

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

Amin, Sachin; Hansen, Alexander; Mugele, Hendrik; Simpson, Lydia; Marume, Kyohei; Moore, Jonathan; Cornwell, William; Lawley, Justin

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- Title: High intensity exercise and passive hot water immersion cause similar post intervention
 changes in peripheral and cerebral shear.
- 3
- 4 Authors: Sachin B Amin¹ sachin.amin@uibk.ac.at, Alexander B Hansen¹ –
- 5 Alexander.Hansen73@outlook.com, Hendrik Mugele¹ hendrik.mugele@uibk.ac.at,
- 6 Lydia L. Simpson¹ lydia.simpson@uibk.ac.at, Kyohei Marume⁵ kyohei.marume@uibk.ac.at,
- 7 Jonathan P. Moore⁴ j.p.moore@bangor.ac.uk, William K. Cornwell III MD, MSCS^{2,3} -
- 8 william.cornwell@ucdenver.edu, Justin S Lawley^{1*†} justin.lawley@uibk.ac.at
- 9
- 10 Affiliations:
- 11¹ University Innsbruck, Department Sport Science, Innsbruck, Austria
- ² Department of Medicine Cardiology. University of Colorado Anschutz Medical Campus,
- 13 Aurora CO.
- ³ Clinical and Translational Research Center, University of Colorado Anschutz Medical Campus,
 Aurora CO.
- ⁴ School of Sport, Health & Exercise Science, Bangor University, Bangor, United Kingdom
 17
- 18 *Correspondence to: Justin.Lawley@uibk.ac.at
- 19 †Address for correspondence to: Department of Sport Science, Division of Performance
- 20 Physiology & Prevention, University of Innsbruck, Fürstenweg 185, A-6020 Innsbruck, Austria.

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

83 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide and has been linked to the 84 development of cognitive diseases including dementia (Stampfer et al. 2006), (Tini et al. 2020) 85 86 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 87 Santos Picanco et al. 2018). Exercise is often cited as the most effective intervention for the 88 prevention and management of CVD (Piepoli et al. 2016) and has also been reported as the most 89 effective modifiable intervention for reducing the development of Alzheimer's disease (Barnes et 90 al. 2011). Unfortunately, one in four adults and 81% of adolescents fail to meet government 91 physical activity recommendations, which has contributed to the unprecedented rise in the 92 incidence of CVD and cerebrovascular diseases (Biswas et al. 2015). 93

94 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 95 96 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 97 vascular endothelial growth factor (VEGF), a precursor for angiogenesis (Chiu et al. 2009), thus 98 contributing to increased capillarisation, enhanced oxygen delivery and clearance of metabolic 99 by-products (Laughlin & Roseguini, 2008). Habitual exercise that repetitively elevates shear 100 stress also increases NO bioavailability (Casey at al. 2017), ultimately aiding vascular 101 102 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 103 thought to promote the clearance of insoluble amyloid β (A β), a protein associated with plaque 104 formation leading to cerebral inflammation and cognitive impairment (Stillman et al. 2017). 105

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. 113 2017). Whilst these data highlight that passive heat therapy can target the peripheral vasculature, 114 potential mechanism(s) that could crossover to directly improve cerebral vascular health are not 115 clear. For example, while epidemiological evidence has linked an increased frequency of sauna 116 use (9-12 times a month versus 4 times a month) with a reduced risk of Dementia (Knekt et al. 117 2020), heat stress typically reduces blood flow (thus shear rate) to the brain due to 118 hyperventilation induced hypercapnia (Bain et al. 2013; Nelson et al. 2011; Brothers et al. 2009). 119 One potential explanation for these divergent findings maybe that blood flow to the brain and 120 intracranial shear stress are elevated in the post heating period, due to an increase in cerebral 121 metabolic rate (Bain et al. 2020) that is not restrained by hyperventilation induced hypocapnia. 122 However, it is worth mentioning that despite clamping end-tidal carbon dioxide during heat 123 124 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 125 vascular resistance i.e. autoregulation (Olesen et al. 2013) that would oppose hypotension post 126 passive heating (or exercise). Thus, it cannot be assumed that changes in shear stress observed in 127 128 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 129 130 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 131 immersion (PHWI) is equivalent to performing low intensity exercise in healthy individuals 132 (29% VO₂ max) (Amin et al. 2020). Yet a recent study reported similar increases in brachial and 133 superficial femoral artery shear rates up to 40 minutes post moderate intensity exercise (60% 134 VO₂ max) and PHWI (Francisco et al. 2021). Therefore, our aim was to extend this evidence 135 base that the recovery period post exercise/heating represents a key window for adaptation 136 (Romero et al. 2017) and determine if similar results could be obtained in the peripheral 137 vasculature compared to high intensity exercise (HIIE). Moreover, complementing these 138 peripheral data with a regional assessment of CBF and cerebral conduit artery shear rate. 139 We measured common femoral artery (CFA), internal carotid artery (ICA) and vertebral artery 140

141 (VA) blood flow and calculated shear rate at 20-minute intervals for up to 80 minutes after each

142 intervention. We hypothesized that CFA shear rate would remain elevated for longer after HIIE

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

148 METHODS

149 Participants

A total of 15 participants including ten males and five females (age, 27 ± 4 years, height, $175 \pm$ 150 53 cm, weight, 69.79 ± 8.72 kg; VO_{2max}, 55.82 ± 10.42 ml·kg·min⁻¹), free from cardiovascular, 151 respiratory, metabolic and neuromuscular diseases, were recruited via personal communication. 152 All experimental procedures had Institutional Review Board approval from Innsbruck University 153 and conformed to the latest revision of the Declaration of Helsinki, except for registration in a 154 database. Written informed consent was obtained after verbal and written explanation of the 155 study protocol and potential risks associated with study participation. All participants were asked 156 to abstain from strenuous physical activities and alcohol (24 hours) as well as caffeine (12 hours) 157 before testing. Female participants were tested during the early follicular phase of their menstrual 158 cycle or the placebo phase of oral contraceptive use. 159

160

161 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.

