $R^2$ of 3.6% reflects variance explained by the fixed effect alone, after the random intercept has absorbed stable between-subject differences in resting vascular caliber – as indicated by the ICC of 0.888. A modest marginal $R^2$ is, therefore, the expected result for a within-person effect in this design; it reflects that each measure captures a distinct observable manifestation of latent endothelial function with its own measurement noise, not an absence of association.

The EFA of person-centered scores yielded equal loadings for both indicators ($\lambda = 0.844$; $h^2 = 0.712$), with a single factor explaining 71.2% of within-person shared variance. Although this analysis is saturated (df = 0) and, therefore, descriptive rather than confirmatory, it is consistent with the interpretation that ssFMD and ssFMS reflect a common latent endothelial response construct under sustained shear stress. Taken together, the LME fixed effect and EFA converge on the conclusion that ssFMS is a valid functional surrogate for ssFMD: the criterion is capacity to track the same within-person endothelial response trajectory as the shear stimulus increases, not numerical interchangeability. Future confirmatory factor analysis or structural equation modeling with larger samples is warranted to formally test the single-factor structure.

*Comparison to Literature*

Our findings complement and extend previous work. The observed ~13% ssFMD and ~20% ssFMS are physiologically significant and demonstrate a robust endothelial response to sustained shear stress. Our analyses confirmed that the shear stress response was significantly associated with both ssFMD (ES: 1.10, $p < 0.001$) and ssFMS (ES: −0.71, $p < 0.001$). This study builds directly on the findings of Stoner et al. [12], who showed that an endothelial dysfunction protocol led to an increase in PWV. The current study provides the critical missing evidence, demonstrating that a sustained shear stress experimental protocol, designed to enhance endothelial function, leads to the expected opposite effect, a decrease in PWV. Together, these studies provide strong evidence that brachial-to-radial PWV can track bidirectional changes in endothelial function.

The hemodynamic context of these vascular adaptations warrants discussion, particularly in interpreting whether the intervention induced systemic versus local-only responses. Our data suggests the protocol elicited modest systemic hemodynamic changes. CO increased by approximately 1.5 L/min to meet the elevated metabolic demands of the heated and exercising forearm. This increase was achieved via a 7–8 bpm elevation in HR as SV did not change significantly. MAP increased by 5–7 mm Hg, likely as a compensatory mechanism to maintain TPR. In the current study, the relatively small systemic hemodynamic perturbations suggest that the DIA increase and PWV reduction predominantly reflect localized conduit artery endothelial adaptation, although modest systemic influences cannot be excluded.

The significant within-person inverse association between ssFMD and ssFMS ($\beta = -0.200$, 95% CI: [−0.302, −0.098], $p < 0.001$) provides direct evidence of the mechanical and physiological link between endothelium-dependent vasodilation and arterial compliance during acute intervention. The high ICC (0.888) confirms strong model fit, reflecting that the within-person fixed effect is estimated against a background of substantial stable between-subject variance in resting vascular caliber. According to the Moens-Korteweg equation, PWV is inversely proportional to vessel DIA [36, 37]; thus, the observed 13% DIA increase would mechanistically explain a substantial portion of the 20% PWV reduction. Furthermore, modest HR elevation may modulate the magnitude of shear stress exposure per cardiac cycle, thereby influencing the cumulative endothelial stimulus. However, given the stability of TPR and SV, the PWV response appears predominantly driven by local endothelial-mediated vasodilation, with contributions from CO-mediated increases in flow and pressure.

