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# Whole body passive heating versus dynamic lower body exercise: A comparison of peripheral hemodynamic profiles

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## New & Noteworthy

Passive heating and exercise increase blood flow through arteries generating a frictional force, termed shear rate, which is associated with positive vascular health. Few studies have compared the increase in arterial blood flow and shear rate elicited by passive heating to dynamic continuous exercise. We found thirty minutes of whole-body passive hot water immersion (42 °C bath) increased femoral artery blood flow and shear rate equivalent to exercising at a moderate intensity (~57% $HR_{max}$).

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# ABSTRACT

Passive heating has emerged as a therapeutic intervention for the treatment and prevention of cardiovascular disease. Like exercise, heating increases peripheral artery blood flow and shear rate which is thought to be a primary mechanism underpinning endothelium mediated vascular adaptation. However, few studies have compared the increase in arterial blood flow and shear rate between dynamic exercise and passive heating. In a fixed crossover design study, 15 moderately trained healthy participants (25.6 ± 3.4 years) (5 female) underwent 30 minutes of whole body passive heating (42 °C bath), followed on a separate day by 30 minutes of semi-recumbent stepping exercise performed at two workloads corresponding to the increase in cardiac output (Qc) (Δ 3.72 $l \cdot min^{-1}$) and heart rate (HR) (Δ 40 bpm) recorded at the end of passive heating. Results: At the same Qc (Δ 3.72 $l \cdot min^{-1}$ vs 3.78 $l \cdot min^{-1}$), femoral artery blood flow (1599 ml/min vs 1947 ml/min) ($p=0.596$) and shear rate (162 $s^{-1}$ vs 192 $s^{-1}$) ($p=0.471$) measured by ultrasonography were similar between passive heating and stepping exercise. However, for the same HR matched intensity, femoral blood flow (1599 $ml \cdot min^{-1}$ vs 2588 $ml \cdot min^{-1}$) and shear rate ($161s^{-1}$ vs $271s^{-1}$) were significantly greater during exercise, compared with heating (both $P=<0.001$). The results indicate that, for moderately trained individuals, passive heating increases common femoral artery blood flow and shear rate similar to low intensity continuous dynamic exercise (29% $VO_{2max}$), however exercise performed at a higher intensity (53% $VO_{2max}$) results in significantly larger shear rates towards the active skeletal muscle.

Key Words: passive heating, dynamic exercise, leg blood flow, ultrasound, shear rate

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## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide. In 2016, the worldwide mortality rate for CVD was ~31%, a figure greater than the nine other leading causes of death combined (46). Exercise is often cited as the most effective non-pharmacological intervention for the prevention and management of CVD (29). The protective effects of exercise on vascular structure and function are partly mediated by the frictional force generated between the endothelium and increased blood flow (shear), resulting in nitric oxide (NO) dependent endothelial vasodilation (16). Unfortunately, a large majority of the global population fails to adhere to the recommended guidelines for physical activity (45), which has led to the unprecedented rise in global obesity and consequently, CVD (4). Therefore, alternative therapies which reduce the risk of CVD are widely sought.

Passive heating has emerged as a potential therapy for CVD with the notion it may induce vascular adaptations comparable to exercise (3). Indeed, Brunt et al. (2016) reported improvements in brachial artery flow mediated dilation, and superficial femoral artery (SFA) compliance and stiffness, following 8 weeks of passive hot water immersion in young healthy sedentary volunteers. Additionally, Romero et al. (2017) reported improvements in macro- and microvascular function in healthy elderly individuals following lower limb hot water immersion; and, Bailey et al. (2016) reported improvements in brachial flow mediated dilatation (~1.71%), as well as a reduction in heat induced hypoperfusion in healthy females following 8 weeks of passive lower body hot water immersion (42ºC). These benefits, observed in healthy volunteers, are now being translated into clinical populations. Neff et al. (2016) reported a reduction in mean arterial pressure in peripheral artery disease (PAD) patients following leg thermotherapy via a water perused suit (48ºC). Similarly, Thomas et al. (2017) reported decreases in blood pressure, increases in popliteal antegrade shear rate, and reductions in both central and peripheral pulse wave velocity in PAD patients following 30 minutes of passive lower limb hot water immersion (42ºC).

Although early evidence demonstrates the therapeutic benefits of passive heating, a key question will be to what extent passive heating provides benefits relative to the most effective non-pharmacological intervention for CVD, exercise. Mechanistically, heating increases cutaneous blood flow to support heat dissipation for maintenance of temperature homeostasis, with exercise increasing skeletal muscle perfusion to meet the metabolic demands of movement. Thus, both

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interventions rely on increasing conduit artery blood flow and shear rate, which have been established as a primary driver mediating vascular adaptation (42). Yet it is not entirely clear what intensity of dynamic exercise should be performed to match vascular shear to passive heating, which must be ascertained before studies can be designed to directly compare chronic passive heating with exercise training, To our knowledge, only one study has directly compared local blood flow and shear rate responses between exercise and passive heating. Thomas et al. (2016) reported a ~232% (181 $s^{-1}$) increase in superficial femoral artery (SFA) shear rate following 30 minutes of passive heating, compared with only a ~146% (104 $s^{-1}$) increase following 30 minutes of treadmill running at ~65% of maximum heart rate. These results suggest whole body passive heating may provide a greater vascular shear stimulus compared with exercise. However, as acknowledged by the authors, shear rates within the SFA i.e. the “active” skeletal muscle, were likely severely underestimated in the exercise condition, as shear was quantified ~5-10 minutes after each trial. After passive heating, core and skin temperature remain elevated with a persistent reduction in downstream resistance maintaining conduit artery blood flow and shear rate (37). Whereas after exercise, the rapid reduction in oxygen demand causes a near instantaneous reduction in perfusion due to tight metabolic flow coupling.

While not providing a direct comparison to passive heating, several studies suggest that shear rates towards active skeletal muscle during exercise (e.g. forearm during handgrip) (14), (quadricep during leg kicking) (33), (quadricep during leg kicking) (43; 44), maybe similar, or substantially higher than values reported for passive heating (28), (35). Indeed, Dawson et al. (2017) reported a mean brachial shear value of 283 $s^{-1}$ during 30 minutes of cycling at 80% maximum heart rate and Padilla et al. (2011) found similar values of 260 $s^{-1}$ after 60 minutes semi-recumbent cycling at 120 watts.

Therefore, the aim of this study was to directly compare both brachial and femoral artery blood flow and shear rate during passive hot water immersion with dynamic lower body exercise performed at a matched cardiovascular demand. To account for the different cardiac responses between heating (heart rate only) and exercise (stroke volume and heart rate), we compared exercise at two clamped workloads, which corresponded to 1) the increase in cardiac output (Qc) and 2) increase in heart rate (HR) recorded at the end of whole body heating. We hypothesized that increases in femoral blood flow and shear rate would be similar when Qc during exercise was matched to heating, but significantly lower when HR during exercise was matched to heating. As Qc typically increases by 3-4 liters during whole body heating (13; 8), primarily

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mediated by an increase in HR approximately 40 beats·min$^{-1}$ (13;12), we hypothesized that this would equate to approximately ~45-50% of maximum HR (~195 - 200 bpm) during running exercise in  young healthy population. Finally, brachial artery blood flow and shear rates would be significantly higher after 30 minutes of heating compared with both Qc and HR matched exercise, due to exercise induced vasoconstriction in non-active skeletal muscle (18).

## METHODS

### Ethical Approval

Written informed consent was provided from all participants following detailed verbal explanations of the experimental protocol which included information regarding all potential risks. The study conformed to the standards set out by the Declaration of Helsinki, except for registration in a database, and was approved by the ethics committee of the University of Innsbruck.