168

Experimental trials. Thereafter, all participants completed three intervention trials (PHWI, HIIE, 169 170 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. 171 Upon arrival at the laboratory, participants were positioned and instrumented in the semi-172 recumbent position (angle, 30°). After 20-minutes of quiet rest, to allow for haemodynamic 173 stabilisation, baseline cardiovascular, cerebrovascular, respiratory, thermoregulatory and 174 perceptual measurements were made. After completion of each intervention (details below), 175 participants transitioned back to the semi-recumbent position and all measurements were 176 repeated immediately post, and at 20, 40, 60 and 80 minutes, except for haemoglobin 177 concentration, which was only re-assessed immediately after and at 80 minutes. Participants 178

were also provided with 300 ml of water after the first set of post intervention measurements had 179 been performed, most notably following measurement of haemoglobin concentrations. 180 Measurement of haemoglobin was used to indicate sweat loss and subsequent 181 haemoconcentration which would elevate oxygen carrying capacity and increase blood viscosity 182 and therefore decrease CBF and shear rate, thus providing some mechanistic insight into 183 potential reasons for changes in CBF and shear rate between the three interventions. An 80-184 minute time frame was chosen as extensive pilot testing revealed that all physiological variables 185 had returned to baseline following exercise and PHWI. Furthermore, a similar study by 186 Francisco et al. (2021) demonstrated that superficial femoral artery shear rate had returned to 187 baseline 60 minutes post exercise and PHWI. 188

189

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).

195

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.

202

<u>Threshold running</u>. Following a 5-minute warm-up, participants performed 30 minutes of steadystate 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.

211 Experimental measurements.

Thermoregulatory parameters. Rectal temperature was monitored with a thermomister (DeRoyal, 212 Powell, TN, USA), which was self-inserted 15 cm past the anal sphincter (Tram-rac, Solar 8000M 213 GE, Marquette, USA). Forearm skin temperature and cutaneous red cell flux was recorded via an 214 integrated thermistor and laser-Doppler flowmeter (Moor Instruments, Devon, UK). Measuring 215 blood flow through a conduit artery (see below), is the combination of both downstream muscle 216 and cutaneous conductance. Thus, the combination of conduit artery flow via ultrasonography 217 and cutaneous red cell flux is used to try and separate the contribution of skin and muscle blood 218 flow to conduit artery shear rate. To quantify exercise intensity and thermal responses during 219 exercise, heart rate, rating of perceived exertion (RPE; Borg, 1998), thermal comfort (Hollies et 220 221 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 =222 223 comfortable; 13= So hot I am sick and nauseated).

224

225 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 226 227 by electrosphygmomanometry (Tango, M2, SunTechMedical Instruments Inc., USA) in duplicate, and used to calculate mean arterial pressure (MAP, Equation 1). Haemoglobin 228 229 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 (ETCO₂) 230 231 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-232 233 Charbonney et al. 2011).

234

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 andperceptual data.

242

Regional cerebral and leg blood flow. Blood flow of the ICA, VA and CFA were obtained via 243 ultrasonography. Both ultrasound machines were interfaced with a custom designed audio-244 recording software (DUC2) that captured the timed-averaged mean blood flow velocity (TAMV) 245 in the forward and reverse domains using an inbuilt algorithm (Romero et al. 2015). 246 Furthermore, ICA and VA diameters were captured in real time and analysed post-hoc using 247 video recording and custom-made wall tracking software. CFA diameter was measured 248 immediately after TAMV and analysed post-hoc using an offline version of the same custom 249 designed wall tracking software. Carotid artery vessels were imaged with a 15-MHz linear-array 250 251 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 252 measurements were captured from the same segment of the artery between trials. Furthermore, 253 basic ultrasound settings including depth, gain, power and sample volume were kept constant for 254 255 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 256 257 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). 258

259

260 Data acquisition and analyses.

261 <u>Maximal exercise test</u>. The highest 15-s average in oxygen uptake and heart rate was defined as 262 VO_{2max} and HR_{Max} . The ventilatory threshold and respiratory compensation point were 263 determined by two independent researchers using a combination of plots including the V-slope 264 method and the ventilatory equivalents of O₂ and CO₂ (Gaskill et al. 2001).

- 265
- 266 <u>Experimental trials.</u> Continuous variables were sampled at 250 Hz using PowerLab acquisition
- 267 system (AD Instruments, UK) and core temperature, blood pressure, haemoglobin, thermal
- 268 comfort and RPE were measured independently and noted in Labchart (LabChart 8; AD
- 269 Instruments, UK). All continuous data were averaged over one minute.
- 270

Total blood flow as well as antegrade and retrograde blood flow were calculated using equation

272 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).

278

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

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

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

279

280 Statistical Analysis

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

283 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

286 (time) ANOVAs with Tukey's multiple comparisons test.

287 <u>Comparisons between interventions.</u> 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
- 290 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 modelANOVA.

294 Stress Index. To examine the cumulative stress associated with each intervention, a repeated-

295 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.

- 298 <u>Correlation analysis</u>. To demonstrate if there was a relationship between the rate of reduction in 299 femoral blood flow post intervention and individual cardio-respiratory fitness, we first performed 300 individual regression analysis for each participant by plotting femoral blood flow against time 301 (post, 20, 40 and 60 mins). Thereafter, the individual regression slope was plotted against each 302 individual's absolute and relative VO_2 max using a Pearson correlation coefficient. This analysis 303 was performed *post hoc* after observing a swift but heterogeneous normalization of femoral flow 304 and shear post interventions in our cohort.
- 305 <u>Power calculation</u>. During moderate exercise brain blood flow increases by $\sim 15\%$ (Tomoto et al.

2021). Therefore, to have similar benefits to brain health, the post exercise (or passive heating)

307 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
- 311 (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 $P \le 0.05$. Values are presented as mean (±SD) since they were normally distributed.
- 315

316 **RESULTS**

317 Maximal exercise test

Average VO₂ max was $55.8 \pm 10.4 \text{ ml} \cdot \text{kg} \cdot \text{min}^{-1}$ and maximum heart rate was $191 \pm 7 \text{ beats} \cdot \text{min}^{-1}$ ¹. Peak respiratory exchange ratio was 1.17 ± 0.06 and the average RCP occurred at 85% of VO₂ max.

