High intensity exercise and passive hot water immersion cause similar post intervention changes in peripheral and cerebral shear.

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ABSTRACT

Passive hot water immersion (PHWI) provides a peripheral vasculature shear stimulus comparable to low intensity exercise within the active skeletal muscle, whereas moderate and high intensity exercise elicit substantially greater shear rates in the peripheral vasculature, likely conferring greater vascular benefits. Notably, few studies have compared post intervention shear rates in the peripheral and cerebral vasculature following high intensity exercise and PHWI, especially considering that the post intervention recovery period represents a key window in which adaptation occurs. Therefore, we aimed to compare shear rates in the internal carotid artery (ICA), vertebral artery (VA) and common femoral artery (CFA) between high intensity exercise and whole-body PHWI for up to 80 minutes post intervention. Fifteen healthy (27 ± 4 years), moderately trained individuals underwent three-time matched interventions in a randomised order which included 30 minutes of whole-body immersion in a 42°C hot bath, 30 minutes of treadmill running and 5x4 minute high intensity intervals (HIIE). There were no differences in ICA (P= 0.4643) and VA (P=0.1940) shear rates between PHWI and exercise (both continuous and HIIE) post intervention. All three interventions elicited comparable increases in CFA shear rate post intervention (P=0.0671), however, CFA shear rate was slightly higher 40 minutes post threshold running (P=0.0464) and, slightly higher, although not statically for HIIE (P=0.0565) compared with PHWI. Our results suggest that time and core temperature matched high intensity exercise and PHWI elicit limited changes in cerebral shear and comparable increases in peripheral vasculature shear rates when measured for up to 80 minutes post intervention.

Key points

What is the central question of this study?

- The study aimed to compare shear rates in lower limb and extracranial cerebral blood vessels for up to 80 minutes following high intensity exercise and whole-body passive hot water immersion (PHWI).

What is the main finding and its importance?

- Time and core temperature matched high intensity exercise and whole body PHWI both elicited minimal, but comparable post intervention changes in cerebral artery shear rate. Furthermore, 30 minutes of PHWI caused a similar post intervention increase in femoral shear rate as high intensity exercise, however femoral shear remained slightly elevated for a longer period following high intensity exercise. These results suggest that PHWI provides post intervention changes in lower limb peripheral shear rates comparable to intense exercise and is likely a therapeutic alternative in individuals unable to perform exercise.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide and has been linked to the development of cognitive diseases including dementia (Stampfer et al. 2006), (Tini et al. 2020) and stroke (Arboix et al. 2015). Alzheimer's disease, the most common form of dementia is rapidly rising with estimates predicting a fourfold increase in the number of cases by 2050 (Dos Santos Picanco et al. 2018). Exercise is often cited as the most effective intervention for the prevention and management of CVD (Piepoli et al. 2016) and has also been reported as the most effective modifiable intervention for reducing the development of Alzheimer's disease (Barnes et al. 2011). Unfortunately, one in four adults and 81% of adolescents fail to meet government physical activity recommendations, which has contributed to the unprecedented rise in the incidence of CVD and cerebrovascular diseases (Biswas et al. 2015).

Mechanistically, one avenue through which aerobic exercise exerts a protective effect on the cerebral and peripheral vessels is via an increase in blood flow and shear stress. The increase in shear results in endothelial mediated nitric oxide (NO) production and vascular vasodilation (Green et al. 2017). In addition, an elevation in arterial shear stress stimulates expression of vascular endothelial growth factor (VEGF), a precursor for angiogenesis (Chiu et al. 2009), thus contributing to increased capillarisation, enhanced oxygen delivery and clearance of metabolic by-products (Laughlin & Roseguini, 2008). Habitual exercise that repetitively elevates shear stress also increases NO bioavailability (Casey at al. 2017), ultimately aiding vascular compliance and lowering blood pressure compared with a sedentary lifestyle (Campbell et al. 2011). Furthermore, in the brain, an elevation in cerebral blood flow (CBF) and shear stress is thought to promote the clearance of insoluble amyloid β (Aβ), a protein associated with plaque formation leading to cerebral inflammation and cognitive impairment (Stillman et al. 2017).

In the setting of low adherence to exercise (McArthur et al. 2014), alternative modalities to promote vascular health are warranted. Like exercise, whole body passive heating increases arterial blood flow to support conductive and convective cooling. As such, the increase in blood flow through the conduit arteries causes an increase in shear stress and has been shown to improve endothelial function, peripheral arterial vascular stiffness and blood pressure in young, sedentary individuals (Brunt et al. 2016). Furthermore, lower leg passive heating improves macro- and microvascular function in elderly individuals (Romero et al. 2017) and decreases

central and peripheral pulse wave velocity in peripheral artery disease patients (Thomas et al. 2017). Whilst these data highlight that passive heat therapy can target the peripheral vasculature, potential mechanism(s) that could crossover to directly improve cerebral vascular health are not clear. For example, while epidemiological evidence has linked an increased frequency of sauna use (9-12 times a month versus 4 times a month) with a reduced risk of Dementia (Knekt et al. 2020), heat stress typically reduces blood flow (thus shear rate) to the brain due to hyperventilation induced hypercapnia (Bain et al. 2013; Nelson et al. 2011; Brothers et al. 2009). One potential explanation for these divergent findings maybe that blood flow to the brain and intracranial shear stress are elevated in the post heating period, due to an increase in cerebral metabolic rate (Bain et al. 2020) that is not restrained by hyperventilation induced hypocapnia. However, it is worth mentioning that despite clamping end-tidal carbon dioxide during heat stress, blood flow to the brain is only minimally affected by the independent increase in core temperature (Caldwell et al. 2020) and is generally well maintained by an increase in cerebral vascular resistance i.e. autoregulation (Olesen et al. 2013) that would oppose hypotension post passive heating (or exercise). Thus, it cannot be assumed that changes in shear stress observed in the major peripheral arteries (brachial/femoral) are similar in the cerebral circulation.

An additional consideration when attempting to compare the potential benefits of passive heating to exercise is the choice of exercise intensity. During exercise or passive heating, we have previously shown that the increase in femoral shear rates during whole body passive hot water immersion (PHWI) is equivalent to performing low intensity exercise in healthy individuals (29% VO_2 max) (Amin et al. 2020). Yet a recent study reported similar increases in brachial and superficial femoral artery shear rates up to 40 minutes post moderate intensity exercise (60% VO_2 max) and PHWI (Francisco et al. 2021). Therefore, our aim was to extend this evidence base that the recovery period post exercise/heating represents a key window for adaptation (Romero et al. 2017) and determine if similar results could be obtained in the peripheral vasculature compared to high intensity exercise (HIIE). Moreover, complementing these peripheral data with a regional assessment of CBF and cerebral conduit artery shear rate.

We measured common femoral artery (CFA), internal carotid artery (ICA) and vertebral artery (VA) blood flow and calculated shear rate at 20-minute intervals for up to 80 minutes after each intervention. We hypothesized that CFA shear rate would remain elevated for longer after HIIE

compared with threshold running and PHWI, but due to rapid cerebral autoregulation, ICA and VA blood flow and shear rate would return to baseline immediately after completion of all interventions.

METHODS

Participants

A total of 15 participants including ten males and five females (age, 27 ± 4 years, height, 175 ± 53 cm, weight, 69.79 ± 8.72 kg; VO_{2max}, 55.82 ± 10.42 ml·kg·min^{-1}), free from cardiovascular, respiratory, metabolic and neuromuscular diseases, were recruited via personal communication. All experimental procedures had Institutional Review Board approval from Innsbruck University and conformed to the latest revision of the Declaration of Helsinki, except for registration in a database. Written informed consent was obtained after verbal and written explanation of the study protocol and potential risks associated with study participation. All participants were asked to abstain from strenuous physical activities and alcohol (24 hours) as well as caffeine (12 hours) before testing. Female participants were tested during the early follicular phase of their menstrual cycle or the placebo phase of oral contraceptive use.

Experimental protocol.

Maximal exercise test. Participants performed an incremental exercise test to exhaustion on a separate day prior to the experimental trials. Tests were performed on a motorized treadmill (HP cosmos, Pulsar, Germany) for the determination of maximal oxygen uptake (VO_{2max}, Oxycon Pro, Jäger, Germany) and maximal heart rate (HR_{Max}). The exercise protocol commenced at a speed of 8 km·h^{-1} with a 1% incline. Speed was increased by 1 km·h^{-1} every minute until 12 km·h^{-1}, thereafter the incline was increased by 1% every 30 seconds until volitional exhaustion.