### Participants

Ten male and five female participants (25.6 ± 3.4 years, height, 1.76 ± 0.1 m, weight, 73.6 ± 9.3 kg; $VO_{2max}$, 54.4 ± 7.8 ml·kg·min$^{-1}$) were recruited from the University of Innsbruck. All participants were healthy, non-smokers and free from cardiovascular, metabolic and neuromuscular diseases. Female participants were tested during the early follicular phase of their cycle, this included participants taking oral contraceptives who were tested during the placebo phase of their cycle (low hormone)

### *Experimental Design*

All participants underwent two trials in a fixed crossover study design (Figure 1). Participants were instructed to abstain from strenuous exercise and avoid consumption of caffeine and alcohol for 24 hours prior to each testing day. We advised participants to keep diet consistent between trials and made every effort to perform the stepping test at the same time of day as the heating trial. The first trial involved 30 minutes of passive hot water immersion (PHWI) in a 42 °C bath. This was followed on a separate day by 30 minutes of graded semi-recumbent stepping exercise. All participants undertook the heating trial prior to the stepping trial. A fixed order was required as the cardiovascular demand elicited by passive heating (Δ Qc and Δ HR) was used to target the

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intensity of stepping exercise. The heating trial was undertaken in a physiology laboratory during the winter months (October-January) and the exercise trial was performed during the summer months (May-June) in an environmentally controlled (Ta, 22 °C, relative humidity 40%) chamber (Küba Blue Line DE Professional, Kelvion Holding GmbH, Germany) at the University of Innsbruck.

*Heating Trial*

Upon arrival, participants changed into swimwear (males shorts; females sport shorts and bra) and self-inserted a rectal probe (DeRoyal, Powell, TN, USA) 15 cm past the anal sphincter for monitoring of core temperature. Body weight was recorded (Kern DS 150k1, Kern & Sohn, Germany) and participants positioned themselves on a semi-recumbent bed. After instrumentation and 20 minutes of quiet rest, baseline continuous haemodynamic data were recorded over one minute in a semi recumbent posture. HR was measured from a three-lead electrocardiogram (Tram-rac, Solar 8000M, GE- Marquette, USA). Forearm skin temperature and blood flow were obtained via an integrated thermistor and laser-Doppler flowmeter (Moor Instruments, Devon, UK). Arterial pressure was measured, in duplicate, via electro-sphygmomanometry (Tango, SunTechMedical Instruments Inc., USA) with a microphone placed over the brachial artery to detect Korotkoff sounds. Qc was measured and stroke volume calculated via inert gas rebreathing (Innovision DK-5260, Denmark) (10), alongside a measure of $VO_2$ Thereafter, brachial and common femoral artery blood flow and shear rate were measured using ultrasound (see below). Following acquisition of baseline variables, participants were transferred to a hot bath (42 °C) and immersed up to the height of the mid-sternum with both arms rested at heart level outside the bath (Figure 1), identical to the semi-recumbent posture during baseline measurements. After 30 minutes of heating, brachial blood flow,Qc and $VO_2$ were measured, and the bath was partially drained. Once the water drained to just below the iliac crest, femoral blood flow was measured (2-3 mins) whilst the participant remained seated in the bath.

*Stepping Exercise*

On a subsequent day, upon arrival to the environmental chamber, participants were positioned on the same semi-recumbent medical bed used for the heating trial. To enable participants to perform stepping exercise in the same semi-recumbent position, a cardio-stepper (Ergospect

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medical technology, Innsbruck, Austria) was custom-fixed onto the end of the bed (Figure 2). Following instrumentation, which replicated the heating trial and included measurement of core temperature via a rectal probe (DeRoyal, Powell, TN, USA), in addition to forearm skin temperature and blood flow via an integrated thermistor and laser-Doppler flowmeter (Moor Instruments, Devon, UK), baseline heamodynamic data were recorded following 20 minutes of quiet semi-recumbent rest. This included, blood pressure measured in duplicate by electro-sphygmomanometry and Qc and $VO_2$ assessed by inert gas rebreathing, as during the heating trial. Participants were then instructed to begin stepping exercise and intensity was manipulated such that Qc increased to levels recorded at the end of passive heating. Based on pilot testing, the workload was increased until heart rate was elevated by 20 beats per min, in order to account for the exercise-induced increase in stroke volume that is not apparent with passive heating. Thereafter Qc and $VO_2$ were determined via a inter-gas rebreathe to confirm the correct intensity had been obtained (Qc matched) and the workload was adjusted if required. After five minutes of steady-state exercise at the target workload, continuous haemodynamics and blood pressure measurements were taken alongside simultaneous assessment of brachial and femoral artery blood flow. Subsequently, exercise intensity was increased until HR reached the subject specific target, that was determined from the value recorded at the end of the passive heating trial. Exercise at this workload was maintained for 25 minutes at which a rebreathe was performed for determination of Qc and $VO_2$ alongside measurements of blood pressure (in duplicate) and brachial and femoral blood flow during exercise. To assess blood flow kinetics post-exercise, participants were given a three-second countdown and told to stop exercising where upon a support was placed immediately under the left leg to allow complete relaxation of the limb and facilitate a five-minute continuous measure of femoral blood flow.

### *Ultrasound*

Brachial and common femoral artery blood flow of the left arm and leg were measured using a 9-MHz linear-array Doppler probe (iE33, Philips, Netherlands) by continuous duplex vascular sonography (iE33, Philips, Netherlands). Arterial diameter was imaged using two-dimensional B mode over 30 seconds and measured offline during diastole (in triplicate) by the same investigator. Anatomical landmarks visible during B-mode measurements of diameter were noted to ensure probe placement remained consistent between baseline and all subsequent recordings, as well as between trials. Thereafter, the time average mean blood velocity (TAMV) was

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recorded at an insonation angle of 60° for between 30-60 seconds and imported into Labchart via a Doppler audio converter (Penn State, Hershey, Pennsylvania, USA) (Herr et al. 2010). Antegrade and retrograde blood flows were derived from the TAMV and recorded in separate channels in labchart (see Figure 3 for an example of individual flow profiles). Ultrasound assessments in both trials were conducted by the same investigators. Local arm and leg cooling was applied to the skin (fan and wet towels) if diastolic blood flow appeared elevated during resting baseline measures in order to limit the effect of skin temperature and skin blood flow on the assessment of skeletal muscle blood flow (23).

*Maximal Exercise Test*

All but two participants (due to unrelated injuries) completed a treadmill (HP cosmos, Pulsar, Germany) maximal exercise test for determination of $VO_{2max.}$ The test commenced at a speed of 8 $km \cdot h^{-1}$ with a ~1% incline. Each minute speed was increased by 1 $km \cdot h^{-1}$ until 12 $km \cdot h^{-1}$, thereafter incline was increased by ~1% every 30 seconds until participants reached volitional exhaustion. Breath-by-Breath gas analysis was continuously sampled using an open spirometric system (Oxycon Pro, CareFusion GmbH, Hoechbach, Germany), which was calibrated prior to each measurement according to the manufacturer's guidelines. HR was determined by chest belt (Wear Link, Polar, Kempele, Finland) and transmitted to the spirometric device. $VO_{2max}$ was defined as the highest 30s average in oxygen uptake and maximal heart rate ($HR_{max}$) as the highest 10s average during the test.

A previous study by Bachler et al. (2017) compared $VO_{2max}$ between treadmill running and the cardio stepper used in the current study, whereby $VO_{2max}$ was ~23% higher on the treadmill in similarly trained participants (54.4 $ml \cdot kg \cdot min^{-1}$ versus 54.7 $ml \cdot kg \cdot min^{-1}$). Therefore an estimated stepping VO2max of 42.1 $ml \cdot kg \cdot min^{-1}$ was used to determine the percentage workload during Qc and HR matched intensities while stepping.