321 Haemodynamic variables during PHWI and exercise

There were no differences in baseline values for HR (P=0.5778), systolic (SBP) (P=0.6696), 322 diastolic (DBP) (P=0.6708) and mean arterial pressure (MAP) (P=0.8023) between interventions. 323 324 HR, SBP, DBP, and MAP were significantly elevated immediately post exercise interventions, 325 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 326 327 HIIE and threshold running compared with PHWI (P<0.0001). By 80 minutes, blood pressure 328 had returned to baseline values for all interventions, although HR remained significantly elevated 329 following HIE (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). 330

331 Core temperature and forearm skin temperature and blood flow

- 332 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
- 336 (P=0.0899) (Table 1). Values at 80 minutes for passive heating (P=0.2923), threshold running
- 337 (P=0.9821) and HIIE (P=0.9992) had returned to baseline levels. Forearm skin temperature and
- 338 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
- 340 P=0.9078) and remained similar at all subsequent time points (Table 1).

341 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), 60 346 (0.9967), or 80 minutes (P=0.9209). Combined, this resulted in no difference to global cerebral 347 blood flow between conditions at any time point (Figure 2A). There were minimal but 348 comparable increases in ICA shear rate post intervention between all three conditions 349 (P=0.4643). Moreover, there were no differences in ICA shear rate at 20 (P=0.2294), 40 350 (P=0.6245), 60 (P=0.6672) or 80 minutes (P=0.6328) between interventions (Figure 3A). While 351 VA shear rate was slightly elevated immediately post both exercise interventions, and PHWI 352 (although not reaching a statistical threshold), this was transient and in absolute terms the 353 increase in shear was minimal. Indeed, statistically no difference could be observed between 354 intervention groups (P=0.1940, Figure 3B). Relative to baseline, cerebral conductance was 355 significantly higher immediately after passive heating compared to threshold running (P=0.0479) 356 and HIIE (P=0.0011) (Figure 2D). Nevertheless, after 20 minutes, conductance had returned 357 towards baseline values for all conditions and remained quantitively similar at 40 (P=0.0461), 60 358 (P=0.7820) and 80 minutes (P=0.4146) (Figure 2B). 359

- ETCO₂ was also similar at baseline between interventions (P=0.7997), but HIIE caused a
- decrease in ETCO₂ compared with passive heating (P=0.0017) and threshold running
- (P=0.0013), post intervention. ETCO₂ remained significantly different between interventions at
- 363 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).

365

366 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=0.0001), 40 (P=0.0004) and 60 (P=0.0141) minutes before returning to baseline by 80 (P=0.4169) minutes (Table 3).

375 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
- 382 (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
- 385 (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 387 retrograde shear. Femoral antegrade shear was elevated by a quantitatively similar magnitude 388 immediately post (P=0.0771), and at 20 (P=0.5312) and 80 minutes (P=0.3903) after all 389 interventions (Figure 5). At 40 (P=0.0341) and 60 minutes (P=0.0500), antegrade shear was 390 statistically higher for HIIE compared with passive heating (Figure 5), albeit mild in magnitude. 391 In contrast, femoral retrograde shear demonstrated comparable decreases for all conditions 392 immediately post intervention (P=0.8226). Thereafter, retrograde shear increased at all 393 394 subsequent time points, but remained slightly lower than baseline values by 80 minutes for all interventions (Figure 5). 395
- 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).

401 Comparison of arterial diameters to baseline

402 ICA (P=0.5377), VA (P=0.1948) and CFA (P=0.3550) diameters were unchanged when 403 measured post PHWI, however ICA (P=0.0032) and VA (P=<0.0001) diameters were

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

407 Correlational analysis

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

412 Comparison of stress index between interventions

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

425 **DISCUSSION**

The novel findings of the current investigation were that 30 minutes of whole body PHWI 426 427 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, 428 for the most part, similar between interventions. Moreover, 30 minutes of PHWI caused a similar 429 post intervention increase in femoral shear rate as threshold running and HIIE, albeit femoral 430 shear remained slightly elevated for a longer period post threshold running. These results suggest 431 that PHWI and exercise do not cause dramatic changes in cerebrovascular shear rates post 432 intervention, however peripheral vascular shear rates are high, and quantitatively similar after all 433 three interventions Therefore, these data support the application of PHWI as a suitable 434 intervention to supplement classic exercise training programs to target the peripheral conduit 435 artery shear in young healthy individuals and warrant further investigation as a therapeutic 436 alternative in diseased populations. 437

438

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

440 Optimizing therapeutic interventions to increase cerebral vascular shear depends on several important variables, including exercise intensity and concomitant changes in arterial blood gases. 441 442 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, 443 444 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 445 blood flow during exercise up to 60% VO₂ peak (291 \pm 16 ml min⁻¹), which subsequently 446 decreased when exercise intensity was increased to 80% of VO₂ peak ($258 \pm 13 \text{ ml min}^{-1}$). In 447 448 contrast, VA blood flow continued to increase up to 80% of VO₂ peak, before plateauing (144 \pm 14 ml min⁻¹), due to a hyperventilatory induced hypocapnia, and subsequent cerebral 449 450 vasoconstriction (Moraine et al. 1993). Interestingly, Furlong et al. (2020) reported continued intensity matched elevations in middle cerebral artery blood velocity during higher intensity 451 452 running exercise compared with cycling, in individuals with higher aerobic fitness (VO₂ max >45 ml·kg·min⁻¹), suggesting the modality of exercise and influence of training status may alter 453 cerebral autoregulation and/or CO₂ reactivity. With passive heating, several studies (Nelson et al. 454 2011; Brothers et al. 2009 & Bain et al. 2013) have observed a robust reduction in blood flow 455

456 (and assumingly shear stress) to both the anterior and posterior cerebral conduit arteries. In these 457 studies, passive heating via a water perfused suit increased core temperature by 1.3° C to 2° C and 458 caused hyperthermia induced hyperventilation and subsequent hypocapnia. Since hypocapnia is a 459 powerful vasoconstrictor within the brain, correction of end-tidal PCO₂ by end-tidal forcing 460 restored CBF to baseline levels (Bain et al. 2013).