Experimental trials. Thereafter, all participants completed three intervention trials (PHWI, HIIE, threshold running), in a randomised cross over design study, separated by a minimum of 48 hours. All trials were conducted at the same time of day (09:00 am) by the same investigators. Upon arrival at the laboratory, participants were positioned and instrumented in the semi-recumbent position (angle, 30°). After 20-minutes of quiet rest, to allow for haemodynamic stabilisation, baseline cardiovascular, cerebrovascular, respiratory, thermoregulatory and perceptual measurements were made. After completion of each intervention (details below), participants transitioned back to the semi-recumbent position and all measurements were repeated immediately post, and at 20, 40, 60 and 80 minutes, except for haemoglobin concentration, which was only re-assessed immediately after and at 80 minutes. Participants

were also provided with 300 ml of water after the first set of post intervention measurements had been performed, most notably following measurement of haemoglobin concentrations. Measurement of haemoglobin was used to indicate sweat loss and subsequent haemoconcentration which would elevate oxygen carrying capacity and increase blood viscosity and therefore decrease CBF and shear rate, thus providing some mechanistic insight into potential reasons for changes in CBF and shear rate between the three interventions. An 80-minute time frame was chosen as extensive pilot testing revealed that all physiological variables had returned to baseline following exercise and PHWI. Furthermore, a similar study by Francisco et al. (2021) demonstrated that superficial femoral artery shear rate had returned to baseline 60 minutes post exercise and PHWI.

Passive hot water immersion. Participants were immersed to the level of the mid-sternum for 30 minutes in a 42°C hot bath with both arms rested at heart level outside the bath (Figure 1). To quantify thermal and cardiovascular responses during hot water immersion, rectal temperature, thermal comfort, blood pressure and heart rate were recorded at 10-minute intervals and recorded for up to 80 minutes post intervention (Figure 1).

High-intensity interval exercise. Following a 5-minute warm-up, participants performed 5x4 minutes high-intensity interval treadmill runs (HP cosmos, Pulsar, Germany), at an intensity corresponding to 85-95% of their maximal heart rate, interspersed with 2 minutes of walking at 3 km/h. Exercise intensity was determined from VO_2 max assessment during which maximal heart rate was recorded. Furthermore, rectal temperature was measured during and up to 80 minutes post exercise with values noted every 10 minutes.

Threshold running. Following a 5-minute warm-up, participants performed 30 minutes of steady-state treadmill running (HP cosmos, Pulsar, Germany) at an intensity equivalent to their respiratory compensation point (RCP). The RCP was chosen as it replicates the type of maximal tempo run that would fulfil the recommended governmental guidelines for physical activity (30 minutes moderate-intensity exercise five days per week) (Bull et al. 2020). Heart rate was continuously recorded and used to guide exercise intensity. Furthermore, rectal temperature was measured during and up to 80 minutes post exercise with values noted every 10 minutes.

Experimental measurements.

Thermoregulatory parameters. Rectal temperature was monitored with a thermomister (DeRoyal, Powell, TN, USA), which was self-inserted 15 cm past the anal sphincter (Tram-rac, Solar 8000M GE, Marquette, USA). Forearm skin temperature and cutaneous red cell flux was recorded via an integrated thermistor and laser-Doppler flowmeter (Moor Instruments, Devon, UK). Measuring blood flow through a conduit artery (see below), is the combination of both downstream muscle and cutaneous conductance. Thus, the combination of conduit artery flow via ultrasonography and cutaneous red cell flux is used to try and separate the contribution of skin and muscle blood flow to conduit artery shear rate. To quantify exercise intensity and thermal responses during exercise, heart rate, rating of perceived exertion (RPE; Borg, 1998), thermal comfort (Hollies et al. 1979) and core temperature were recorded at the end of each interval. Thermal comfort was assessed with the McGinnis 13-point thermal comfort scale (1= So cold I am helpless; 7 = comfortable; 13= So hot I am sick and nauseated).

Cardiovascular and respiratory parameters. Heart rate was recorded via a Bluetooth polar chest belt (Wear link, Polar Electro, Finland). Arterial blood pressure was measured from the right arm by electrosphygmomanometry (Tango, M2, SunTechMedical Instruments Inc., USA) in duplicate, and used to calculate mean arterial pressure (MAP, Equation 1). Haemoglobin concentration was measured from a capillary blood sample obtained from the ear lobe (Hemocue, Hb 201, Ängelholm, Sweden). Breath-by-breath end-tidal carbon dioxide ($ETCO_2$) was recorded during measurements of CBF, through a rapid responding gas analyser (AD Instruments, UK) due to the known influence of carbon dioxide tension on CBF (Battisti-Charbonney et al. 2011).

Stress index. Values for heart rate, core temperature, thermal comfort and RPE for each variable were taken at 10, 20 and 30 minutes and multiplied by time (10, 20, 30 minutes) to indicate a cumulative stress index for each intervention. The use of a thermal stress index has been adopted in previous studies (Moron et al. 2000; Lumingu & Dessureault, 2009) using a variety of physiological metrics including HR, core temperature and thermal comfort and attempts to

provide a simple comparison of thermal stress from a combination of physiological and perceptual data.

Regional cerebral and leg blood flow. Blood flow of the ICA, VA and CFA were obtained via ultrasonography. Both ultrasound machines were interfaced with a custom designed audio-recording software (DUC2) that captured the timed-averaged mean blood flow velocity (TAMV) in the forward and reverse domains using an inbuilt algorithm (Romero et al. 2015). Furthermore, ICA and VA diameters were captured in real time and analysed post-hoc using video recording and custom-made wall tracking software. CFA diameter was measured immediately after TAMV and analysed post-hoc using an offline version of the same custom designed wall tracking software. Carotid artery vessels were imaged with a 15-MHz linear-array Doppler probe (uSmart 3300, Terason, USA) and the CFA with a 9-MHz linear-array Doppler probe (iE33, Philips, Netherlands). Time was taken to ensure the TAMV and diameter measurements were captured from the same segment of the artery between trials. Furthermore, basic ultrasound settings including depth, gain, power and sample volume were kept constant for each participant between trials. If necessary, local skin cooling of the left leg was applied via a fan and wet towels when constant diastolic blood flow appeared elevated during resting baseline measures to limit the effect of skin temperature and skin blood flow on the assessment of baseline skeletal muscle blood flow (Limberg et al. 2020).

Data acquisition and analyses.

Maximal exercise test. The highest 15-s average in oxygen uptake and heart rate was defined as VO_{2max} and HR_{Max}. The ventilatory threshold and respiratory compensation point were determined by two independent researchers using a combination of plots including the V-slope method and the ventilatory equivalents of O_2 and CO_2 (Gaskill et al. 2001).

Experimental trials. Continuous variables were sampled at 250 Hz using PowerLab acquisition system (AD Instruments, UK) and core temperature, blood pressure, haemoglobin, thermal comfort and RPE were measured independently and noted in Labchart (LabChart 8; AD Instruments, UK**).** All continuous data were averaged over one minute.

Total blood flow as well as antegrade and retrograde blood flow were calculated using equation 2. Total cerebral blood flow was estimated, assuming bilateral symmetry of the ICA and VA, as the product of the right ICA and left VA blood flow multiplied by two (equation 3). Total blood vessel shear rates, including antegrade and retrograde shear, were calculated using equation 4. Oscillatory shear index (OSI) was calculated using equation 5 and represents the temporal fluctuations in direction and magnitude of shear between systole and diastole (Evans et al. 2021). Values range between 0 (no oscillations) to 0.5 (high oscillations) (Peiffer et al. 2013).

Equation 1: $\mathrm{MAP} = \mathrm{DB} + \frac{1}{3} \times (\mathrm{SBP} - \mathrm{DBP})$

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

Equation 3: Total cerebral blood flow = (ICA blood flow x 2) + (VA Blood flow x 2)

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

Equation 5: $\mathrm{OSI} = \frac{\boldsymbol{retrograde\ shear}}{(\boldsymbol{antegrade\ shear + retrograde\ shear})}$

Statistical Analysis

A Shapiro-Wilks test performed on Graph pad prism 9.20 confirmed normal distribution of all data.

Effect of timing post interventions. To examine changes in cardiovascular, thermal and perceptual variables over time during (Baseline versus 10, 20, 30 minutes), and following (baseline versus post, 20, 40, 60 & 80 minutes) each intervention, we used repeated-measures (time) ANOVAs with Tukey's multiple comparisons test.