*Data analysis*

All continuous measurements were sampled at 250 Hz (Powerlab, ADInstruments, Oxford, UK) and analyzed via an offline data acquisition system (LabChart 8; AD Instruments; Oxford, UK). Brachial and femoral artery blood flow were expressed in ml $min^{-1}$ using the equation below (equation 1), where TAMV was recorded in cm $s^{-1}$, vessel diameters in cm and 60 was used to convert from $ml \cdot s^{-1}$ to $ml \cdot min^{-1}$. Antegrade and retrograde blood flow were also derived using the same equation. Mean arterial pressure (MAP) was calculated from systolic and diastolic values

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from automated measures obtained via electro sphygmomanometer (equation 2). Total blood vessel shear rate, including antegrade and retrograde shear were calculated and expressed in $s^{-1}$. Oscillatory shear index (OSI), which represents the direction and magnitude of flow between systole and diastole was also calculated. Values range between 0 (no oscillations) to 0.5 (high oscillations).

Equation 1: $Blood\ flow = TAMV\ x\ \pi\ (\frac{artery\ diameter\ (mm)}{2})^2\ x\ 60$

Equation 2: $\mathrm{MAP} = \mathrm{DB} + \frac{1}{3} \times (\mathrm{SB} - \mathrm{DP})$

Equations 3: $shear\ rate = 4 \times (\frac{TAMV}{diameter})$

Equation 4: $OSI = \frac{retrograde\ shear}{(antegrade\ shear + retrograde\ shear)}$

### Statistical Analyses

A total of 20 participants, consisting of eleven males and nine females undertook the heating trial. One male volunteer was unable to complete the heating trial and was excluded from analysis. The same ten males and five females undertook the stepping exercise trial. Four females dropped out of the exercise trial, two due to external sporting injuries and two moved away from the area. Therefore, a total of 15 participants took part in both the heating and stepping exercise trials and were included in the analysis.

To identify the independent effect of passive heating, all outcome variables were compared between baseline rest and 30 minutes passive heating using either a paired samples *t*-test, or a Wilcoxon rank test. Comparisons for the exercise trial were made using a repeated measures analysis of variance (ANOVA) with Bonferroni correction to determine changes between baseline, the $Qc_{\mathrm{MATCHED}}$ (5 mins) intensity and the $HR_{\mathrm{MATCHED}}$ intensity (30 mins). To compare passive heating to exercise, change scores were calculated for each variable relative to the appropriate baseline control value and compared using repeated measures ANOVA with Bonferroni correction. To examine the time course of femoral blood flow offset kinetics post exercise, a repeated measures ANOVA was performed with multiple Bonferroni corrections to determine difference from the cessation of exercise (time point 0) until the end of the measurement recording (300 seconds). All values are expressed as mean ± standard deviation with statistical significance set at $P \leq 0.05$.

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Statistical analysis including Levene test of homogeneity of variance was performed using SPSS version 25 (SPSS Inc., IBM, Chicago, IL, USA) and Prism 8 (GraphPad Software Inc., La Jolla, CA, USA).

## RESULTS

### *Maximal Exercise Test*

Average $VO_{2max}$ was 54.7 ± 7.89 ml·kg·min$^{-1}$ with maximum HR recorded at 189 ± 6 beats·min$^{-1}$. This equated to an estimated stepping $VO_{2max}$ of 42.1 ml·kg·min$^{-1}$.

### *Passive hot water immersion*

Thirty minutes of PHWI increased core temperature by 1.3 ± 0.37°C ($P \leq 0.001$) and Qc by 3.72 ± 1.9 l·min$^{-1}$ ($P<0.001$), which was entirely mediated by an increase in HR (38 ± 15 beats·min$^{-1}$) ($P<0.001$) as stroke volume ($P=0.884$) showed little change (Table 2).

PHWI increased femoral artery blood flow by 1303 ± 363 ml·min$^{-1}$ ($P<0.001$) and brachial artery blood flow by 210 ± 64 ml·min$^{-1}$ ($P<0.001$). The increase in blood flow through both conduit arteries corresponded with increased antegrade shear ($P<0.001$) and decreased retrograde shear ($P<0.001$) (Table 1).

### *Stepping exercise*

Stepping exercise was successfully matched to the two targeted intensities. The first exercise workload ($Qc_{MATCHED}$) matched the increase in Qc during PHWI (Ä PHWI;- Ä 3.72 vs $Qc_{MATCHED}$;- Ä 3.78 l·min$^{-}$1, $P \geq 0.999$) and the second intensity ($HR_{MATCHED}$) matched the increase in HR recorded at the end of PHWI (Ä PHWI;- Ä 38 vs $HR_{MATCHED;-}$ Ä 40 beats·min$^{-1}$, $P \geq 0.999$).

Stepping exercise performed at the $Qc_{MATCHED}$ intensity (absolute Qc, 11.41 l·min$^{-1}$) increased femoral blood flow by 1470 ± 464 ml·min$^{-1}$ ($P<0.001$) which manifested to an increase in femoral antegrade shear rate by Ä 144 ± 56 s$^{-1}$ ($P<0.001$) and decreased retrograde shear rate by Ä 7 ± 4 s$^{-1}$ ($P<0.001$). When exercise was performed at the $HR_{MATCHED}$ intensity (absolute HR, 103 beats·min$^{-1}$), femoral blood flow increased by Ä 2123 ± 524 ml min$^{-1}$ ($P<0.001$) with

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antegrade shear rate increasing by Ä 221 ± 58 s$^{-1}$ (P<0.001) and retrograde shear rate decreasing by Ä 8 ± 4 s$^{-1}$ (P<0.001).

Brachial blood flow did not change during stepping at the Qc$_{MATCHED}$ (Ä 2 ± 12 ml·min$^{-1}$, P=0.753), but both brachial antegrade shear rate (Ä 32 ± 22 s$^{-1}$, P<0.001) and retrograde shear rate (Ä 23 ± 18 s$^{-1}$, P<0.001) increased. Stepping exercise performed at the HR$_{MATCHED}$ intensity increased brachial blood flow (Ä 72 ± 61 ml·min$^{-1}$, P≤0.001), with a further increase in antegrade shear rate (Ä 119 ± 78 s$^{-1}$, P<0.001), but only a small increase in retrograde shear rate from baseline (Ä 8 ± 21 s$^{-1}$, P<0.179).

### *Comparison of passive hot water immersion versus stepping exercise*

The increase in femoral blood flow and total shear rate were similar after 30 minutes of PHWI compared to five-minutes stepping exercise performed at the Qc$_{MATCHED}$ intensity, however femoral blood flow and shear rate were significantly greater during exercise performed at the HR$_{MATCHED}$ intensity (both P<0.001, Figure 2A). Femoral antegrade shear rate was similar between heating and exercise performed at the Qc$_{MATCHED}$ intensity (161 ± 58 s$^{-1}$ vs 193 ± 55 s$^{-1}$, P=0.559), but was significantly greater when exercise was performed at the HR$_{MATCHED}$ intensity (161 ± 58 s$^{-1}$ vs 270 ± 59 s$^{-1}$, P<0.001). Femoral retrograde shear rate decreased to 0 s$^{-1}$ (P<0.001) following 30 minutes of passive heating, which was almost identical to the shear rate recorded after five minutes of exercise at the Qc matched exercise intensity (-0.6 ± 1.1 s$^{-1}$). Femoral retrograde shear rate remained at a similar value when recorded at 30 minutes of exercise at the HR$_{MATCHED}$ (-0.05 ± 0.09 s$^{-1}$) intensity.