461 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. 462 Similarly, while ICA and VA shear rate were statistically increased post exercise, this effect was 463 lost after just over 20 minutes. The increase in ICA and VA shear was mostly likely due to 464 465 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 466 467 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 468 469 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 470 471 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 472 473 minimal effects on cerebral vasculature shear during the post intervention period, despite modest yet persistent perturbations in core temperature, end-tidal carbon dioxide (ETCO₂) and arterial 474 blood pressure. Ultimately it seems that the post intervention period is not an optimal window for 475 shearing the brain. 476

477 Cerebral regulatory mechanisms post exercise and passive hot water immersion.

The mechanism(s) responsible for regulating CBF during and after exercise or passive heating 478 479 are multifactorial, with the interaction of ETCO₂ and core temperature through hyperventilatory 480 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 481 hyperthermia post exercise and PHWI, ICA and VA blood flow remained constant due to a 482 483 decrease (post exercise) or increase (post heat stress) in cerebral conductance. These opposing 484 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 485

by the observation that core temperature increased similarly between all three trials and $ETCO_2$ 486 was reduced immediately post exercise, but unchanged post PHWI where an increase in 487 conductance was observed. Interestingly, the initial post exercise reduction in ETCO₂ for both 488 threshold running and HIIE aligned with significant decreases in ICA and VA diameter, which 489 slowly returned towards baseline in synergy with restoration of ETCO₂ (Table 3). In contrast, 490 ETCO₂ was unchanged post PHWI and accordingly both ICA and VA diameter remained similar 491 to baseline. Collectively, these data provide supporting evidence for the sensitivity of CBF to 492 ETCO₂ and demonstrate that blood pressure plays a powerful regulatory role on the cerebral 493 circulation and needs to be considered post any therapeutic intervention if "shearing the brain 494 (Carr et al. 2020)" is a focus. 495

496 Femoral blood flow and shear rate

497 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 498 499 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 500 501 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 502 503 for HIIE), the magnitude of the difference was minimal ($\sim 30 \text{ s-1}$). Thus, these findings suggest that a relatively short (30 minutes) bout of passive heat stress (+1.4°C) provides comparable post 504 intervention elevations in total femoral shear compared with high intensity exercise. Our data are 505 supported by findings from Francisco et al. (2021) that established comparable brachial and 506 superficial femoral artery shear rates 20 minutes post exercise (60% VO₂ peak) and PHWI, 507 following matched elevations in core temperature. Interestingly, in that study, brachial and 508 superficial femoral shear rates remained elevated at 40- and 60-minutes post moderate exercise. 509 In contrast, femoral shear was back to normal after 40 minutes of threshold running and 60 510 minutes post HIIE in our study. The difference in the rate of reduction in shear rate between our 511 data and Francisco et al. (2021) may relate to the interaction between the duration of the heating 512 intervention (60 mins, Francisco et al. 2021), compared with our study (30 mins) and the 513 participant training status. While the training status of the participants from Francisco et al. 514 (2021) is not known, our highly active and moderately trained (VO_{2max}, 55.82 \pm 10.42 515

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 VO₂ 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 populations (30 minutes running and HIIE), which comply with World Health Organisation 524 525 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, which is unnatural following exercise and significantly alters cardiovascular (Hastreiter & 528 Young, 1997), (Takahashi et al. 2005) and blood flow haemodynamics (Nishiyasu et al. 2007), 529 thus influencing interpretation of the effects of the intervention. We also provided participants 530 with a select amount of fluid after the first set of post intervention measurements had been 531 performed. This enabled us to deduce the initial effects of potential dehydration on CBF and 532 prevent haemoconcentration caused by plasma volume loss influencing the subsequent measures 533 of CBF and shear (Trangmar et al. 2015). Finally, we matched the increase in core temperature 534 535 between interventions, thus helping elucidate heat specific elevations in shear rate relative to exercise. We also documented thermal comfort and RPE for the interventions, thereby allowing a 536 comparison between physiological stress and perceptual experience, which is important to know 537 when considering adherence and compliance to exercise and heating interventions. 538

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 546 variables. Moreover, while we did not determine sweat loss from each intervention, which would 547 have strengthened the study design, the measurement of haemoglobin concentration confirmed 548 physiologically that haemoconcentration was avoided and thus isolates our findings from this 549 confounding effect. Moreover, we also acknowledge that it would have been more pertinent to 550 measure skin temperature and cutaneous red cell flux in the leg rather than the forearm, yet we 551 were not confident in submerging the laser doppler probe in hot water and choose the arms as a 552 553 suitable surrogate.

554

555 Implications

Our data revealed that in the post intervention period, high intensity exercise and PHWI 556 caused minimal changes in shear rates on the brain's extracranial arteries. Thus, the cerebral 557 vascular benefits of exercise training likely occur during the intervention itself when CBF and 558 shear are high (Sato et al. 2011). Alternatively, passive heating generally causes a reduction in 559 brain blood flow during the intervention (Nelson et al. 2011), and based on the current data, no 560 561 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). 562 563 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 564 565 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. 566 567 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 568 569 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 570 571 stress required to increase shear and potentially improve peripheral vascular function with passive heating (Thomas et al. 2017; Neff et al. 2016). 572

573

574 Conclusion

575 Our data suggest that time and core temperature matched high intensity exercise and whole body 576 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.