Comparisons between interventions. To examine differences between the three interventions, change scores were calculated relative to baseline and compared between interventions (Post, 20, 40, 60 80 minutes) using repeated-measures (intervention group) ANOVAs with Tukey's multiple comparisons test. Due to a missing blood pressure measurement at 80 minutes post threshold running, all corresponding data including systolic, diastolic, and mean arterial pressure,

as well as cerebral and femoral conductance at this time point were analysed with a mixed model ANOVA.

Stress Index. To examine the cumulative stress associated with each intervention, a repeated-measures ANOVA with Tukey's multiple comparisons test was used to compare absolute values for all stress index parameters at 10, 20 and 30 minutes, apart from RPE which was compared using a paired samples T-Test between the two exercise interventions.

Correlation analysis. To demonstrate if there was a relationship between the rate of reduction in femoral blood flow post intervention and individual cardio-respiratory fitness, we first performed individual regression analysis for each participant by plotting femoral blood flow against time (post, 20, 40 and 60 mins). Thereafter, the individual regression slope was plotted against each individual's absolute and relative VO_2 max using a Pearson correlation coefficient. This analysis was performed *post hoc* after observing a swift but heterogeneous normalization of femoral flow and shear post interventions in our cohort.

Power calculation. During moderate exercise brain blood flow increases by ~15% (Tomoto et al. 2021). Therefore, to have similar benefits to brain health, the post exercise (or passive heating) elevation in brain blood flow should be similar in magnitude. Based on middle cerebral artery velocity and/or intracranial carotid artery blood flow data from Furlong et al. (2020) & Gibbons et al. (2021), an effect size (Cohen's d) of between 0.72 to 0.91 was calculated. Thus, to achieve a statistical power of 90% with a 5 group repeated measures analysis of variance with moderate (r=0.6) correlation between variables and a high dispersion pattern, a predicted sample size ranged from 8 to 14 participants (Basuell & Li, 2002).

Analyses were performed using Prism 9.0.2 (GraphPad, USA) and priori significance was set at $P \leq 0.05$. Values are presented as mean (±SD) since they were normally distributed.

RESULTS

Maximal exercise test

Average VO_2 max was 55.8 ± 10.4 ml·kg·min^{-1} and maximum heart rate was 191 ± 7 beats·min^{-1}. Peak respiratory exchange ratio was 1.17 ± 0.06 and the average RCP occurred at 85% of VO_2 max.

Haemodynamic variables during PHWI and exercise

There were no differences in baseline values for HR (P=0.5778), systolic (SBP) (P=0.6696), diastolic (DBP) (P=0.6708) and mean arterial pressure (MAP) (P=0.8023) between interventions. HR, SBP, DBP, and MAP were significantly elevated immediately post exercise interventions, whereas, only HR was elevated post PHWI, with SBP remaining unchanged and both DBP and MAP falling. (Table 1). As a result, all cardiovascular parameters were significantly higher after HIIE and threshold running compared with PHWI (P<0.0001). By 80 minutes, blood pressure had returned to baseline values for all interventions, although HR remained significantly elevated following HIIE (P=0.0009) and threshold running (P=0.0004) compared with PHWI (Table 1). Haemoglobin concentration was not different between groups at any time point (Table 1).

Core temperature and forearm skin temperature and blood flow

Core temperature was similar at baseline (P=0.5150) with comparable increases in core body temperature during passive heating (+1.5°C), threshold running (+1.5°C) and HIIE (+1.4°C, P=0.5742). Core temperature decreased similarly in all interventions and was not significantly or physiologically different at 20 (P=0.1236), 40 (P=0.2159) and 60 minutes post-intervention (P=0.0899) (Table 1). Values at 80 minutes for passive heating (P=0.2923), threshold running (P=0.9821) and HIIE (P=0.9992) had returned to baseline levels. Forearm skin temperature and cutaneous red cell flux was not different at baseline between interventions and increased by a similar absolute magnitude post intervention (skin temp P=0.0742, skin blood flow flux P=0.9078) and remained similar at all subsequent time points (Table 1).

Cerebral blood flow, shear rate and conductance

ICA blood flow demonstrated little change relative to baseline following all three interventions and, therefore, was not different between conditions post (P=0.6677), at 20 (P=0.5528), 40 (P=0.1061), 60 (P=0.6942), or 80 minutes (P=0.7782). VA blood flow produced a similar response, also not deviating from baseline immediately after all interventions and therefore was

also not different between conditions post (P=0.3651) at 20 (P=0.9516), 40 (P=0.7916), 60 (0.9967), or 80 minutes (P=0.9209). Combined, this resulted in no difference to global cerebral blood flow between conditions at any time point (Figure 2A). There were minimal but comparable increases in ICA shear rate post intervention between all three conditions (P=0.4643). Moreover, there were no differences in ICA shear rate at 20 (P=0.2294), 40 (P=0.6245), 60 (P=0.6672) or 80 minutes (P=0.6328) between interventions (Figure 3A). While VA shear rate was slightly elevated immediately post both exercise interventions, and PHWI (although not reaching a statistical threshold), this was transient and in absolute terms the increase in shear was minimal. Indeed, statistically no difference could be observed between intervention groups (P=0.1940, Figure 3B). Relative to baseline, cerebral conductance was significantly higher immediately after passive heating compared to threshold running (P=0.0479) and HIIE (P=0.0011) (Figure 2D). Nevertheless, after 20 minutes, conductance had returned towards baseline values for all conditions and remained quantitively similar at 40 (P=0.0461), 60 (P=0.7820) and 80 minutes (P=0.4146) (Figure 2B).

$ETCO_2$ was also similar at baseline between interventions (P=0.7997), but HIIE caused a decrease in $ETCO_2$ compared with passive heating (P=0.0017) and threshold running (P=0.0013), post intervention. $ETCO_2$ remained significantly different between interventions at 20 (P=<0.0015), 40 (P=0.0384) and 60 minutes (P=0.0382); however, values between interventions were not different at 80 minutes (P=0.1659).

Comparison of femoral shear rate to baseline

Femoral shear rate remained significantly elevated immediately after PHWI (P<0.0001) and at 20 (P<0.0001) and 40 (P<0.0457) minutes, however, was similar to baseline by 60 (P=0.5872) minutes. Similarly, femoral shear rate was significantly elevated post (P=<0.0001) threshold running and remained elevated at 20 (P<0.0001), 40 (P=0.0003) and 60 minutes (P<0.0549), before returning to baseline values. HIIE produced shear rates that were significantly elevated post (P<0.0001) exercise and remained elevated at 20 (P<0.0001), 40 (P=0.0004) and 60 (P=0.0141) minutes before returning to baseline by 80 (P=0.4169) minutes (Table 3).

Comparison between interventions for femoral blood flow, shear rate and conductance

Femoral blood flow increased by a similar magnitude between all interventions when measured post PHWI and exercise (P=0.4283). Femoral blood flow remained elevated, to a similar extent at 20, 60 and 80 minutes for all conditions (Figure 4A). However, at 40 minutes, femoral blood flow was statistically higher for HIIE compared with passive heating (P=0.0157) but remained similar to threshold running (P=0.5116). Femoral shear rate demonstrated a comparable trend, being elevated by a similar magnitude following all three interventions immediately after (P=0.0671), at 20 (P=0.6356), 60 (P=0.1015) and 80 minutes post interventions (P=0.1455). However, at 40 minutes, femoral shear rate was statistically higher for threshold running compared with passive heating (P=0.0464) and higher for HIIE compared with heating (P=0.0565), although it did not reach the defined statistical threshold. Moreover, the magnitude in the differences between delta shear rates were marginal (Figure 5).

The increase in femoral shear was mediated by both increases in antegrade and decreases in retrograde shear. Femoral antegrade shear was elevated by a quantitatively similar magnitude immediately post (P=0.0771), and at 20 (P=0.5312) and 80 minutes (P=0.3903) after all interventions (Figure 5). At 40 (P=0.0341) and 60 minutes (P=0.0500), antegrade shear was statistically higher for HIIE compared with passive heating (Figure 5), albeit mild in magnitude. In contrast, femoral retrograde shear demonstrated comparable decreases for all conditions immediately post intervention (P=0.8226). Thereafter, retrograde shear increased at all subsequent time points, but remained slightly lower than baseline values by 80 minutes for all interventions (Figure 5).

Femoral conductance increased for all conditions and was significantly higher for passive heating compared with threshold running (P=0.0115) and HIIE (P=0.0136) post intervention. However, conductance was not different at 20 (P=0.5557), 60 (P=0.0942) or 80 minutes (P=0.1328) between interventions but was significantly lower for passive heating compared with HIIE at 40 minutes (P=0.0419) (Figure 4B).