In contrast to the femoral artery, brachial blood flow and total shear rate were significantly higher after 30 minutes of PHWI compared with exercise performed at both the Qc$_{MATCHED}$ and HR$_{MATCHED}$ intensities (both P<0.001, Figure 2C). Moreover, PHWI caused a greater increase in brachial antegrade shear rate (245 ± 64 s$^{-1}$) than both the Qc$_{MATCHED}$ (32 ± 22 s$^{-1}$) and HR$_{MATCHED}$ (119 ± 78 s$^{-1}$) intensities (P<0.001) and caused a reduction in brachial retrograde shear rate (Ä 10.7 s$^{-1}$). In contrast, stepping exercise performed at the Qc$_{MATCHED}$ intensity resulted in an increase in retrograde shear rate (Ä -23 ± 18 s$^{-1}$, P<0.001), which although decreased by Ä 14.7 s$^{-1}$ after 25 minutes at the HR$_{MATCHED}$ intensity, remained significantly greater than the reduction caused by PHWI (PHWI, Ä 10.7 s$^{-1}$ vs HR$_{MATCHED}$, Ä -8.0 s$^{-1}$).

### *Time course of post exercise femoral shear rate*.

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Peak femoral artery shear rate measured during exercise was 271 ± 59 $s^{-1}$. Thirty seconds after stopping exercise, shear rate was significantly lower (200 ± 50 $s^{-1}$, $P<0.001$) and continued to decrease at each subsequent 30 second time point. At three minutes (180 sec), shear rate started to plateau, but continued to decline slowly and was less than half the peak value when recorded five minutes post exercise (99 ± 35 $s^{-1}$, Figure 3B).

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## DISCUSSION

The main findings of the present study were that, 30 minutes of PHWI, which elicits a substantial increase in core temperature (+1.3 °C) in young moderately trained individuals, increased femoral artery blood flow and altered shear patterns similar to those observed when performing low to moderate intensity exercise (equivalent to approximately~29% stepping $VO_{2max}$). When stepping exercise was performed at a higher $HR_{MATCHED}$ intensity, (approximately ~53% stepping $VO_{2max}$) femoral blood flow and shear rate were substantially greater during exercise compared with PHWI (both $P<0.001$, Figure 2). In contrast, brachial blood flow and total shear rate were significantly higher after 30 minutes of PHWI compared with exercise performed at both the $Qc_{MATCHED}$ and $HR_{MATCHED}$ intensities (both $P<0.001$, Figure 2). Thus, while sauna bathing and other forms of heat therapy may be a beneficial strategy to improve vascular function and cardiovascular risk factors (22), its recommendation should be presented with the caveat that exercise may elicit substantially greater vascular hemodynamics in active limbs.

### *Whole body passive hot water immersion*

Heat therapy is an emerging strategy that has been found to reduce vascular stiffness and endothelial dysfunction in young healthy individuals (5) and consequently could potentially be applied for treatment and prevention of CVD. Passive exposure to heat increases skin and core temperature, decreases downstream vascular resistance and thus increases blood flow through conduit arteries. As a result, shear forces are produced on the endothelium, which can trigger an array of molecular pathways and alter both antiatherogenic and proatherogenic genes to favor vascular health (24). Indeed, we found that sitting in a hot bath (42 °C) for 30 minutes increased skin (~430%) and rectal temperature (1.3 °C), decreased total peripheral resistance (~32%) and substantially elevated blood flow through the common femoral (~442%) and brachial (~488%) arteries. Ultimately, this produced substantial shear rates on both arteries (common femoral, 161 $\pm$ 59 $s^{-1}$; and brachial, 312 $\pm$ 76 $s^{-1}$), with similar degrees of shear (126 $s^{-1}$) being observed in the common femoral artery when core temperature was elevated to 38.4°C via a water perfused suit (7). Others have also measured increases in arterial shear within the brachial (28, 260 $s^{-1}$), superficial femoral (40, 265 $s^{-1}$) (33, 387 $s^{-1}$,) and popliteal (39, 89 $s^{-1}$), arteries during passive heating. While large differences exist in the absolute shear rates between studies, they are most likely due to the choice of artery and crucially the ultimate increase in skin and core temperature.

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Indeed, Chiesa et al. (2016) have documented that a dose response relationship exists between leg temperature and blood flow through the common femoral and superficial femoral arteries. Nonetheless, other potential differences include the interaction between postural unloading of the baroreceptors and heightened sympathetic nerve activity (25) as well as hydrostatic forces due to the level of water immersion between studies.

### *Semi-recumbent stepping exercise*

Aerobic exercise is known to produce a range of vascular benefits including improved vessel compliance, blood perfusion and increased NO bioavailability (17), all of which are suspected to be mediated through an increase in vascular shear stress (16). However, despite these potential benefits, relatively few studies have been able to simultaneously quantify shear rates in vascular territories perfusing non-active and active skeletal muscle during continuous dynamic exercise involving a large muscle mass. Quantifying blood flow and patterns of shear rate during this type of exercise is important as it represents a more ecologically valid form of rhythmic exercise, whereby stroke volume and arterial pulse pressure are increasing alongside a reduction in total peripheral resistance. Similar to previous studies (28), we observed that short (5 minute) bouts of mild intensity lower limb exercise caused minimal changes in brachial blood flow and total shear rate (non-active skeletal muscle), but with prolonged (30 minutes) moderate intensity exercise, brachial blood flow and total shear rate increased slightly. The reason blood flow is increased towards non-active tissue with prolonged lower limb exercise is likely due to the observed increase in downstream forearm vascular conductance, mediated by the slight increase in core and skin temperature and dilation of the cutaneous circulation to aid thermoregulation (37).

To the best of our knowledge, the current study is the only investigation to measure blood flow and shear rate in the common femoral artery (active skeletal muscle) during true dynamic lower body exercise. Stepping for 25 minutes at the highest workload caused an increase in cardiac output to 14.8 $l \cdot min^{-1}$ (heart rate 103 $beats \cdot min^{-1}$; stroke volume 143 ml), a rise in arterial pulse pressure (47 mmHg) and a decrease in total peripheral resistance (5.93 $mmHg \cdot ml^{-1} \cdot min^{-1}$). Under the current experimental conditions, mean femoral blood flow and shear rates were recorded at 2588 $ml \cdot min^{-1}$ and 271 $s^{-1}$ respectively. Similar values for femoral blood flow (2480 $ml \cdot min^{-1}$) and shear rates (254 $s^{-1}$) have been observed during ~3 minutes of progressive rhythmic knee extension exercise at similar cardiovascular workloads (43; 44). Together, these

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findings demonstrate that dynamic leg exercise is a profound stimulus to elevate vascular shear stress towards the active tissue.

*Comparison of passive hot water immersion with stepping exercise*

As passive hot water immersion has emerged as a potential non-pharmacological therapeutic strategy to increase shear rate and thus improve vascular function, it is important to ascertain its potential, relative to other interventions such as exercise. In order to contextualize the shear rates during passive heating, we compared passive heating to exercise at an intensity matched to the increase in Qc and HR measured at the end of PHWI (i.e. matched for cardiovascular demand). Both PHWI and exercise reduced retrograde blood flow and retrograde shear rate in the femoral artery (i.e. in active skeletal muscle) to almost zero in all conditions. However, PHWI only produced an increase in antegrade blood flow and shear rate similar to the $Qc_{MATCHED}$ trial, which was equivalent to low intensity running exercise (approximately ~27% $VO_{2max}$). Indeed, stepping performed at the $HR_{MATCHED}$ intensity (approximately ~45% running $VO_{2max}$) produced a ~77% greater increase in femoral antegrade shear rate compared with PHWI. These data have three important implications. First, they outline the importance of measurement timing by contrasting the findings reported by Thomas et al. (2016) in which higher shear rates were observed in the SFA following 30 minutes of passive heating (259 $s^{-1}$) compared with 30 minutes of treadmill running (175 $s^{-1}$). Thomas et al. (2016) measured femoral blood flow 5-10 minutes after exercise, which likely resulted in a substantial underestimation of exercise blood flow and shear rate due to the rapid reduction in blood flow following cessation of muscle contraction (30). Indeed, we demonstrated that peak shear rate decreased by 71 $s^{-1}$, within as little as 30 seconds post exercise and was reduced by 172 $s^{-1}$ when measured five minutes after exercise (Figure 3B).