Our results also align with the review by Tremblay and Pyke [13], which posits that sustained and transient shear stress stimuli may offer unique insights into endothelial health. Unlike transient reactive hyperemia (which stimulates rapid, NO-dependent vasodilation), sustained shear stress engages a broader array of endothelial signaling pathways that may include EDHFs and prostaglandins [38]. This mechanistic distinction has important implications: sustained shear stress FMD has been shown to detect endothelial dysfunction in populations where reactive hyperemia FMD remains normal, suggesting differential vulnerability of these pathways to cardiovascular risk factors. Young male smokers with short smoking histories exhibit significantly blunted handgrip exercise-induced sustained ssFMD compared with nonsmokers, whereas reactive hyperemia FMD did not differ between groups [39]. Similarly, obese young men demonstrate markedly reduced sustained ssFMD (~50% lower) compared with lean controls, without differences in standard 5-min occlusion reactive hyperemia FMD [23]. In individuals with uncomplicated type 1 diabetes (without microangiopathic complications), FMD was impaired versus matched controls only in response to sustained shear

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stress [22]. The demonstration that brachial-to-radial PWV decreases following an endothelial enhancement protocol further supports the notion that PWV is not merely a structural property of the arterial wall but is acutely modifiable by endothelial function. This finding extends the utility of regional PWV beyond risk stratification, positioning it as a viable tool for assessing acute vascular responsiveness to physiological interventions.

*Implications*

The primary implication of our research is that ssFMS, measured as a change in PWV, can serve as a valid, user-objective, and technically simpler alternative to the operator-dependent ultrasound-based DIA measurement (ssFMD) for assessing acute changes in vascular responsiveness to a sustained shear stress stimulus. Traditional FMD requires high-frequency ultrasound, specialized image analysis software, and extensive operator training to achieve acceptable reproducibility, whereas automated oscillometric PWV devices enable standardized measurements with minimal operator skill. This practical advantage substantially reduces technical variability and could transform the feasibility of large-scale epidemiological studies and clinical intervention trials where endothelial function assessment is currently cost-prohibitive. The ability to track both impairment [12] and enhancement (current study) positions FMS as a powerful tool for bidirectional monitoring of vascular health. This is particularly relevant for clinical translation, where acute responsiveness to therapeutic interventions such as exercise, dietary modification, or pharmacological agents could be assessed objectively and repeatedly without the technical burden of serial FMD studies. The demonstration that regional PWV acutely decreases following endothelial enhancement challenges the traditional view of arterial stiffness as a static structural property, instead revealing it as a dynamic, endothelium-modulated parameter with implications for cardiovascular risk stratification.

The translational pathway for FMS requires systematic validation across multiple domains [40]. *Proof of concept*: the current study, together with prior work demonstrating FMS responsiveness to endothelial impairment [12], establishes that FMS can track bidirectional changes in endothelial function in controlled laboratory settings. *Prospective validation*: future studies must establish FMS and ssFMS performance characteristics in diverse populations, including clinical cohorts with established cardiovascular disease, diabetes, or chronic kidney disease. Critical steps include determining test-retest reliability across multiple visits, establishing minimal clinically important differences in PWV change corresponding to meaningful alterations in vascular health, and defining normative reference ranges stratified by age, sex, and ethnicity. *Incremental value*: comparative effectiveness studies are needed to determine whether FMS and ssFMS provide diagnostic or prognostic information beyond traditional FMD or other emerging endothelial function assessments. The significant within-person inverse association between ssFMD and ssFMS observed here – consistent with the Moens-Korteweg mechanical link between vessel DIA and PWV – suggests that ssFMS captures the mechanical consequences of endothelial activation in real time, potentially offering advantages over DIA-based assessments alone. *Clinical utility*: implementation science research must evaluate whether FMS and ssFMS assessment influences clinical decision-making and patient management in real-world practice settings, including the feasibility of integration into cardiovascular risk screening protocols and therapeutic monitoring programs. *Clinical outcomes*: longitudinal cohort studies are required to determine whether FMS and ssFMS independently predict cardiovascular events, mortality, and response to interventions, thereby establishing its prognostic value for risk stratification and treatment guidance. *Cost-effectiveness*: health economic analyses must quantify whether the reduced technical complexity and operator time of FMS and ssFMS, relative to traditional FMD, translate into cost savings sufficient to justify widespread clinical implementation, particularly in resource-limited settings where endothelial function assessment is currently impractical.

From a mechanistic perspective, pharmacological studies employing selective inhibition of nitric oxide, prostaglandins, and endothelium-derived hyperpolarizing factors are needed to elucidate which endothelial signaling pathways contribute to the observed PWV reductions during sustained shear stress. Understanding these mechanisms will clarify the differential sensitivity of sustained-shear versus reactive hyperemia stimuli and inform optimal protocols for detecting early-stage endothelial dysfunction across diverse pathophysiological conditions.