Comparison of arterial diameters to baseline

ICA (P=0.5377), VA (P=0.1948) and CFA (P=0.3550) diameters were unchanged when measured post PHWI, however ICA (P=0.0032) and VA (P=<0.0001) diameters were

404 significantly smaller and CFA (P=0.0029) diameter was significantly larger post threshold
405 running, Similarly, HIIE caused a significant decrease in ICA (P=0.0003) and VA (P=<0.0001)
406 diameters as well as a significant increase in CFA (P=0.0022) diameter (Table 4).

407 **Correlational analysis**

408 Following all three interventions, there was a general trend whereby the individuals with the
409 greatest fitness, i.e. VO_2max, showed the fastest rate of reduction in femoral blood flow. Albeit
410 the magnitude of the relationship and statistical significance varied depending on the type of
411 intervention and if VO_2max is presented in absolute or relative terms (see Table 5).

412 **Comparison of stress index between interventions**

413 Cumulative physiological and perceptual stress over the duration of all interventions was
414 determined from summation of HR, core temperature, thermal comfort and ratings of perceived
415 exertion. Cumulative stress for HR over the duration of the interventions was significantly
416 greater for both exercise interventions compared with PHWI (both P=<0.0001). Similarly,
417 cumulative stress for core temperature was significantly higher for both threshold running
418 (P=0.0246) and HIIE (P=0.0204) compared with PHWI, but there was no difference between
419 exercise interventions (P=0.8395). However, this was not matched by thermal comfort data
420 which demonstrated that participants perceived all interventions to be equally thermally
421 challenging (P=0.2993). Furthermore, RPE data revealed that participants felt both exercise
422 conditions were equally physically demanding (P=0.8762), which was expected given that HR
423 and core temperature differences between exercise interventions were comparable (Table 2).

424

DISCUSSION

The novel findings of the current investigation were that 30 minutes of whole body PHWI compared to time and core temperature matched threshold running and HIIE elicited minimal, but comparable post intervention changes in CBF. Consequently, ICA and VA shear rate were, for the most part, similar between interventions. Moreover, 30 minutes of PHWI caused a similar post intervention increase in femoral shear rate as threshold running and HIIE, albeit femoral shear remained slightly elevated for a longer period post threshold running. These results suggest that PHWI and exercise do not cause dramatic changes in cerebrovascular shear rates post intervention, however peripheral vascular shear rates are high, and quantitatively similar after all three interventions Therefore, these data support the application of PHWI as a suitable intervention to supplement classic exercise training programs to target the peripheral conduit artery shear in young healthy individuals and warrant further investigation as a therapeutic alternative in diseased populations.

Cerebral blood flow and cerebral vascular shear rate post exercise and PHWI

Optimizing therapeutic interventions to increase cerebral vascular shear depends on several important variables, including exercise intensity and concomitant changes in arterial blood gases. Previous studies have reported increases in middle cerebral artery velocity during low intensity aerobic exercise (Jørgensen et al. 1992; Nybo & Nielsen 2001; Poulin et al. 1999). However, regional differences have been observed during higher intensity exercise (Smith et al. 2012; Herholz et al. 1987). For example, Sato et al. (2011) reported a progressive increase in ICA blood flow during exercise up to 60% VO_2 peak (291 ± 16 ml min^{-1}), which subsequently decreased when exercise intensity was increased to 80% of VO_2 peak (258 ± 13 ml min^{-1}). In contrast, VA blood flow continued to increase up to 80% of VO_2 peak, before plateauing (144 ± 14 ml min^{-1}), due to a hyperventilatory induced hypocapnia, and subsequent cerebral vasoconstriction (Moraine et al. 1993). Interestingly, Furlong et al. (2020) reported continued intensity matched elevations in middle cerebral artery blood velocity during higher intensity running exercise compared with cycling, in individuals with higher aerobic fitness (VO_2 max >45 $ml \cdot kg \cdot min^{-1}$), suggesting the modality of exercise and influence of training status may alter cerebral autoregulation and/or CO_2 reactivity. With passive heating, several studies (Nelson et al. 2011; Brothers et al. 2009 & Bain et al. 2013) have observed a robust reduction in blood flow

(and assumingly shear stress) to both the anterior and posterior cerebral conduit arteries. In these studies, passive heating via a water perfused suit increased core temperature by 1.3°C to 2°C and caused hyperthermia induced hyperventilation and subsequent hypocapnia. Since hypocapnia is a powerful vasoconstrictor within the brain, correction of end-tidal PCO_2 by end-tidal forcing restored CBF to baseline levels (Bain et al. 2013).

In the recovery period post exercise, our findings demonstrate that both threshold running and HIIE (89% vs 92% HR_{Max}) produced minimal changes in either ICA or VA blood flow. Similarly, while ICA and VA shear rate were statistically increased post exercise, this effect was lost after just over 20 minutes. The increase in ICA and VA shear was mostly likely due to hypocapnia (Table 1) induced vasoconstriction of the two conduit arteries (Table 4), see details below. Yet it should be highlighted that while quantitively elevated with a marginal statistical significance at some early timepoints (table 3), these data do not represent a robust increase in shear to the brain's extracranial arteries. After 30 minutes of PHWI, CBF and shear rate in the ICA and VA were essentially unchanged compared to baseline. Such findings, along with previous research outlined above, indicate that shear rates in the brain are optimised during moderate and high intensity exercise, and quickly return to baseline post intervention due to tight cerebral autoregulatory mechanisms. In contrast, moderate heat stress via PHWI appears to have minimal effects on cerebral vasculature shear during the post intervention period, despite modest yet persistent perturbations in core temperature, end-tidal carbon dioxide ($ETCO_2$) and arterial blood pressure. Ultimately it seems that the post intervention period is not an optimal window for shearing the brain.

Cerebral regulatory mechanisms post exercise and passive hot water immersion.

The mechanism(s) responsible for regulating CBF during and after exercise or passive heating are multifactorial, with the interaction of $ETCO_2$ and core temperature through hyperventilatory and blood pressure regulations being critical influencers (Bain et al. 2013; Caldwell et al. 2020). However, an interesting observation from the current study was that despite modest hyperthermia post exercise and PHWI, ICA and VA blood flow remained constant due to a decrease (post exercise) or increase (post heat stress) in cerebral conductance. These opposing changes in cerebral vascular tone likely reflect autoregulatory mechanisms to maintain blood flow constant in the face of hyper- or hypotension respectively. This interpretation is supported

by the observation that core temperature increased similarly between all three trials and $ETCO_2$ was reduced immediately post exercise, but unchanged post PHWI where an increase in conductance was observed. Interestingly, the initial post exercise reduction in $ETCO_2$ for both threshold running and HIIE aligned with significant decreases in ICA and VA diameter, which slowly returned towards baseline in synergy with restoration of $ETCO_2$ (Table 3). In contrast, $ETCO_2$ was unchanged post PHWI and accordingly both ICA and VA diameter remained similar to baseline. Collectively, these data provide supporting evidence for the sensitivity of CBF to $ETCO_2$ and demonstrate that blood pressure plays a powerful regulatory role on the cerebral circulation and needs to be considered post any therapeutic intervention if "shearing the brain (Carr et al. 2020)" is a focus.

Femoral blood flow and shear rate

We demonstrated comparable increases in femoral blood flow and shear rate post intervention between all conditions (Figure 4&5). Due to the greater metabolic increase in blood flow during high intensity exercise compared to PHWI (Amin et al. 2020), we hypothesised that femoral blood flow and shear rate would be higher after both exercise interventions compared with PHWI. Interestingly, shear rates were very comparable post interventions and while femoral shear appeared higher for both exercise conditions (being statistically significant at 40 minutes for HIIE), the magnitude of the difference was minimal (~30 s-1). Thus, these findings suggest that a relatively short (30 minutes) bout of passive heat stress (+1.4°C) provides comparable post intervention elevations in total femoral shear compared with high intensity exercise. Our data are supported by findings from Francisco et al. (2021) that established comparable brachial and superficial femoral artery shear rates 20 minutes post exercise (60% VO_2 peak) and PHWI, following matched elevations in core temperature. Interestingly, in that study, brachial and superficial femoral shear rates remained elevated at 40- and 60-minutes post moderate exercise. In contrast, femoral shear was back to normal after 40 minutes of threshold running and 60 minutes post HIIE in our study. The difference in the rate of reduction in shear rate between our data and Francisco et al. (2021) may relate to the interaction between the duration of the heating intervention (60 mins, Francisco et al. 2021), compared with our study (30 mins) and the participant training status. While the training status of the participants from Francisco et al. (2021) is not known, our highly active and moderately trained (VO_{2max}, 55.82 ± 10.42

516 ml·kg·min^{-1}) cohort may possess certain endurance training adaptations including plasma
517 volume expansion, which aids their ability to dissipate heat (Périard et al. 2016) and/or a
518 potentially greater VO_2 offset kinetics, which would more rapidly reduce the metabolic demand
519 of the muscle and as such the need for blood flow post exercise. These assumptions are generally
520 supported by the negative trend between the rate of reduction in femoral blood flow and training
521 status in our cohort (Table 5).