Second, the first five minutes of exercise performed at the $Qc_{MATCHED}$ intensity did not increase core temperature, yet increased femoral flow and shear rate equivalent to 30 minutes of passive heating, thus demonstrating the effectiveness of exercise hyperemia at increasing shear rate in response to muscle contraction. Had the $Qc_{MATCHED}$ intensity been extended to 30 minutes, core temperature may have increased slightly, but likely contributing minimally to femoral blood flow relative to the exercise hyperemia. Indeed, 30 minutes of stepping exercise at almost twice the intensity ($HR_{MATCHED}$) only increased core temperature by 0.39 °C, which was far lower than PHWI (+1.31 °C), suggesting low intensity exercise may be a more tolerable intervention for

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providing a vascular shear stimulus. In this regard, emphasis should be placed on the potential of dynamic exercise to increase vascular shear. Studies using the thermodilution technique have reported leg blood flow values of ~5.81 $l \cdot min^{-1}$ (35), ~5.57 $l \cdot min^{-1}$ (21), ~5.58 $l \cdot min^{-1}$ (1), ~8.0 $l \cdot min^{-1}$ (26) and ~8.8 $l \cdot min^{-1}$ (36) during leg extensor exercise of various workloads. Moreover, single leg blood flow values of ~9.10 $l \cdot min^{-1}$ (6) and ~12.52 $l \cdot min^{-1}$ (14) have been measured during maximal diagonal striding (cross-country skiing) and cycling exercise respectively. As retrograde blood flow and thus velocity through the common femoral artery is minimal during rhythmic exercise (see table 2, although likely higher during muscle contraction with resistance type exercise such as leg kicking), a reasonable estimation of vascular shear rate can be recalculated from these blood flow values, assuming a common femoral artery diameter of 0.958 cm for modestly trained individuals (current study) and a diameter of 1.053 cm for elite level athletes (20) (Figure 8). Using these values, vascular shear appears to be linearly related to workload and substantially greater values can be achieved compared to passive heating. Moreover, common femoral artery blood flow is increased up to 1.24 $l \cdot min^{-1}$ (7) when core temperature is elevated by 1.5 °C, yet no further increases can be obtained despite core temperature being elevated by 2.0 °C. Thus, it appears that passive heating has a celling effect for increasing vascular shear in the femoral artery somewhere comparable to exercising at a mild to moderate intensity (Figure 4).

Third, in contrast to the femoral artery, PHWI did provide a larger shear stimulus in the brachial artery compared to exercise, suggesting that passive heating increases flow and shear more globally to vascular beds throughout the body than exercise. This observation suggests that passive heat therapy may theoretically show greater improvements in brachial artery function (i.e. flow mediated dilation) compared to moderate lower body exercise training. However, for a more accurate comparison, passive heat therapy should be compared to longer durations of intense exercise where both core and forearm skin temperatures would be substantially elevated.

## Clinical Implications

In terms of vascular shear, our data quantifies that being exposed to a high degree of whole body heat stress (+1.3°C) is comparable to low intensity lower body exercise (approx. (~27% running $VO_{2max}$) in young healthy individuals. These data should help guide future studies aiming to compare chronic passive heating with exercise training, alongside future studies aiming to define and prescribe suitable doses of heating and exercise training in clinical populations. Additionally,

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the data place passive heating into context with exercise and may help the general population understand the powerful benefits of even low intensity exercise.

That being said, we fully accept that passive heating provides a whole-body shear stimulus the equivalent of low intensity exercise, supporting its application in clinical and elderly populations who are limited in their capacity to exercise. Indeed, Thomas et al. (2017) demonstrated comparable increases in popliteal shear rates following 3 minutes of treadmill walking at 3km/h with a ~10% incline (standard test used for diagnosis of PAD) and 30 minutes of lower limb heating in PAD patients. Critically, these patients report claudication during short bouts of walking, (10 mins) making heating a much more suitable intervention that provides a comparable shear stimulus to exercise. Furthermore, heating can be endured for a prolonged period compared with exercise in this population, thereby potentially providing greater vascular adaptations.

### *Limitations*

During the exercise trial, we successfully matched both exercise intensities to the intended cardiovascular loads of passive heating. However, we did not match the duration of each workload relative to the time spent under passive heating. For example, the $Qc_{MATCHED}$ intensity was only measured after 5 minutes. While this may limit our interpretation slightly, it is unlikely that exercising at such a relative low steady-state workload (~27% running $VO_{2max}$) for a further 25 minutes would have substantially altered the physiological response we observed after 5 minutes. Furthermore, we did not match core temperature changes between trials, which would separate differences in heat induced increases in blood flow from exercise. Another limitation is that we did not perform repeat measures of shear rate in the brachial and femoral artery post heating. After passive heating, core and skin temperature remain elevated with a persistent reduction in downstream vascular resistance, which is in opposition to acute mild to moderate intensity exercise. Therefore, to precisely compare passive heating with exercise, several hours of shear need to be recorded during and after varying degrees of heat stress and exercise at various intensities/durations. In addition, we did not assess thermal comfort which would provide support for out statement regarding the tolerability of passive heating compared with exercise. However, we based this statement on the substantially elevated core and skin temperatures which are associated with thermal comfort (11). Furthermore, we referred to participants performing stepping exercise at 27 % ($Qc_{MATCHED}$) and 45% ($HR_{MATCHED}$) of their running $VO_2$ max, however this was an estimate based on the comparison of $VO_2$ max scores between treadmill

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running, cycle ergometry and cardio-stepping (Bachlet et al. 2017). Whilst we did not measure $VO_2$ max on our stepper, the paper referenced used young healthy participants who were well matched in terms of cardiorespiratory fitness (treadmill $VO_2$ max 54.4 $ml \cdot kg \cdot min^{-1}$ ) compared with out participants (54.7 $ml \cdot kg \cdot min^{-1}$), therefore we felt justified in making this comparison but should emphasise that these values were estimates. Finally, we acknowledge the time gap between trials (4 months) may have biased our measurements due to potential changes in lifestyle factors or training habits. The time gap was due to logistically issues concerning the location and transportation of expensive equipment between laboratories. However, all participants were instructed to maintain their normal day-to-day training habits between trials, with emphasis placed on replicating their diet and daily activities 24 hours before testing sessions. We also assessed baseline parameters before both trials and found similar values for Qc, HR and stroke volume (Table 3) providing some evidence that training status remained relatively consistent between trials. Moreover, our measurements of blood flow and shear rates at rest and during exercise are in line with previous literature, suggesting these effects are likely minimal (32). Finally, our study was conducted in a young healthy population and we acknowledge that the practical application of many passive heating interventions are targeted at elderly or clinical populations unable to exercise, consequently future studies should focus on such groups to determine whether these populations have similar increases in blood flow and shear rate under matched conditions.

## Conclusion

These findings suggest that whilst whole body heating provides a shear rate stimulus that matches low intensity exercise, it may be more challenging to endure compared with time matched exercise owing to the greater increase in core temperature (1.31 ± 0.37 vs 0.39 ± 0.19 °C). Furthermore, if higher exercise intensities can be performed, exercise provides a substantially greater shear stimulus toward the active skeletal muscle, which is likely to confer superior vascular adaptations in young healthy individuals.

## ADDITONAL INFORMATION

### *Competing Interests*

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None of the authors have any conflicts of interests.