## Conclusions

A protocol of sustained increases in shear rate via localized heating and exercise induced a significant increase in brachial artery DIA and a concomitant decrease in brachial-radial PWV. A significant within-person

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inverse association between these measures confirms their co-variation in the theoretically predicted direction, consistent with both ssFMD and ssFMS tracking the same acute endothelial response trajectory. These findings suggest that ssFMS is a viable, user-objective tool for assessing acute enhancements in endothelial function.

## Statement of Ethics

This study protocol was reviewed and approved by the Cardiff School of Sport and Health Sciences Ethics Committee, Cardiff Metropolitan University, Approval No. STA-9009, and conformed to the ethical standards established by the Declaration of Helsinki (2013), excluding prior registration in a database. All participants provided written informed consent prior to participating in the study.

## Conflict of Interest Statement

All authors declare that they have no conflicts of interest relevant to the content of this manuscript.


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## Author Contributions

K.S., B.M., S.F., and L.S. conceived and designed the research and drafted the initial manuscript. K.S., T.G., T.D.G., and A.W. performed the experiments. K.S. and L.S. analyzed the data. L.S., B.M., S.F., T.G., T.D.G., J.F., A.W., C.J.P., G.Z., A.J.C., C.P., and K.S. reviewed and edited draft manuscripts and subsequently approved the final version.

## Data Availability Statement

The data that support the findings of this study are not publicly available due to commercial restrictions but are available from the corresponding author upon reasonable request.

## References


1 Cahill PA, Redmond EM. Vascular endothelium-gatekeeper of vessel health. Atherosclerosis. 2016;248:97–109. https://doi.org/10.1016/j.atherosclerosis.2016.03.007
2 Augustin HG, Koh GY. A systems view of the vascular endothelium in health and disease. Cell. 2024;187(18):4833–58. https://doi.org/10.1016/j.cell.2024.07.012
3 Green DJ, Jones H, Thijssen D, Cable NT, Atkinson G. Flow-mediated dilation and cardiovascular event prediction: does nitric oxide matter? Hypertension. 2011;57(3):363–9. https://doi.org/10.1161/HYPERTENSIONAHA.110.167015
4 Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. Int J Cardiol. 2013;168(1):344–51. https://doi.org/10.1016/j.ijcard.2012.09.047
5 Stoner L, Sabatier MJ. Use of ultrasound for non-invasive assessment of flow-mediated dilation. J Atheroscler Thromb. 2012;19(5):407–21. https://doi.org/10.5551/jat.11395
6 Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 2019;40(30):2534–47. https://doi.org/10.1093/eurheartj/ehz350
7 Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation. 2007;115(10):1285–95. https://doi.org/10.1161/CIRCULATIONAHA.106.652859
8 Pereira T, Almeida A, Conde J. Flow-mediated slowing as a methodological alternative to the conventional echo-tracking flow-mediated dilation technique for the evaluation of endothelial function: a preliminary report. Mayo Clin Proc Innov Qual Outcomes. 2018;2(2):199–203. https://doi.org/10.1016/j.mayocpiqo.2018.02.002
9 Naka KK, Tweddel AC, Doshi SN, Goodfellow J, Henderson AH. Flow-mediated changes in pulse wave velocity: a new clinical measure of endothelial function. Eur Heart J. 2006;27(3):302–9. https://doi.org/10.1093/eurheartj/ehi619
10 Nichols W, O'Rourke M, Vlachopoulos C. McDonald's blood flow in arteries. 6th ed. Theoretical, Experimental and Clinical Principles; 2011.
11 Thijssen DH, Dawson EA, Tinken TM, Cable NT, Green DJ. Retrograde flow and shear rate acutely impair endothelial function in humans. Hypertension. 2009;53(6):986–92. https://doi.org/10.1161/HYPERTENSIONAHA.109.131508
12 Stoner L, Stone K, Zieff G, Blackwell J, Diana J, Credeur DP, et al. Endothelium function dependence of acute changes in pulse wave velocity and flow-mediated slowing. Vasc Med. 2020;25(5):419–26. https://doi.org/10.1177/1358863X20926588
13 Tremblay JC, Pyke KE. Flow-mediated dilation stimulated by sustained increases in shear stress: a useful tool for assessing endothelial function in humans? Am J Physiol Heart Circ Physiol. 2018;314(3):H508–20. https://doi.org/10.1152/ajpheart.00534.2017
14 Pyke KE, Jazuli F. Impact of repeated increases in shear stress via reactive hyperemia and handgrip exercise: no evidence of systematic changes in brachial artery FMD. Am J Physiol Heart Circ Physiol. 2011;300(3):H1078–89. https://doi.org/10.1152/ajpheart.00736.2010
15 Trinity JD, Wray DW, Witman MAH, Layec G, Barrett-O'Keefe Z, Ives SJ, et al. Ascorbic acid improves brachial artery vasodilation during progressive handgrip exercise in the elderly through a nitric oxide-mediated mechanism. Am J Physiol Heart Circ Physiol. 2016;310(6):H765–74. https://doi.org/10.1152/ajpheart.00817.2015
16 Pyke KE, Poitras V, Tschakovsky ME. Brachial artery flow-mediated dilation during handgrip exercise: evidence for endothelial transduction of the mean shear stimulus. Am J Physiol Heart Circ Physiol. 2008;294(6):H2669–79. https://doi.org/10.1152/ajpheart.01372.2007
17 Wray DW, Witman MAH, Ives SJ, McDaniel J, Fjeldstad AS, Trinity JD, et al. Progressive handgrip exercise: evidence of nitric oxide-dependent vasodilation and blood flow regulation in humans. Am J Physiol Heart Circ Physiol. 2011;300(3):H1101–7. https://doi.org/10.1152/ajpheart.01115.2010