522 **Strengths**

523 We specifically chose two common and popular modes of exercise performed by general
524 populations (30 minutes running and HIIE), which comply with World Health Organisation
525 recommendations for daily exercise (Bull et al. 2020). Furthermore, all interventions were time
526 matched, and measurements performed in the upright posture, thus mimicking real life
527 behaviour. Most studies perform integrative post exercise measurements in the supine posture,
528 which is unnatural following exercise and significantly alters cardiovascular (Hastreiter &
529 Young, 1997), (Takahashi et al. 2005) and blood flow haemodynamics (Nishiyasu et al. 2007),
530 thus influencing interpretation of the effects of the intervention. We also provided participants
531 with a select amount of fluid after the first set of post intervention measurements had been
532 performed. This enabled us to deduce the initial effects of potential dehydration on CBF and
533 prevent haemoconcentration caused by plasma volume loss influencing the subsequent measures
534 of CBF and shear (Trangmar et al. 2015). Finally, we matched the increase in core temperature
535 between interventions, thus helping elucidate heat specific elevations in shear rate relative to
536 exercise. We also documented thermal comfort and RPE for the interventions, thereby allowing a
537 comparison between physiological stress and perceptual experience, which is important to know
538 when considering adherence and compliance to exercise and heating interventions.
539

540 **Study limitations**

541 Our measurements of ICA, VA and CFA were performed between 2 and 10 minutes after
542 cessation of all interventions; therefore, the data reflects post intervention responses and
543 interpretations about trends during the interventions cannot be made except from previous data
544 outline above. Furthermore, all measurements for each participant were performed in a 7-day
545 window for females and 10-day window for males, yet baseline data for all cardiorespiratory

variables (Table 1) were identical suggesting that we limited the influence of confounding variables. Moreover, while we did not determine sweat loss from each intervention, which would have strengthened the study design, the measurement of haemoglobin concentration confirmed physiologically that haemoconcentration was avoided and thus isolates our findings from this confounding effect. Moreover, we also acknowledge that it would have been more pertinent to measure skin temperature and cutaneous red cell flux in the leg rather than the forearm, yet we were not confident in submerging the laser doppler probe in hot water and choose the arms as a suitable surrogate.

Implications

Our data revealed that in the post intervention period, high intensity exercise and PHWI caused minimal changes in shear rates on the brain's extracranial arteries. Thus, the cerebral vascular benefits of exercise training likely occur during the intervention itself when CBF and shear are high (Sato et al. 2011). Alternatively, passive heating generally causes a reduction in brain blood flow during the intervention (Nelson et al. 2011), and based on the current data, no change in the post intervention period. Thus, alternative mechanism(s) are likely to explain epidemiological data linking heat exposure and a reduced risk of Dementia (Knekt et al. 2020). While at present speculative, a detailed review has recently outlined the multifactorial pathways through which heat shock proteins (HSP's) influence the repair and removal of misfolded proteins, contribute to mitophagy and signalling of extra cellular vesicles, all of which reduce inflammation and oxidative stress and may improve cerebral vascular health (Von Schulze et al. 2020). In terms of the peripheral vasculature, all interventions elicited favourable shear profiles by increasing femoral antegrade and/or reducing retrograde shear which have been associated with enhanced endothelial function in young (Tinken et al. 2009), sedentary (Brunt et al. 2016) and diseased (Imamura et al. 2001) populations. These findings add insight to the degree of heat stress required to increase shear and potentially improve peripheral vascular function with passive heating (Thomas et al. 2017; Neff et al. 2016).

Conclusion

Our data suggest that time and core temperature matched high intensity exercise and whole body PHWI elicit minimal changes in cerebral vasculature shear rates up to 80 minutes post

intervention. However, post intervention shear rates in a major peripheral (femoral) conduit artery are comparable between high intensity exercise and PHWI, albeit high intensity exercise does maintain shear rates slightly higher for longer post intervention compared with PHWI. These data lend support for the application of passive heating as a targeted therapeutic intervention to increase peripheral vascular shear but cast doubt on this mechanism to improve cerebral vascular health via heat stress.

ADDITONAL INFORMATION

Competing Interests

None of the authors have any conflicts of interests.

Author Contributions

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

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Figure Legends

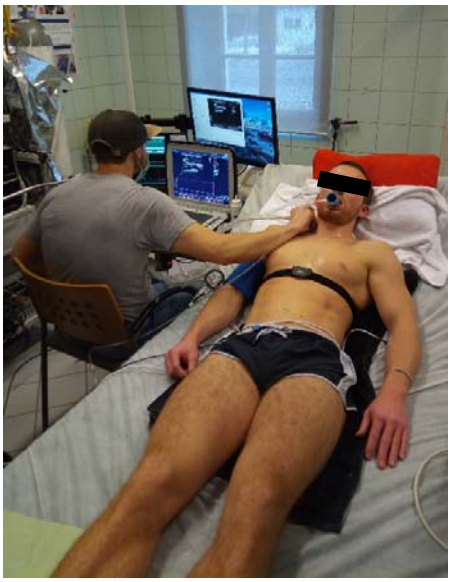
Figure 1. Images of two participants post PHWI (left) and exercise (right) having measurements of cerebral and common femoral artery blood flow performed alongside measurements of HR, ETCO2, mean arterial pressure, core temperature and forearm skin temperature and skin blood flow

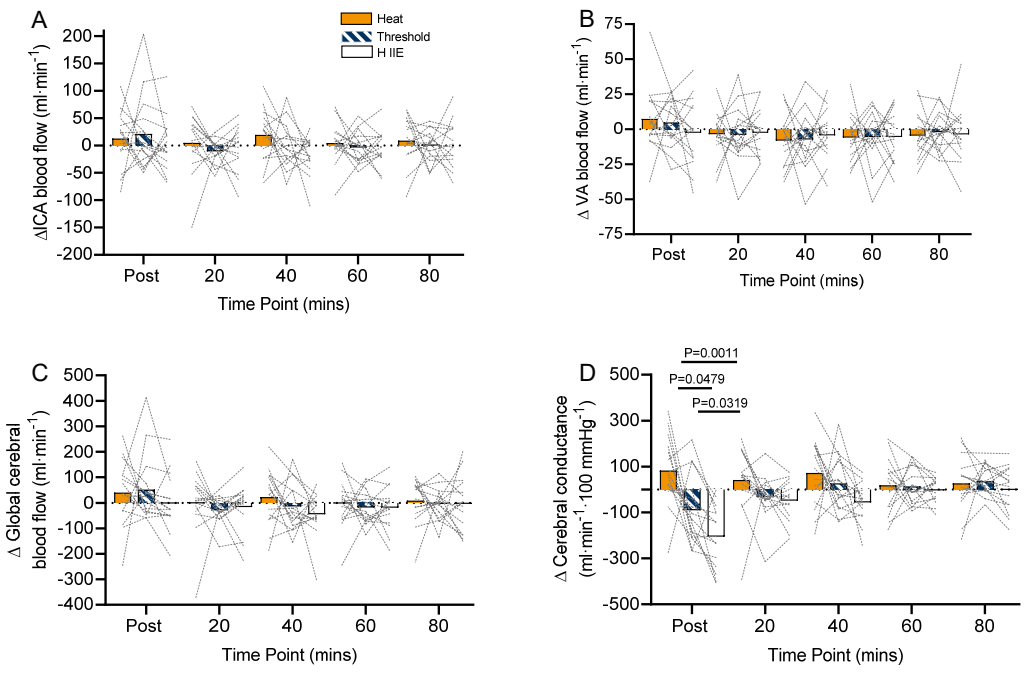
Figure 2. Change in ICA (A), VA (B) blood flow, global cerebral blood flow (C) and cerebral conductance (D) from baseline for each intervention. A repeated measures ANOVA performed at each time point revealed no difference between groups for blood flow; however, conductance was different between groups post intervention. Data are mean ± SD (n=15).