583 584

585 ADDITONAL INFORMATION

586 *Competing Interests*

587 None of the authors have any conflicts of interests.

588

589 Author Contributions

590 Conception/design of the work: JSL, WKC III, JPM. Acquisition/analysis of data for the work:

591 SBA, JSL, HM, ABH, LSS, KM. Drafting and revisions of the work: All authors. Final approval:

592 All authors.

593

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596

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601

603 **References**

- Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. J Intern
 Med 260: 211-223, 2006.
- Tini G, Scagliola R, Monacelli F, La Malfa G, Porto I, Brunelli C, and Rosa GM.
 Alzheimer's Disease and Cardiovascular Disease: A Particular Association. Cardiol Res Pract
 2020: 2617970, 2020.
- Arboix A. Cardiovascular risk factors for acute stroke: Risk profiles in the different
 subtypes of ischemic stroke. World J Clin Cases 3: 418-429, 2015.
- 4. Dos Santos Picanco LC, Ozela PF, de Fatima de Brito Brito M, Pinheiro AA, Padilha EC,
- Braga FS, de Paula da Silva CHT, Dos Santos CBR, Rosa JMC, and da Silva Hage-Melim LI.
- 613 Alzheimer's Disease: A Review from the Pathophysiology to Diagnosis, New Perspectives for
- 614 Pharmacological Treatment. Curr Med Chem 25: 3141-3159, 2018.
- 5. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT,
- 616 Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Richard Hobbs FD, Løchen ML, Löllgen H,
- 617 Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, Bart
- van der Worp H, van Dis I, and Monique Verschuren WM. 2016 European Guidelines on
 cardiovascular disease prevention in clinical practice. Rev Esp Cardiol (Engl Ed) 69: 939, 2016.
- 6. Barnes DE, and Yaffe K. The projected effect of risk factor reduction on Alzheimer's
 disease prevalence. Lancet Neurol 10: 819-828, 2011.
- 622 7. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, and Alter DA.
 623 Sedentary time and its association with risk for disease incidence, mortality, and hospitalization
 624 in adults: a systematic review and meta-analysis. Ann Intern Med 162: 123-132, 2015.
- 625 8. Green DJ, Hopman MT, Padilla J, Laughlin MH, and Thijssen DH. Vascular Adaptation
 626 to Exercise in Humans: Role of Hemodynamic Stimuli. Physiol Rev 97: 495-528, 2017.
- 627 9. Chiu JJ, Usami S, and Chien S. Vascular endothelial responses to altered shear stress:
 628 pathologic implications for atherosclerosis. Ann Med 41: 19-28, 2009.
- Laughlin MH, and Roseguini B. Mechanisms for exercise training-induced increases in
 skeletal muscle blood flow capacity: differences with interval sprint training versus aerobic
 endurance training. J Physiol Pharmacol 59 Suppl 7: 71-88, 2008.

- Casey DP, Ueda K, Wegman-Points L, and Pierce GL. Muscle contraction induced
 arterial shear stress increases endothelial nitric oxide synthase phosphorylation in humans. Am J
 Physiol Heart Circ Physiol 313: H854-H859, 2017.
- Campbell R, Fisher JP, Sharman JE, McDonnell BJ, and Frenneaux MP. Contribution of
 nitric oxide to the blood pressure and arterial responses to exercise in humans. J Hum Hypertens
 25: 262-270, 2011.
- 638 13. Stillman CM, Lopez OL, Becker JT, Kuller LH, Mehta PD, Tracy RP, and Erickson KI.
 639 Physical activity predicts reduced plasma β amyloid in the Cardiovascular Health Study. Annals
 640 of Clinical and Translational Neurology 4: 284-291, 2017.
- 14. McArthur D, Dumas A, Woodend K, Beach S, and Stacey D. Factors influencing
 adherence to regular exercise in middle-aged women: a qualitative study to inform clinical
 practice. BMC Womens Health 14: 49, 2014.
- Brunt VE, Howard MJ, Francisco MA, Ely BR, and Minson CT. Passive heat therapy
 improves endothelial function, arterial stiffness and blood pressure in sedentary humans. J
 Physiol 594: 5329-5342, 2016.
- Romero SA, Gagnon D, Adams AN, Cramer MN, Kouda K, and Crandall CG. Acute
 limb heating improves macro- and microvascular dilator function in the leg of aged humans. Am
 J Physiol Heart Circ Physiol 312: H89-H97, 2017.
- Thomas KN, van Rij AM, Lucas SJ, and Cotter JD. Lower-limb hot-water immersion
 acutely induces beneficial hemodynamic and cardiovascular responses in peripheral arterial
 disease and healthy, elderly controls. Am J Physiol Regul Integr Comp Physiol 312: R281-R291,
 2017.
- Knekt P, Järvinen R, Rissanen H, Heliövaara M, and Aromaa A. Does sauna bathing
 protect against dementia? Prev Med Rep 20: 101221, 2020.
- Bain AR, Smith KJ, Lewis NC, Foster GE, Wildfong KW, Willie CK, Hartley GL,
- Cheung SS, and Ainslie PN. Regional changes in brain blood flow during severe passive
 hyperthermia: effects of PaCO2 and extracranial blood flow. J Appl Physiol (1985) 115: 653659, 2013.
- 660 20. Nelson MD, Haykowsky MJ, Stickland MK, Altamirano-Diaz LA, Willie CK, Smith KJ,
- Petersen SR, and Ainslie PN. Reductions in cerebral blood flow during passive heat stress in
 humans: partitioning the mechanisms. J Physiol 589: 4053-4064, 2011.

Brothers RM, Wingo JE, Hubing KA, and Crandall CG. The effects of reduced end-tidal
carbon dioxide tension on cerebral blood flow during heat stress. J Physiol 587: 3921-3927,
2009.

Bain AR, Hoiland RL, Donnelly J, Nowak-Flück D, Sekhon M, Tymko MM, Greiner JJ,
DeSouza CA, and Ainslie PN. Cerebral metabolism, oxidation and inflammation in severe
passive hyperthermia with and without respiratory alkalosis. J Physiol 598: 943-954, 2020.

Caldwell HG, Coombs GB, Howe CA, Hoiland RL, Patrician A, Lucas SJE, and Ainslie
PN. Evidence for temperature-mediated regional increases in cerebral blood flow during
exercise. J Physiol 598: 1459-1473, 2020.

672 24. Olesen ND, Fischer M, and Secher NH. Sodium nitroprusside dilates cerebral vessels and
673 enhances internal carotid artery flow in young men. J Physiol 596: 3967-3976, 2018.

Amin SB, Hansen AB, Mugele H, Willmer F, Gross F, Reimeir B, Cornwell WK,
Simpson LL, Moore JP, Romero SA, and Lawley JS. Whole body passive heating versus
dynamic lower body exercise: a comparison of peripheral hemodynamic profiles. J Appl Physiol
(1985) 130: 160-171, 2021.