*Author Contributions*

Conception/design of the work: JSL, WKC III, JPM, SAR. Acquisition/analysis of data for the work: All Authors. Drafting and revisions of the work: SBA, JSL, HM, ABH, LSS. Final approval: All authors.

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## Table and Figure Captions

**Figure 1**. Schematic of experimental design and set up of heating and exercise trial. Note values are estimated to demonstrate matching of intensity and do not reflect those recorded in study.

**Figure 2**. Comparison of the changes in femoral and brachial blood flow (Panel A), alongside changes in mean, antegrade and retrograde shear rate in the femoral (Panel B) and brachial (Panel C) arteries after 30 minutes PHWI (42 °C) versus semi recumbent stepping exercise performed at two workloads equivalent to the increase in cardiac output ($Qc_{MATCHED}$) and heart rate ($HR_{MATCHED}$) measured at the end of 30 minutes passive heating (n=15).

**Figure 3**. (A) Example of beat-by-beat blood flow and shear in the common femoral artery and heart rate during exercise and recovery. On occasion, a transient loss (2-3 seconds) of the femoral flow waveform at the end of exercise was caused by placing support under the participant's leg. (B) Common femoral shear rate measured immediately after cessation of stepping exercise at the $HR_{MATCHED}$ intensity (0) and plotted in 30 second intervals over 5 min of recovery (n=15). All values significantly different from 0 (**$P<0.001$). FA, common femoral; BF, blood flow; and HR, heart rate.

**Figure 4**. Common femoral artery shear rate measured during semi recumbent rest (grey), following 30 minutes PHWI (42 °C) (orange), after stepping exercise at $Qc_{MATCHED}$ and $HR_{MATCHED}$ intensities (blue). The purple bar represents common femoral shear rate recalculated from blood flow data measured using the thermodilution technique. Participants were endurance trained and were cycling at 70 W which produced a mean blood flow of 3.15 $l\cdot min^{-1}$ (Proctor et al. 1988). No femoral diameter was reported in the study therefore, using the mean diameter reported in the present study (0.958), we re-calculated shear rate using the rearranged equation (see below) to derive blood velocity (TAMV) and then applied blood velocity values to estimate shear rate. Additional data include superficial femoral artery shear rate during leg extension exercise in national level cyclists and swimmers (black) (Walther et al. 2008).The brown bar represents common femoral artery shear rate recalculated based on blood flow values reported during knee extension exercise performed at 70 W for one participant. Peak blood flow values were reported as 7.22 $l\cdot min^{-1}$ (Rådegran, 1997), however common femoral artery diameter was not reported therefore using a femoral diameter reported in elite road cyclist (10.053 mm), we

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used the same method mentioned previously to re-estimate shear rate. Finally, the same approach was used to estimate shear rate from (Calbet et al. 2004) and (Gonzaìlez-Alonso & Calbet, 2003), who reported single leg blood flow values of 9.10 $l\cdot min^{-1}$ and 12.52 $l\cdot min^{-1}$ in healthy trained males during cross country skiing and cycling, respectively. The same diameter reported in elite cyclists was used (10.053 mm) for calculation of shear as participants in these studies were also elite level athletes.

**Table 1**. Brachial and femoral artery blood flow and shear rate patterns pre and post 30 minutes of passive hot water (42 °C) immersion.

Data are mean ± standard deviation. n =15. % Ä calculated from baseline. OSI, oscillatory shear index.

**Table 2**. Brachial and femoral blood flow and shear rate patterns measured during stepping exercise matched to the increase in cardiac output and heart rate measured after 30 minutes passive hot water (42 °C) immersion.

Data are mean ± standard deviation. n =15, P<0.05*, P<0.01** compared to baseline. P<0.01† Qc matched compared to HR Matched. % Ä calculated from baseline. Abbreviations: OSI, oscillatory shear index.

**Table 3**. Change in cardiovascular variables at rest and during stepping exercise matched to the increase in cardiac output and heart rate measured after 30 minutes passive hot water (42 °C) immersion.

Data are mean ± standard deviation. n=15.* $P \leq 0.05$ difference to baseline. # $P \leq 0.05$ difference between heating and Qc matched. † $P \leq 0.05$ difference between heating and HR matched. Abbreviations: Qc, cardiac output;- HR, heart rate;- SV, stroke volume;- TPR, total peripheral resistance;- SBP, systolic blood pressure;- DBP, diastolic blood pressure;- MAP, mean arterial pressure;- $T_{REC,}$ rectal temperature. Data for forearm skin temp, forearm blood flow and forearm vascular conductance are from 14 participants. Note the discrepancy in HR and SV calculation of Qc is because HR is presented from resting steady-state ECG, whereas SV is calculated from the

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measured cardiac output and HR during the rebreathing procedure, which tends to increase HR slightly.

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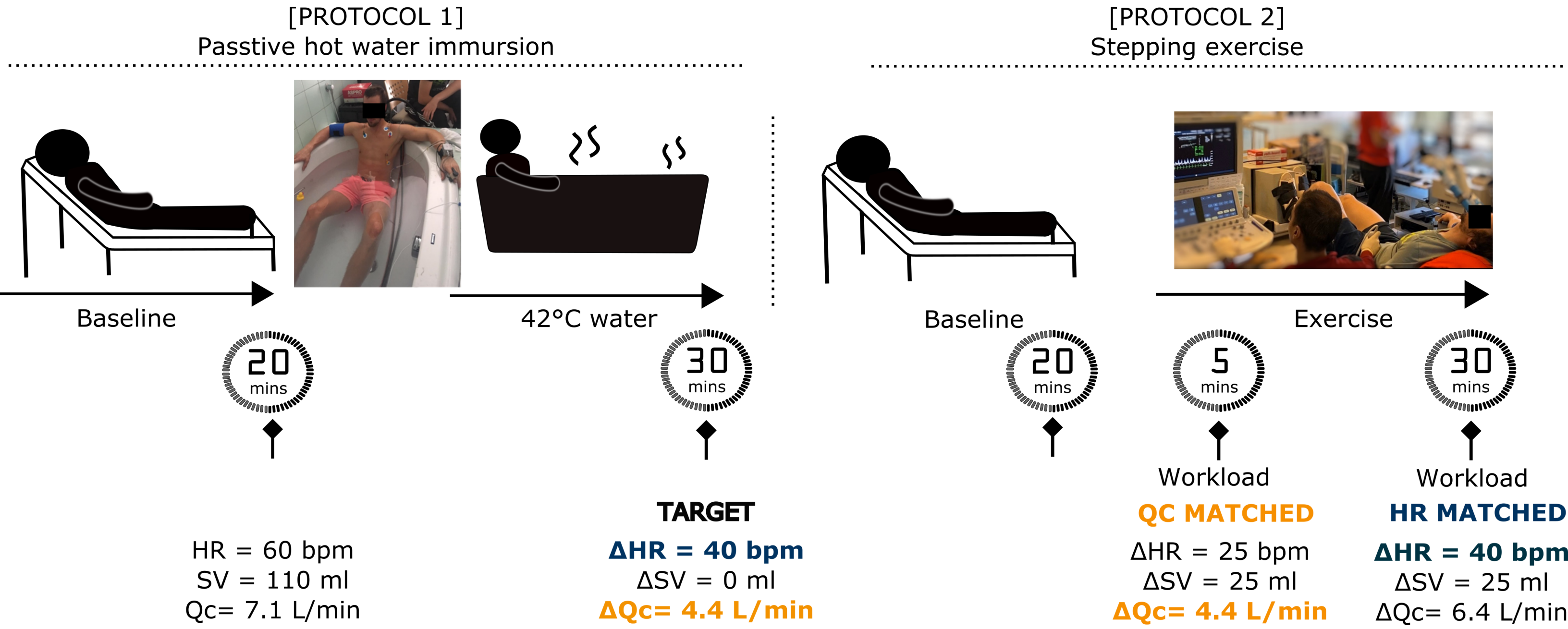