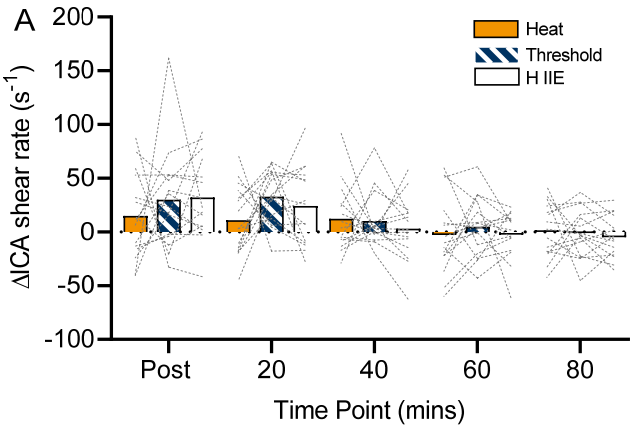
Figure 3. Change in ICA (A) and VA (B) shear rate from baseline for each intervention. A repeated measures ANOVA performed at each time point revealed no difference between groups for both ICA and VA shear rate. Data are mean ± SD (n=15).

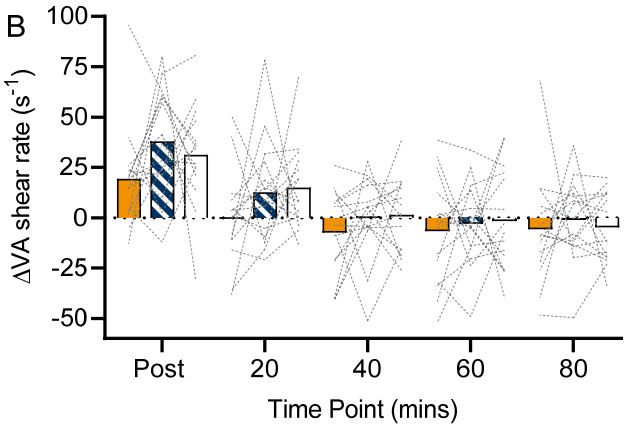
Figure 4. Change in femoral blood flow (A) and conductance (B) from baseline for each intervention. A repeated measures ANOVA performed at each time point revealed a significant difference at 40 minutes for blood flow (P=0.0157) between conditions. Furthermore, a significant difference in conductance between passive heating and threshold running (P=0.0115) and passive heating and HIIE (P=0.0136) post intervention. Conductance was also significantly different at 40 minutes between passive heating and HIIE (P=0.0419). Data are mean ± SD (n=15).

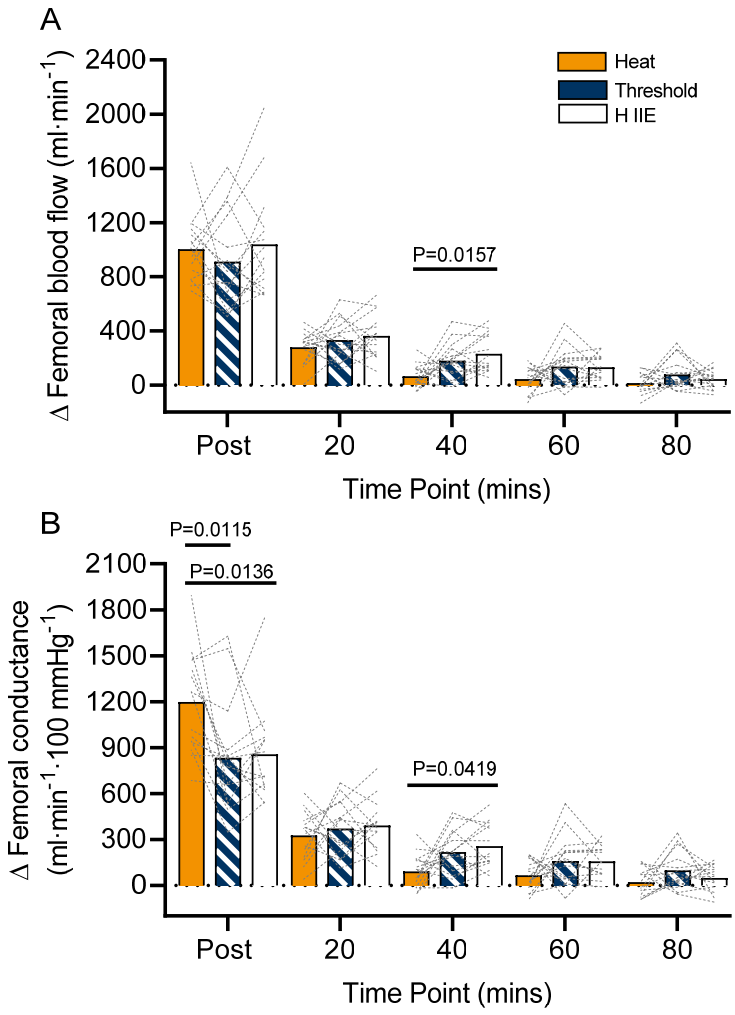
Figure 5. Antegrade and retrograde shear rate at all time points for all three interventions. A repeated measures ANOVA with Tukey's multiple comparison test revealed significant differences in antegrade shear at 40 (P=0.0341) and 60 (P=0.0500) minutes between HIIE and PHWI. There were no differences in retrograde shear rate at any time point. Data are mean ± SD (n=15)











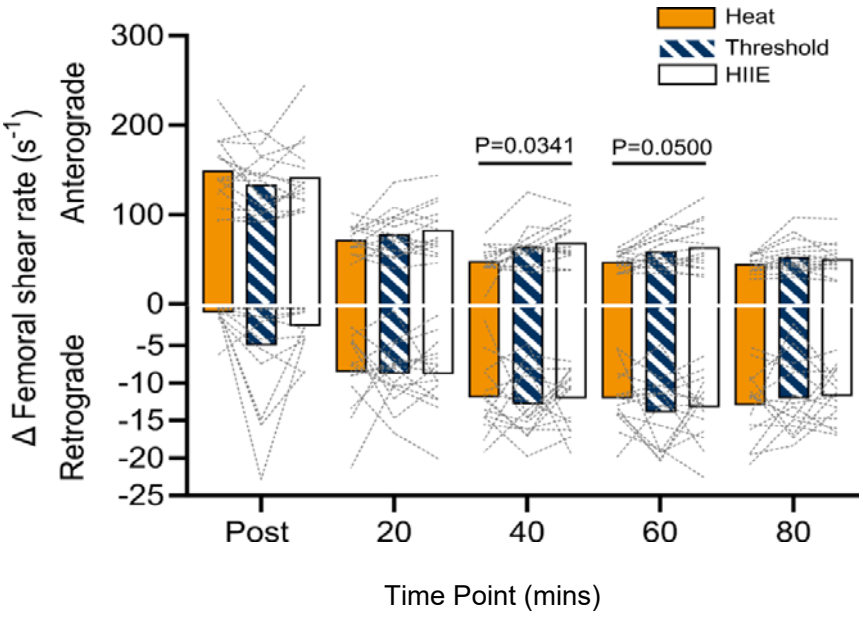


Table 1. Comparison of cardiorespiratory variables between all interventions at all time points.