Downloaded from karger.com/pls/article-pdf/14/1/158/4572901/000553761.pdf by guest on 03 November 2026

18 Bellien J, Iacob M, Remy-Jouet I, Lucas D, Monteil C, Gutierrez L, et al. Epoxyeicosatrienoic acids contribute with altered nitric oxide and endothelin-1 pathways to conduit artery endothelial dysfunction in essential hypertension. Circulation. 2012;125(10):1266–75. https://doi.org/10.1161/CIRCULATIONAHA.111.070680
19 Verbeke FH, Agharazii M, Boutouyrie P, Pannier B, Guérin AP, London GM. Local shear stress and brachial artery functions in end-stage renal disease. J Am Soc Nephrol. 2007;18(2):621–8. https://doi.org/10.1681/asn.2006040400
20 Pyke KE, Dwyer EM, Tschakovsky ME. Impact of controlling shear rate on flow-mediated dilation responses in the brachial artery of humans. J Appl Physiol. 2004;97(2):499–508. https://doi.org/10.1152/japplphysiol.01245.2003
21 Bellien J, Iacob M, Gutierrez L, Isabelle M, Lahary A, Thuillez C, et al. Crucial role of NO and endothelium-derived hyperpolarizing factor in human sustained conduit artery flow-mediated dilatation. Hypertension. 2006;48(6):1088–94. https://doi.org/10.1161/01.HYP.0000246672.72188.bd
22 Bellien J, Costentin A, Dutheil-Maillochaud B, Iacob M, Kuhn JM, Thuillez C, et al. Early stage detection of conduit artery endothelial dysfunction in patients with type 1 diabetes. Diab Vasc Dis Res. 2010;7(2):158–66. https://doi.org/10.1177/1479164109360470
23 Slattery DJ, Stuckless TJR, King TJ, Pyke KE. Impaired handgrip exercise-induced brachial artery flow-mediated dilation in young obese males. Appl Physiol Nutr Metab. 2016;41(5):528–37. https://doi.org/10.1139/apnm-2015-0459
24 Des Jarlais DC, Lyles C, Crepaz N. TREND statement checklist; 2004.
25 Stoner L, McCully KK. Peak and time-integrated shear rates independently predict flow-mediated dilation. J Clin Ultrasound. 2012;40(6):341–51. https://doi.org/10.1002/jcu.21900
26 Kellogg DL Jr., Liu Y, Kosiba IF, O'Donnell D. Role of nitric oxide in the vascular effects of local warming of the skin in humans. J Appl Physiol. 1999;86(4):1185–90. https://doi.org/10.1152/jappl.1999.86.4.1185
27 Taylor WF, Johnson JM, O'Leary D, Park MK. Effect of high local temperature on reflex cutaneous vasodilation. J Appl Physiol Respir Environ Exerc Physiol. 1984;57(1):191–6. https://doi.org/10.1152/jappl.1984.57.1.191
28 Stone K, Fryer S, McDonnell BJ, Meyer ML, Faulkner J, Agharazii M, et al. Aortic-femoral stiffness gradient and cardiovascular risk in older adults. Hypertension. 2024;81(12):e185–96. https://doi.org/10.1161/HYPERTENSIONAHA.124.23392