678 26. Romero SA, Minson CT, and Halliwill JR. The cardiovascular system after exercise. J
679 Appl Physiol (1985) 122: 925-932, 2017.

Francisco MA, Colbert C, Larson EA, Sieck DC, Halliwill JR, and Minson CT.
Hemodynamics of post-exercise vs. post hot water immersion recovery. J Appl Physiol (1985)
2021.

28. Lind-Holst M, Cotter JD, Helge JW, Boushel R, Augustesen H, Van Lieshout JJ, and Pott

FC. Cerebral autoregulation dynamics in endurance-trained individuals. J Appl Physiol (1985)
110: 1327-1333, 2011.

Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput
JP, Chastin S, Chou R, Dempsey PC, DiPietro L, Ekelund U, Firth J, Friedenreich CM, Garcia L,

688 Gichu M, Jago R, Katzmarzyk PT, Lambert E, Leitzmann M, Milton K, Ortega FB, Ranasinghe

689 C, Stamatakis E, Tiedemann A, Troiano RP, van der Ploeg HP, Wari V, and Willumsen JF.

World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J
Sports Med 54: 1451-1462, 2020.

692 30. Borg G. Borg's perceived exertion and pain scales Champaign IL: Human Kinetics,693 1998.

- Hollies N, Custer A, Morin C, and Howard M. A. Human Perception Analysis Approach
 to Clothing Comfort. Textile Research Journal 49: 557–564, 1979.
- Battisti-Charbonney A, Fisher J, and Duffin J. The cerebrovascular response to carbon
 dioxide in humans. J Physiol 589: 3039-3048, 2011.
- Moran DS. Stress evaluation by the physiological strain index (PSI). J Basic Clin Physiol
 Pharmacol 11: 403-423, 2000.
- Jumingu HMM & Dessureault P. Physiological responses to heat strain: A study on
 personal monitoring for young workers, Journal of Thermal Biology, 34: 299-305, 2009.
- 702 35. Romero SA, Ely MR, Sieck DC, Luttrell MJ, Buck TM, Kono JM, Branscum AJ, and
- 703 Halliwill JR. Effect of antioxidants on histamine receptor activation and sustained postexercise

vasodilatation in humans. Exp Physiol 100: 435-449, 2015.

705 36. Limberg JK, Casey DP, Trinity JD, Nicholson WT, Wray DW, Tschakovsky ME, Green

DJ, Hellsten Y, Fadel PJ, Joyner MJ, and Padilla J. Assessment of resistance vessel function in

human skeletal muscle: guidelines for experimental design, Doppler ultrasound, and

pharmacology. Am J Physiol Heart Circ Physiol 318: H301-H325, 2020.

- 37. Gaskill SE, Ruby BC, Walker AJ, Sanchez OA, Serfass RC, and Leon AS. Validity and
 reliability of combining three methods to determine ventilatory threshold. Med Sci Sports Exerc
 33: 1841-1848, 2001.
- Furlong RJ, Weaver SR, Sutherland R, Burley CV, Imi GM, Lucas RAI, and Lucas SJE.
 Exercise-induced elevations in cerebral blood velocity are greater in running compared to
 cycling at higher intensities. Physiol Rep 8: e14539, 2020.
- Gibbons TD, Ainslie PN, Thomas KN, Wilson LC, Akerman AP, Donnelly J, Campbell
 HA, and Cotter JD. Influence of the mode of heating on cerebral blood flow, non-invasive
 intracranial pressure and thermal tolerance in humans. J Physiol 599: 1977-1996, 2021.

40. Bausell BR & Y-F Li. Power analysis for experimental research. Seattle: Cambridge

- 719 University Press., 2002. Bausell BR & Y-F Li.
- 41. Jørgensen LG, Perko G, and Secher NH. Regional cerebral artery mean flow velocity and
- blood flow during dynamic exercise in humans. J Appl Physiol (1985) 73: 1825-1830, 1992.
- 42. Evans PC, Fragiadaki M, Morris PD, and Serbanovic-Canic J. Shear stress: the dark
 energy of atherosclerotic plaques. Cardiovasc Res 117: 1811-1813, 2021.

- Peiffer V, Sherwin SJ, and Weinberg PD. Does low and oscillatory wall shear stress
 correlate spatially with early atherosclerosis? A systematic review. Cardiovasc Res 99: 242-250,
 2013.
- Tomoto T, Liu J, Tseng BY, Pasha EP, Cardim D, Tarumi T, Hynan LS, Munro Cullum
 C, and Zhang R. One-Year Aerobic Exercise Reduced Carotid Arterial Stiffness and Increased
 Cerebral Blood Flow in Amnestic Mild Cognitive Impairment. J Alzheimers Dis 80: 841-853,
 2021.
- 45. Nybo L, and Nielsen B. Middle cerebral artery blood velocity is reduced with
 hyperthermia during prolonged exercise in humans. J Physiol 534: 279-286, 2001.
- 46. Poulin MJ, Syed RJ, and Robbins PA. Assessments of flow by transcranial Doppler
 ultrasound in the middle cerebral artery during exercise in humans. J Appl Physiol (1985) 86:
 1632-1637, 1999.
- 47. Smith KJ, Hoiland RL, Grove R, McKirdy H, Naylor L, Ainslie PN, and Green DJ.
 Matched increases in cerebral artery shear stress, irrespective of stimulus, induce similar changes
 in extra-cranial arterial diameter in humans. J Cereb Blood Flow Metab 39: 849-858, 2019.
- 48. Herholz K, Buskies W, Rist M, Pawlik G, Hollmann W, and Heiss WD. Regional
 cerebral blood flow in man at rest and during exercise. J Neurol 234: 9-13, 1987.
- 49. Sato K, Ogoh S, Hirasawa A, Oue A, and Sadamoto T. The distribution of blood flow in
 the carotid and vertebral arteries during dynamic exercise in humans. J Physiol 589: 2847-2856,
 2011.
- Moraine JJ, Lamotte M, Berré J, Niset G, Leduc A, and Naeije R. Relationship of middle
 cerebral artery blood flow velocity to intensity during dynamic exercise in normal subjects. Eur J
 Appl Physiol Occup Physiol 67: 35-38, 1993.51. Carr JMJR, and Ainslie PN. Shearing the
 brain. J Appl Physiol (1985) 129: 599-602, 2020.
- 52. Hastreiter D, and Young LR. Effects of a gravity gradient on human cardiovascular
 responses. J Gravit Physiol 4: P23-26, 1997.
- 53. Périard JD, Travers GJS, Racinais S, and Sawka MN. Cardiovascular adaptations
 supporting human exercise-heat acclimation. Auton Neurosci 196: 52-62, 2016.
- Takahashi T, Hayano J, Okada A, Saitoh T, and Kamiya A. Effects of the muscle pump
 and body posture on cardiovascular responses during recovery from cycle exercise. Eur J Appl
 Physiol 94: 576-583, 2005.