	Intervention	Baseline	Time points (mins)				
			Post	20	40	60	80
Heart rate (beats·min^{-1})	Heat	63 ± 10	100 ± 15 ** ##	70 ± 12** ##	64 ± 8** ##	60 ± 9** ##	59 ± 9** ##
	Threshold	63 ± 7	171 ± 9†† *	88 ± 9††	78 ± 8††	74 ± 9††	69 ± 11††
	HIIT	64 ± 10	176 ± 8†† #	89 ± 9††	81 ± 12††	75 ± 12††	70 ± 12††
Systolic arterial pressure (mmHg)	Heat	122 ± 10	123 ± 11** ##	122 ± 11	119 ± 10	121 ± 9**	120 ± 10
	Threshold	122 ± 8	151 ± 21††	122 ± 8	117 ± 8	118 ± 9	118 ± 10
	HIIT	121 ± 11	159 ± 26††	124 ± 10	120 ± 10	116 ± 8††	119 ± 9
Diastolic arterial pressure (mmHg)	Heat	75 ± 10	66 ± 7 ** ##	71 ± 8 ** #	71 ± 9 **	72 ± 7	74 ± 8
	Threshold	76 ± 9	85 ± 9 †† *	76 ± 7 †	73 ± 8 *	74 ± 9	75 ± 8
	HIIT	76 ± 10	95 ± 17 †† #	79 ± 8 ††	77 ± 7 †† #	75 ± 7	76 ± 7
Mean arterial pressure (mmHg)	Heat	90 ± 9	84 ± 8 ** ##	87 ± 8 **	86 ± 9 *	88 ± 7	88 ± 8
	Threshold	91 ± 8	106 ± 13 †† *	90 ± 7	87 ± 8 *	88 ± 8	82 ± 8
	HIIT	90 ± 10	115 ± 18 †† #	93 ± 8 ††	90 ± 8 † #	88 ± 7	89 ± 7
Pulse pressure (mmHg)	Heat	47 ± 5	57 ± 8	51 ± 7	47 ± 6	49 ± 6 **	46 ± 5
	Threshold	45 ± 6	66 ± 12	46 ± 6	44 ± 4	44 ± 6	44 ± 6
	HIIT	45 ± 5	64 ± 18	45 ± 6	44 ± 7	41 ± 3 ††	43 ± 4
Forearm skin temperature (°C)	Heat	29.99 ± 1.23	32.53 ± 1.13	31.26 ± 1.00	31.78 ± 0.99	31.58 ± 1.08	31.39 ± 1.37
	Threshold	30.57 ± 1.45	32.03 ± 1.38	32.03 ± 1.03	31.81 ± 1.41	31.94 ± 1.17	31.74 ± 1.18
	HIIT	30.56 ± 1.06	31.67 ± 1.48	31.97 ± 1.12	31.78 ± 1.06	31.88 ± 1.08	31.80 ± 0.99
Forearm skin blood flow flux (PU)	Heat	42 ± 34	471 ± 407	491 ± 530	402± 415	314 ± 405	158 ± 205
	Threshold	39 ± 32	527 ± 608	633 ± 819	485 ± 895	440 ± 744	318 ± 439
	HIIT	30 ± 19	518 ± 532	449 ±304	386 ± 305	267 ± 205	235 ± 223
Core temperature (°C)	Heat	37.0 ± 0.4	38.5 ± 0.7	37.9 ± 0.5	37.5 ± 0.5	37.4 ± 0.5	37.3 ± 0.4*#
	Threshold	36.9 ± 0.3	38.5 ± 0.5	37.6 ± 0.3	37.3 ± 0.3	37.1 ± 0.3	37.0 ± 0.3†
	HIIT	37.0 ± 0.3	38.4 ± 0.4	37.6 ± 0.3	37.3 ± 0.2	37.1 ± 0.3	37.0 ± 0.2†
$ETCO_2$ (%)	Heat	5.62 ± 0.38	5.36 ± 0.44 **	5.51 ± 0.49 **	5.50 ± 0.45	5.58 ± 0.43 *	5.51 ± 0.35
	Threshold	5.65 ± 0.40	5.20 ± 0.36 **	5.41 ± 0.35 *	5.51 ± 0.42 *	5.57 ± 0.47 **	5.55 ± 0.34
	HIIT	5.61 ± 0.31	4.84 ± 0.26 †† ##	5.15 ± 0.36 †† #	5.30 ± 0.31 #	5.33 ± 0.37 † ##	5.41 ± 0.29
Haemoglobin (g·dL^{-1})	Heat	15.4 ± 1.4	15.4 ± 1.4				15.1 ± 1.5
	Threshold	15.3 ± 1.5	15.6 ± 1.4				15.5 ± 1.8
	HIIT	15.4 ± 1.5	15.5 ± 1.3				15.0 ± 1.9

P<0.01 †, P<0.01††, different to Heat. P<0.05#, P<0.01## different to threshold. P<0.05*, P<0.01** difference to HIIT. All arterial pressure measurements at 80 minutes, alongside cerebral and femoral conductance values were analysed using a mixed model ANOVA due to one missing blood pressure measurement. No haemoglobin measurements were taken at 20, 40 or 60 minutes after exercise. Data are mean ± SD (n =15).

Table 2. Stress index for physiological and perceptual parameters

Stress Index	Intervention	Baseline	Time points (mins)			Cumulative index
			10	20	30	
Heart rate (beats·min $^{-1}$)	Heat	63 ± 10	907 ± 160** $^{\#\#}$	2124 ±276** $^{\#\#}$	3310 ± 516 ** $^{\#\#}$	6404 ± 214** $^{\#\#}$
	Threshold	63 ± 7	1665 ± 80†† **	3513 ± 176†† **	5362 ± 326†† **	10603 ± 138†† **
	HIIE	64 ± 10	1547 ± 68$^{\dagger\dagger\#\#}$	3213 ± 184$^{\dagger\dagger\#\#}$	5062 ± 240$^{\dagger\dagger\#\#}$	9886 ± 105$^{\dagger\dagger\#\#}$
Core temperature (°C)	Heat	37.0 ± 0.4	373 ± 3.3$^{\#\#}$**	758 ± 8.4$^{\#}$**	1152 ± 14.5	2320 ± 6$^{\#\#}$**
	Threshold	36.9 ± 0.3	376.4 ± 3.4††	766.8 ± 6.9†	1164.4 ± 11.6	2344 ± 5††
	HIIE	37.0 ± 0.3	377.2 ± 3.6††	769.9 ± 7.2††	1162.8 ± 10.5	2348 ± 4††
Tcomfort	Heat	7 ± 0	86 ± 11	188 ± 20	306 ± 28$^{\#\#}$**	587 ± 12
	Threshold	7 ± 0	79 ± 23	175 ± 53*	282 ± 82††	543 ± 36
	HIIE	7 ± 0	91 ± 10	203 ± 23$^{\#}$	294 ± 43††	595 ± 19
RPE	Heat	-	-	-	-	
	Threshold	-	125 ± 38	284 ± 84	446 ± 134	855 ± 48
	HIIE	-	123 ± 53	285 ± 118	456 ± 188	864 ± 68

Abbreviations – HR – heart rate, Trec – rectal temperature, Tcomfort – thermal comfort, RPE- rating of perceived exertion. Stress index was calculated by multiplying each variable by time (min) with cumulative index reflecting the summation of all values over the 30 minutes. A repeated measures ANOVA was performed for all variables except RPE which was analysed between exercise interventions using a paired samples t-test. Data for RPE and thermal comfort was compared with n=14 due to one missing data set. All other comparison n=15. P<0.01 †, P<0.01††, different to Heat. P<0.05#, P<0.01## different to threshold. P<0.05*, P<0.01** difference to HIIT. Data are mean ± SD.

Table 3. Comparison of shear rates relative to baseline for each intervention.

	Intervention	Time Points (mins)						P-Value		
		Baseline	Post	20	40	60	80	Time	Intervention	Time x Intervention
Femoral shear (s^{-1})	Heat	31 ± 11	149 ± 39**	64 ± 18*	39 ± 13*	35 ± 10	32 ± 7	P≤0.0001	P=0.010	P≤0.0001
	Threshold	32 ± 14	129 ± 36**	70 ± 25**	51 ± 21**	45 ± 17	41 ± 18			
	HIIT	36 ± 16	139 ± 40**	74 ± 30**	57 ± 22**	50 ± 27*	39 ± 17			
ICA shear rate (s^{-1})	Heat	249 ± 39	264 ± 42	260 ± 48	261 ± 43	246 ± 58	250 ± 51	P≤0.0001	P=0.6357	P=0.3169
	Threshold	239 ± 35	268 ± 59	271 ± 46**	249 ± 44	243 ± 40	238 ± 35			
	HIIT	250 ± 40	274 ± 50	253 ± 51	247 ± 37	245 ± 45	245 ± 45			
VA shear rate (s^{-1})	Heat	179 ± 40	198 ± 48	179 ± 41	171 ± 44	171 ± 38	173 ± 43	P≤0.0001	P=0.5012	P=0.4366
	Threshold	165 ± 33	203 ± 24**	178 ± 24	165 ± 20	162 ± 25	164 ± 22			
	HIIT	166 ± 26	197 ± 33**	181 ± 33	167 ± 31	164 ± 35	161 ± 28			
Oscillatory shear index Femoral artery	Heat	-0.578 ± 0.480	-0.007 ± 0.019	-0.172 ± 0.169	-0.384 ± 0.206	-0.410 ± 0.313	-0.428 ± 0.191	P≤0.0001	P=0.2593	P=0.5156
	Threshold	-0.647 ± 0.445	-0.053 ± 0.090	-0.142 ± 0.125	-0.290 ± 0.151	-0.353 ± 0.270	-0.354 ± 0.200			
	HIIT	-0.488 ± 0.261	-0.022 ± 0.030	-0.153 ± 0.113	-0.252 ± 0.139	-0.338 ± 0.207	-0.3740 ± 0.232			

P<0.05*, P<0.01**. A 2-way ANOVA with Tukey's multiple comparison test used to demonstrate changes relative to baseline. Data are mean ± SD (n =15). Oscillatory shear index is for femoral artery as the cerebral vasculature does not have retrograde blood flow, therefore this metric cannot be calculated for the internal carotid or vertebral arteries.