29 Stone K, Fryer S, Faulkner J, Meyer ML, Heffernan K, Kucharska-Newton A, et al. The aortic-femoral arterial stiffness gradient is blood pressure independent in older adults: the Atherosclerosis Risk in Communities (ARIC) study. J Hypertens. 2021;39(12):2361–9. https://doi.org/10.1097/HJH.0000000000002937
30 Woodman RJ, Playford DA, Watts GF, Cheetham C, Reed C, Taylor RR, et al. Improved analysis of brachial artery ultrasound using a novel edge-detection software system. J Appl Physiol. 2001;91(2):929–37. https://doi.org/10.1152/jappl.2001.91.2.929
31 Pucci G, Cheriyan J, Hubsch A, Hickson SS, Gajendragadkar PR, Watson T, et al. Evaluation of the vicorder, a novel cuff-based device for the noninvasive estimation of central blood pressure. J Hypertens. 2013;31(1):77–85. https://doi.org/10.1097/HJH.0b013e32835a8eb1
32 Stoner L, Stone K, Zieff G, Hanson ED, Credeur D, Faulkner J, et al. The impact of upper-limb position on estimated central blood pressure waveforms. J Hum Hypertens. 2019;33(6):444–53. https://doi.org/10.1038/s41371-019-0179-x
33 Overholser BR, Sowinski KM. Biostatistics primer: part I. Nutr Clin Pract. 2007;22(6):629–35. https://doi.org/10.1177/0115426507022006629
34 Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. Med Sci Sports Exerc. 2009;41(1):3–13. https://doi.org/10.1249/MSS.0b013e31818cb278
35 Cohen J. Statisitical power analysis for behavioural sciences. Newy York; London: Academic Press; 1969.
36 Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27(21):2588–605. https://doi.org/10.1093/eurheartj/ehl254
37 Bramwell JC, Hill AV. The velocity of pulse wave in man. Proc R Soc Lond Ser B Containing Pap a Biol Character. 1922;93(652):298–306. https://doi.org/10.1098/rspb.1922.0022
38 Stoner L, Erickson ML, Young JM, Fryer S, Sabatier MJ, Faulkner J, et al. There's more to flow-mediated dilation than nitric oxide. J Atheroscler Thromb. 2012;19(7):589–600. https://doi.org/10.5551/jat.11973
39 Findlay BB, Gupta P, Szijgyarto IC, Pyke KE. Impaired brachial artery flow-mediated vasodilation in response to handgrip exercise-induced increases in shear stress in young smokers. Vasc Med. 2013;18(2):63–71. https://doi.org/10.1177/1358863X13480259
40 Stone K, Veerasingam D, Meyer ML, Heffernan KS, Higgins S, Maria Bruno R, et al. Reimagining the value of brachial-ankle pulse wave velocity as a biomarker of cardiovascular disease Risk-A call to action on behalf of VascAgeNet. Hypertension. 2023;80(10):1980–92. https://doi.org/10.1161/HYPERTENSIONAHA.123.21314

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