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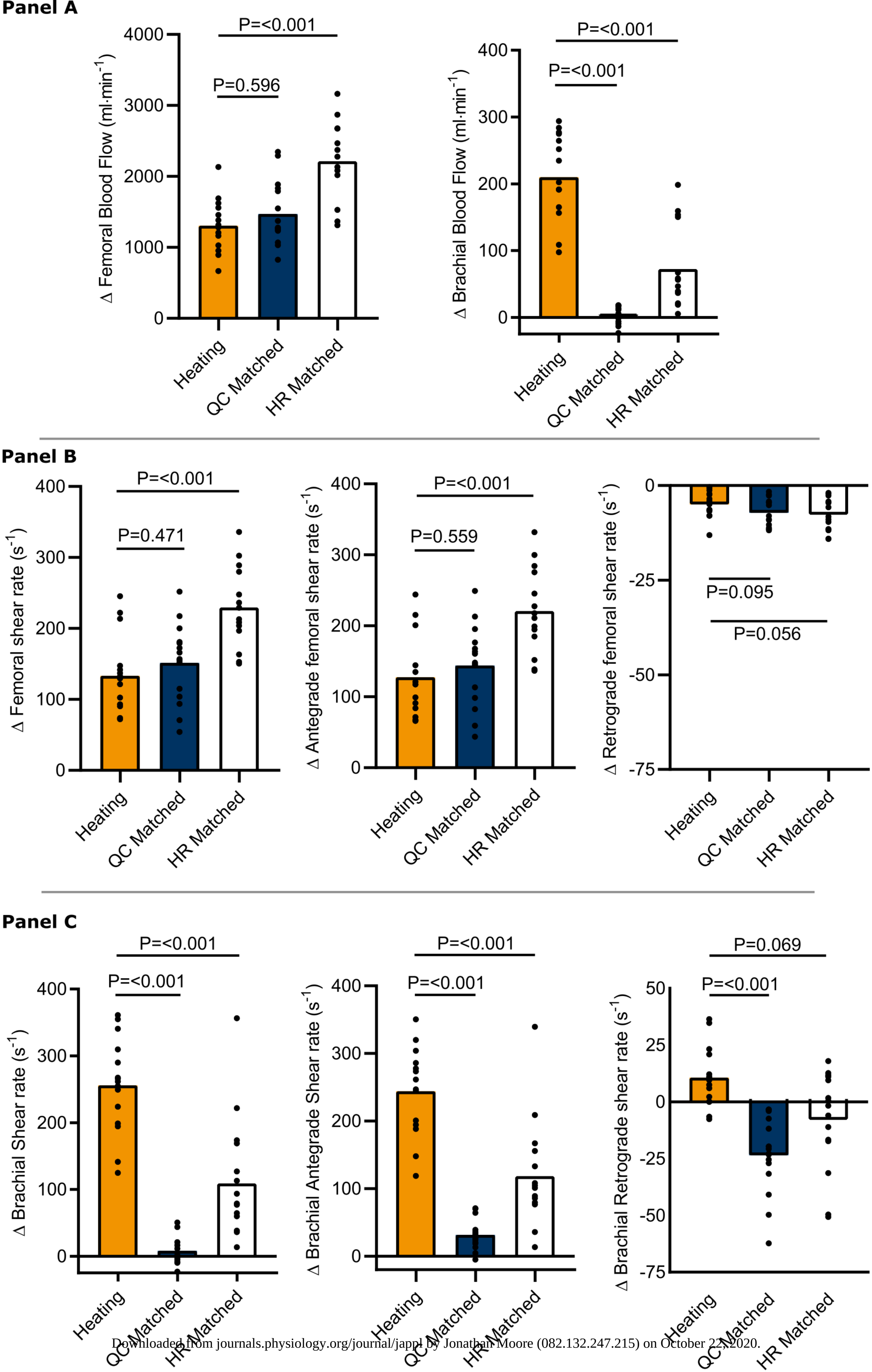

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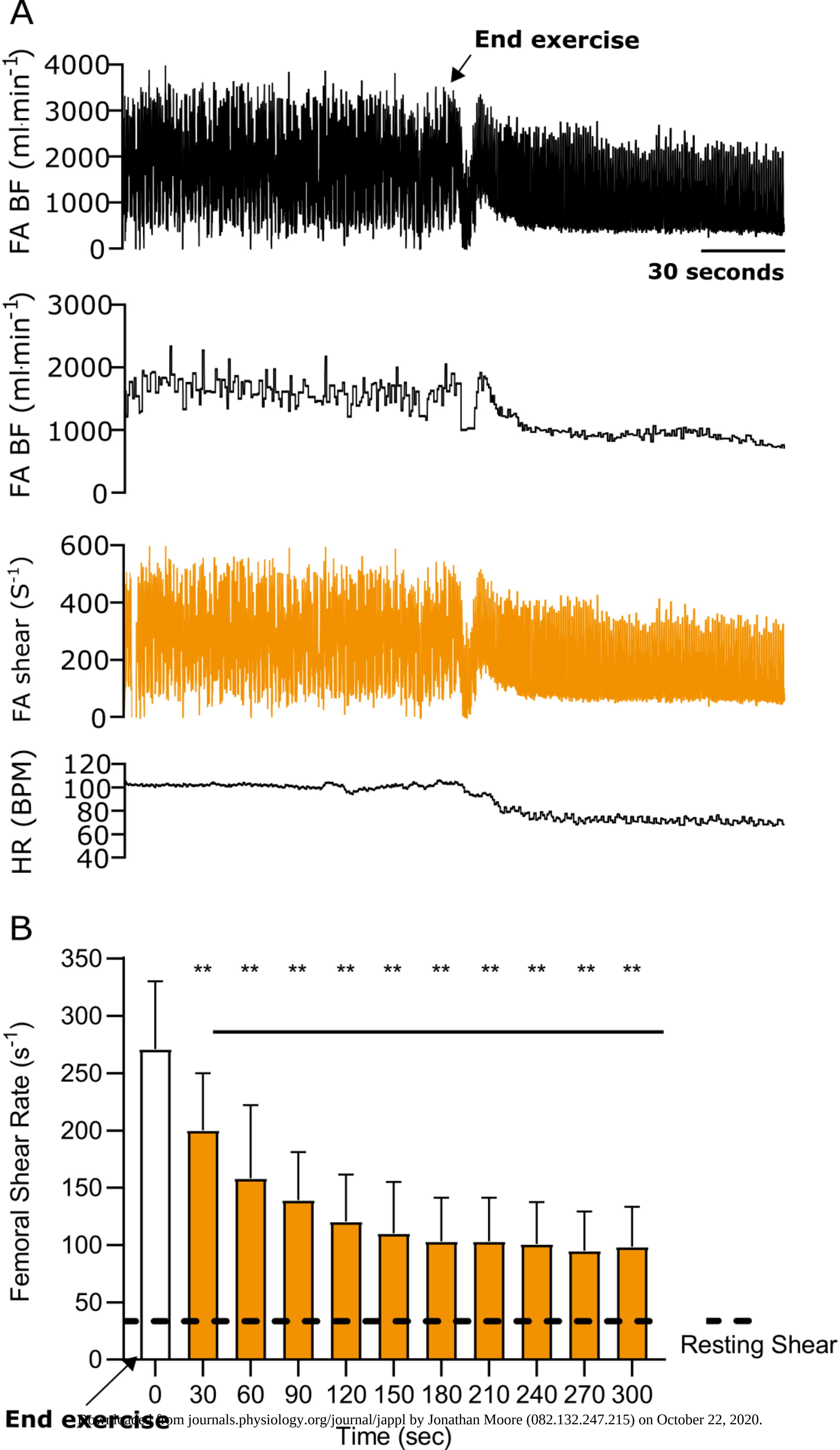