- 55. 755 Nishiyasu T, Hayashida S, Kitano A, Nagashima K, and Ichinose M. Effects of posture on peripheral vascular responses to lower body positive pressure. Am J Physiol Heart Circ 756 757 Physiol 293: H670-676, 2007.
- Trangmar SJ, Chiesa ST, Llodio I, Garcia B, Kalsi KK, Secher NH, and González-56. 758 Alonso J. Dehydration accelerates reductions in cerebral blood flow during prolonged exercise in 759 the heat without compromising brain metabolism. Am J Physiol Heart Circ Physiol 309: H1598-760 1607, 2015. 761
- 57. Von Schulze AT, Deng F, Morris JK, and Geiger PC. Heat therapy: possible benefits for 762 cognitive function and the aging brain. J Appl Physiol (1985) 129: 1468-1476, 2020. 763
- 58. Tinken TM, Thijssen DH, Hopkins N, Black MA, Dawson EA, Minson CT, Newcomer 764 SC, Laughlin MH, Cable NT, and Green DJ. Impact of shear rate modulation on vascular 765 function in humans. Hypertension 54: 278-285, 2009. 766
- 59. Imamura M, Biro S, Kihara T, Yoshifuku S, Takasaki K, Otsuji Y, Minagoe S, Toyama 767 Y, and Tei C. Repeated thermal therapy improves impaired vascular endothelial function in 768 patients with coronary risk factors. J Am Coll Cardiol 38: 1083-1088, 2001. 769
- 60. 770 Neff D, Kuhlenhoelter AM, Lin C, Wong BJ, Motaganahalli RL, and Roseguini BT. Thermotherapy reduces blood pressure and circulating endothelin-1 concentration and enhances 771 772 leg blood flow in patients with symptomatic peripheral artery disease. Am J Physiol Regul Integr Comp Physiol 311: R392-400, 2016. 773

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785	Figure Legends
786	Figure 1. Images of two participants post PHWI (left) and exercise (right) having
787	measurements of cerebral and common femoral artery blood flow performed alongside
788	measurements of HR, ETCO2, mean arterial pressure, core temperature and forearm skin
789	temperature and skin blood flow
790	
791 792 793 794	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 \pm SD (n=15).
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796 797 798	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 \pm SD (n=15).
799	
800 801 802 803 804 805 806	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 \pm SD (n=15).
807	
808	Figure 5. Antegrade and retrograde shear rate at all time points for all three interventions. A
809	repeated measures ANOVA with Tukey's multiple comparison test revealed significant
810	differences in antegrade shear at 40 (P=0.0341) and 60 (P=0.0500) minutes between HIIE
811	and PHWI. There were no differences in retrograde shear rate at any time point. Data are

812 mean \pm SD (n=15)











	T 4 4 ²		Time points (mins)						
	Intervention	Baseline	Post	20	40	60	80		
Heart rate	Heat	63 ± 10	100 ± 15 ** ^{##}	$70 \pm 12^{**}$ ##	64 ± 8 ** ^{##}	60 ± 9 ** ^{##}	59 ± 9 ** ^{##}		
(beats · min ⁻¹)	Threshold	63 ± 7	$171 \pm 9^{\dagger\dagger} *$	$88\pm9^{\dagger\dagger}$	$78\pm8^{\dagger\dagger}$	$74\pm9^{\dagger\dagger}$	$69\pm11^{\dagger\dagger}$		
	HIIT	64 ± 10	$176\pm8^{\dagger\dagger}$	$89\pm9^{\dagger\dagger}$	$81\pm12^{\dagger\dagger}$	$75\pm12^{\dagger\dagger}$	$70\pm12^{\dagger\dagger}$		
Systolic arterial	Heat	122 ± 10	123 ± 11 ** ^{##}	122 ± 11	119 ± 10	$121 \pm 9**$	120 ± 10		
pressure (mmHg)	Threshold	122 ± 8	$151\pm21^{\dagger\dagger}$	122 ± 8	117 ± 8	118 ± 9	118 ± 10		
	HIIT	121 ± 11	$159\pm26^{\dagger\dagger}$	124 ± 10	120 ± 10	$116\pm8^{\dagger\dagger}$	119 ± 9		
Diastolic arterial	Heat	75 ± 10	66 ± 7 ** ^{##}	71 ± 8 ** [#]	71 ± 9 **	72 ± 7	74 ± 8		
pressure (mmHg)	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	Heat	90 ± 9	84 ± 8 ** ^{##}	87 ± 8 **	86 ± 9 *	88 ± 7	88 ± 8		
pressure (mmHg)	Threshold	91 ± 8	106 ± 13 ^{††} *	90 ± 7	87 ± 8 *	88 ± 8	82 ± 8		
	HIIT	90 ± 10	115 ± 18 ^{†† #}	$93\pm8~^{\dagger\dagger}$	90 ± 8 ^{† #}	88 ± 7	89 ± 7		
Pulse pressure	Heat	47 ± 5	57 ± 8	51 ± 7	47 ± 6	49 ± 6 **	46 ± 5		
(mmHg)	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	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		
temperature (°C)	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	Heat	42 ± 34	471 ± 407	491 ± 530	402 ± 415	314 ± 405	158 ± 205		
flow flux (PU)	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	Heat	37.0 ± 0.4	38.5 ± 0.7	37.9 ± 0.5	37.5 ± 0.5	37.4 ± 0.5	$37.3\pm0.4^{*^\#}$		
(°C)	Threshold	36.9 ± 0.3	38.5 ± 0.5	37.6 ± 0.3	37.3 ± 0.3	37.1 ± 0.3	$37.0\pm0.3^\dagger$		
· ·	HIIT	37.0 ± 0.3	38.4 ± 0.4	37.6 ± 0.3	37.3 ± 0.2	37.1 ± 0.3	$37.0\pm0.2^\dagger$		
$ETCO_2(\%)$	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 [#]	$5.33\pm0.37~^{\dagger~\#\#}$	5.41 ± 0.29		
Haemoglobin (g·dL ⁻¹)	Heat	15.4 ± 1.4	15.4 ± 1.4				15.1 ± 1.5		
5 (G /	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		

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

P<0.01 †, 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 \pm SD (n =15).