Table 4. Cerebral and peripheral artery diameters for all interventions displayed at all time points

	Intervention	Time Points (mins)						P-Value		
		Baseline	Post	20	40	60	80	Time	Intervention	Time x Intervention
ICA diameter (cm)	Heat	0.478 ± 0.040	0.474 ± 0.031	0.474 ± 0.036	0.479 ± 0.028	0.484 ± 0.040	0.482 ± 0.038	P=0.0002	P=0.6653	P=0.3388
	Threshold	0.486 ± 0.035	0.476 ± 0.040**	0.461 ± 0.039	0.477 ± 0.043	0.481 ± 0.034	0.486 ± 0.037			
	HIIT	0.480 ± 0.033	0.462 ± 0.036**	0.464 ± 0.039	0.470 ± 0.029	0.480 ± 0.030	0.486 ± 0.022			
VA diameter (cm)	Heat	0.393 ± 0.050	0.383 ± 0.06	0.387 ± 0.059	0.388 ± 0.063	0.390 ±0.061	0.393 ± 0.058	P≤0.0001	P=0.5791	P=0.1263
	Threshold	0.405 ± 0.054	0.381 ± 0.042**	0.390 ±0.041*	0.395 ±0.047	0.401 ± 0.046	0.402 ± 0.047			
	HIIT	0.393 ± 0.050	0.370 ± 0.045**	0.381 ± 0.046**	0.389 ± 0.046	0.391 ± 0.048	0.394 ± 0.044			
Femoral artery diameter (cm)	Heat	0.910 ± 0.097	0.908 ± 0.092	0.907 ± 0.089	0.908 ± 0.086	0.919 ± 0.091	0.915 ± 0.085	P=0.0003	P=0.4585	P=0.0402
	Threshold	0.893 ± 0.103	0.920 ± 0.110**	0.909 ± 0.112	0.905 ± 0.108	0.906 ± 0.110	0.900 ±0.102			
	HIIT	0.907 ± 0.106	0.935 ± 0.109**	0.925 ± 0.099	0.930** ± 0.101	0.922 ± 0.110	0.914 ± 0.107			

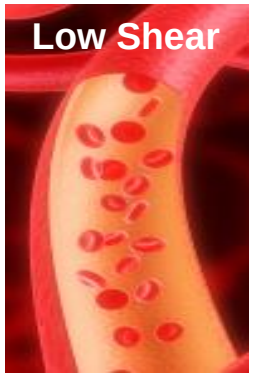
P<0.05*, P<0.01**. A repeated measures ANOVA with Tukey's multiple comparison test used to demonstrate changes relative to baseline. Data are mean ± SD (n =15).

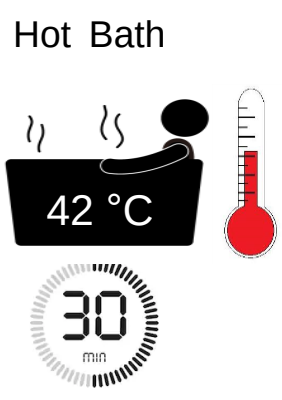
Table 5. Correlation between the rate of reduction in femoral blood flow post interventions and maximal aerobic capacity (i.e. fitness).

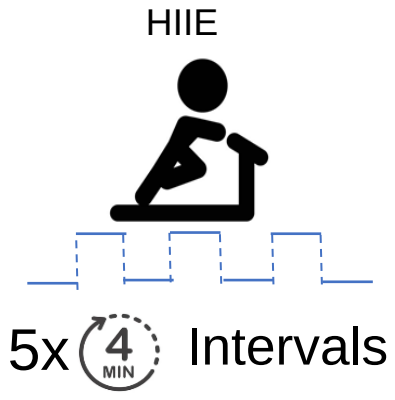
Intervention	**Absolute VO_2 ($ml \cdot min^{-1}$)**		**Relative VO_2 ($ml \cdot kg \cdot min^{-1}$)**	
	r value	P Value	r value	P Value
Heat	-0.55	0.0319	-0.42	0.1211
Threshold	-0.51	0.0514	-0.70	0.0032
HIIE	-0.40	0.1318	-0.45	0.0895

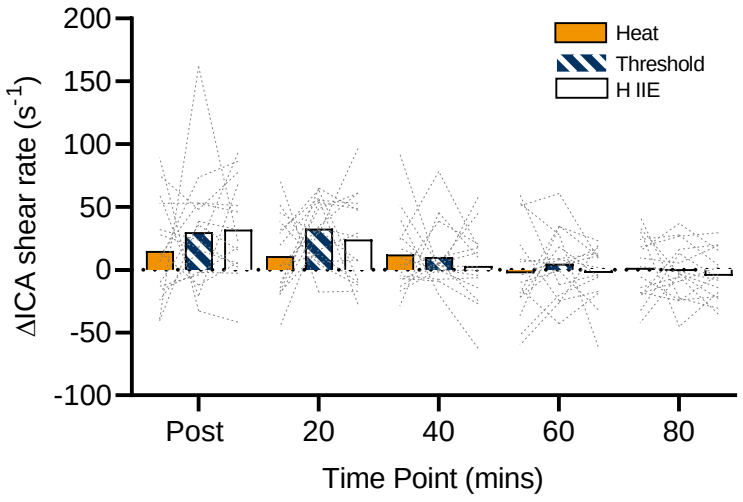
Rate of reduction in femoral blood flow was calculated as the individual regression over time (post, 20, 40 and 60 minutes) for femoral blood flow post intervention for each participant. (n =15).

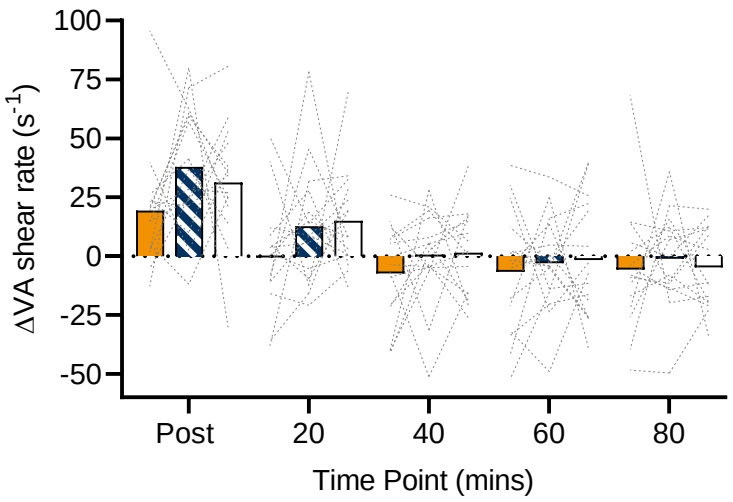
High intensity exercise and passive hot water immersion cause similar post intervention changes in peripheral and cerebral shear

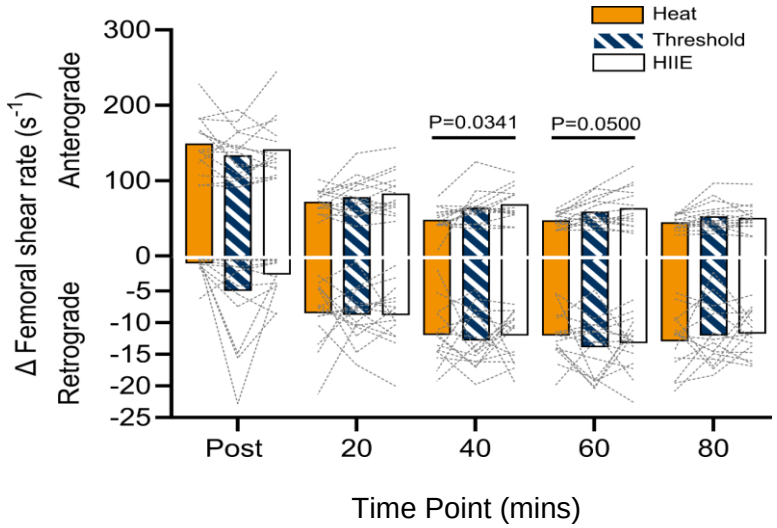












- Time and core temperature matched high intensity exercise and passive hot water immersion elicit limited changes in cerebral shear and comparable increases in peripheral vasculature shear rates when measured for up to 80 minutes post intervention.