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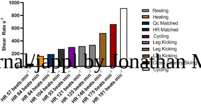

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| | **Baseline** | **Heating** | **% Δ** | **P-Value** |
|---|---|---|---|---|
| **Brachial artery** | | | | |
| Blood Flow ($ml \cdot min^{-1}$) | 44 ± 11 | 254 ± 67 | + 477 | <0.001 |
| Total Shear Rate ($s^{-1}$) | 56 ± 13 | 312 ± 76 | + 457 | <0.001 |
| Antegrade Shear Rate ($s^{-1}$) | 69 ± 15 | 312 ± 74 | + 352 | <0.001 |
| Retrograde Shear Rate ($s^{-1}$) | -13 ± 12 | -2 ± 4 | - 85 | <0.001 |
| OSI | 0.270 ± 0.265 | 0.008 ± 0.016 | - 97 | 0.002 |
| Conductance ($ml \cdot min^{-1} \cdot 100\ mmHg^{-1}$) | 65 ± 16 | 368 ± 79 | + 466 | <0.001 |
| Diameter (cm) | 0.398 ± 0.048 | 0.404 ± 0.054 | | 0.342 |
| **Femoral artery** | | | | |
| Blood Flow ($ml \cdot min^{-1}$) | 295 ± 126 | 1599 ± 402 | + 442 | <0.001 |
| Total Shear Rate ($s^{-1}$) | 28 ± 9 | 161 ± 59 | + 475 | <0.001 |
| Antegrade Shear Rate ($s^{-1}$) | 34 ± 10 | 161 ± 59 | +374 | <0.001 |
| Retrograde Shear Rate ($s^{-1}$) | -5 ± 3 | 0 ± 1 | -100 | <0.001 |
| OSI | 0.200 ± 0.169 | 0.002 ± 0.007 | -99 | <0.001 |
| Conductance ($ml \cdot min^{-1} \cdot 100\ mmHg^{-1}$) | 382 ± 165 | 2051 ± 439 | +437 | <0.001 |
| Diameter (cm) | 0.957 ± 0.117 | 0.959 ± 0.118 | | 0.852 |

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| | Baseline | Qc Matched | % Δ | HR Matched | % Δ | ANOVA P-Value |
|---|---|---|---|---|---|---|
| **Brachial artery** | | | | | | |
| Blood Flow (ml·min$^{-1}$) | 37 ± 19 | 39 ± 21 | +5 | 109 ± 62**† | +195 | 0.0004 |
| Total Shear Rate (s$^{-1}$) | 59 ± 24 | 67 ± 30 | + 14 | 168 ± 84**† | +185 | 0.0003 |
| Antegrade Shear Rate (s$^{-1}$) | 69 ± 21 | 101 ± 26 ** | +46 | 188 ± 74**† | +172 | <0.0001 |
| Retrograde Shear Rate (s$^{-1}$) | -10 ± 8 | -33 ± 23** | -230 | -18 ± 19 | +80 | 0.0023 |
| OSI | 0.22 ± 0.24 | 0.65 ± 0.56** | +195 | 0.15 ± 0.19** | -32 | 0.0011 |
| Conductance (ml·min$^{-1}$·100 mmHg$^{-1}$) | 56 ± 33 | 47 ± 30 | -16 | 117 ± 68*† | +109 | 0.0018 |
| Diameter (cm) | 0.387 ± 0.053 | 0.379 ± 0.048 | | 0.378 ± 0.054 | | 0.0391 |
| **Femoral artery** | | | | | | |
| Blood Flow (ml·min$^{-1}$) | 374 ± 108 | 1844 ± 468** | +393 | 2588 ± 527**† | +592 | <0.0001 |
| Total Shear Rate (s$^{-1}$) | 41 ± 15 | 193 ± 60** | +370 | 271 ± 59**† | +561 | <0.0001 |
| Antegrade Shear Rate (s$^{-1}$) | 49 ± 14 | 193 ± 59** | +294 | 270 ± 59**† | +451 | <0.0001 |
| Retrograde Shear Rate (s$^{-1}$) | -8 ± 4 | -0.6 ± 1** | -93 | -0.05 ± 0.09** | -99 | <0.0001 |
| OSI | 0.23 ± 0.18 | 0.01 ± 0.01** | -96 | 0.00 ± 0.00** | -100 | 0.0002 |
| Conductance (ml·min$^{-1}$·100 mmHg$^{-1}$) | 445 ± 128 | 2121 ± 497** | +377 | 2725 ± 567**† | +512 | <0.0001 |
| Diameter (cm) | 0.931 ± 0.085 | 0.980 ± 0.096 | | 0.938 ± 0.107 | | 0.5581 |

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|  | **Heating** |  | **Exercise** |  |  | **ANOVA P-Value** |
|---|---|---|---|---|---|---|
|  | Baseline Heating | Δ Heating | Baseline Exercise | Δ Qc Matched | Δ HR Matched |  |
| Qc (l·min$^{-1}$) | 7.66 ± 1.4 | 3.72 ± 1.9* | 7.68 ± 1.9 | 3.78 ± 2.00* | 7.02 ± 6.00 † | 0.03 |
| Heart rate (beats·min$^{-1}$) | 65 ±10 | 38 ±15* | 63 ±9 | 18 ±10*# | 40 ±32* | <0.0001 |
| SV (ml) | 111 ± 20 | 1 ±19 | 122 ± 26 | 20 ±24*# | 21 ±57* | 0.19 |
| Femoral TPR (mmHg·ml·min$^{-1}$) | 10.6 ± 2.6 | -3.4* | 11 ± 1.9 | 8 ± 1.1* | 5 ± 1.1*† | 0.02 |
| Femoral conductance (ml·min$^{-1}$·100 mmHg$^{-1}$) | 382 ± 165 | 1669 ± 415* | 445 ± 128 | 1675 ± 495* | 2279 ± 569* † | 0.0009 |
| SBP (mmHg) | 111 ± 9 | 28 ± 21* | 116 ± 9 | 11 ± 12.33*# | 43 ± 19*† | <0.0001 |
| DBP (mmHg) | 61 ± 6 | -13 ± 10* | 68 ± 8 | -5 ± 5*# | -4 ± 14 | 0.03 |
| MAP (mmHg) | 77 ± 6 | 0 ± 11 | 84 ± 7 | 1 ± 5 | 11 ± 11*† | 0.0027 |
| Pulse pressure (mmHg) | 49 ± 11 | 41* | 48 ± 9 | 63 ± 13*# | 95 ± 21* | <0.0001 |
| Rectal temperature (°C) | 36.97 ± 0.20 | 1.31 ± 0.37* | 36.88 ± 0.22 | 0.03 ± 0.11# | 0.39 ± 0.19*† | <0.0001 |
| Forearm skin Temp (°C) | 29.45 ± 1.03 | 3.71 ± 1.39* | 28.44 ± 0.87 | 0.00 ± 0.40$^{\#}$ | 0.66 ± 1.02*† | <0.0001 |
| Forearm skin blood flow (PU) | 51 ± 41 | 132 ± 79* | 30 ± 10 | 14 ± 20*# | 74 ± 47* | 0.003 |
| Forearm cutaneous vascular conductance (a.u$^{1}$·100 mmHg$^{-1}$) | 67 ± 52 | 114 ± 68* | 35 ± 12 | 48 ± 48* | 75 ± 54* | 0.06 |
| $VO_2$ ( ml·kg·min$^{-1}$) | 5.36 ± 1.43 | 0.92 ± 1.40* | 4.51 ± 1.41 | 7.79 ± 2.76*# | 16.52 ± 7.57*† | <0.0001 |

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