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Stress Index	Intervention		Time points (mins) Cumulative ine						
	Intervention	Baseline	10	20	30				
Heart rate	Heat	63 ± 10	907 ± 160 ** ^{##}	2124 ±276** ^{##}	3310 ± 516 ** ^{##}	6404 ± 214 ** ^{##}			
(beats · min ⁻¹)	Threshold	63 ± 7	$1665\pm80^{\dagger\dagger}$ **	$3513 \pm 176^{\dagger\dagger} \texttt{**}$	$5362\pm326^{\dagger\dagger}**$	$10603 \pm 138^{\dagger\dagger} **$			
	HIIE	64 ± 10	$1547\pm68^{\dagger\dagger\#\#}$	$3213 \pm 184^{\dagger\dagger \# \#}$	$5062 \pm 240^{\dagger \dagger \# \#}$	$9886 \pm 105^{\dagger\dagger \# \#}$			
Core	Heat	37.0 ± 0.4	$373 \pm 3.3^{\# * * }$	$758\pm8.4^{\#}{**}$	1152 ± 14.5	$2320 \pm 6^{\# * *}$			
temperature	Threshold	36.9 ± 0.3	$376.4\pm3.4^{\dagger\dagger}$	$766.8\pm6.9^\dagger$	1164.4 ± 11.6	$2344\pm5^{\dagger\dagger}$			
(°C)	HIIE	37.0 ± 0.3	$377.2\pm3.6^{\dagger\dagger}$	$769.9\pm7.2^{\dagger\dagger}$	1162.8 ± 10.5	$2348\pm4^{\dagger\dagger}$			
	Heat	7 ± 0	86 ± 11	188 ± 20	$306 \pm 28^{\# * *}$	587 ± 12			
Tcomfort	Threshold	7 ± 0	79 ± 23	$175 \pm 53*$	$282\pm82^{\dagger\dagger}$	543 ± 36			
	HIIE	7 ± 0	91 ± 10	$203\pm23^{\#}$	$294\pm43^{\dagger\dagger}$	595 ± 19			
	Heat	-	-	-	-				
RPE	Threshold	-	125 ± 38	284 ± 84	446 ± 134	855 ± 48			
	HIIE	-	123 ± 53	285 ± 118	456 ± 188	864 ± 68			

Table 2. Stress index for physiological and perceptual parameters

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 \ddagger , P<0.01 \ddagger , different to Heat. P<0.05#, P<0.01## different to threshold. P<0.05*, P<0.01** difference to HIIT. Data are mean \pm SD.

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

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

 $P<0.05^*$, $P<0.01^{**}$. A 2-way ANOVA with Tukey's multiple comparison test used to demonstrate changes relative to baseline. Data are mean \pm 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.

				Time Poin	ts (mins)	P-Value				
	Intervention	Baseline	Post	20	40	60	80	Time	Intervention	Time x Intervention
	Heat	$0.478 \pm$	$0.474 ~ \pm$	$0.474 ~ \pm$	$0.479 ~ \pm$	$0.484 \pm$	$0.482 \pm$			
ICA		0.040	0.031	0.036	0.028	0.040	0.038			
ICA	Threshold	$0.486 \pm$	$0.476 ~ \pm$	$0.461 \pm$	$0.477 \pm$	$0.481 \pm$	$0.486 \pm$	D_0 0002	D-0 ((52	D_0 2200
(am)		0.035	0.040**	0.039	0.043	0.034	0.037	P=0.0002	P=0.0033	P=0.3388
(cm)	HIIT	$0.480 \pm$	$0.462 \pm$	$0.464 \pm$	$0.470 ~ \pm$	$0.480 \pm$	$0.486 \pm$			
		0.033	0.036**	0.039	0.029	0.030	0.022			
	Heat	$0.393 \pm$	$0.383 \pm$	$0.387 \pm$	$0.388 \pm$	0.390	$0.393 \pm$			
V A		0.050	0.06	0.059	0.063	± 0.061	0.058			
VA diamatar	Threshold	$0.405 \pm$	$0.381 \pm$	0.390	0.395	$0.401 \pm$	$0.402 \pm$	D <0.0001	P-0 5701	D-0 1263
(cm)		0.054	0.042**	$\pm 0.041*$	± 0.047	0.046	0.047	1 20.0001	1-0.3791	1-0.1203
(cm)	HIIT	$0.393 \pm$	$0.370 \pm$	$0.381 \pm$	$0.389 \pm$	$0.391 \pm$	$0.394 \pm$			
		0.050	0.045**	0.046**	0.046	0.048	0.044			
	Heat	$0.910 \ \pm$	$0.908 \pm$	$0.907 \pm$	$0.908 \pm$	$0.919 \pm$	$0.915 \pm$			
Femoral		0.097	0.092	0.089	0.086	0.091	0.085			
artery	Threshold	$0.893 \pm$	$0.920 \ \pm$	$0.909 \pm$	$0.905 \pm$	$0.906 \ \pm$	0.900	P-0.0003	P-0.4585	P-0.0402
diameter		0.103	0.110**	0.112	0.108	0.110	± 0.102	1-0.0003	1-0.4383	1-0.0402
(cm)	HIIT	$0.907 \pm$	$0.935 \pm$	$0.925 \pm$	0.930**	$0.922 \pm$	$0.914 ~ \pm$			
		0.106	0.109**	0.099	± 0.101	0.110	0.107			

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

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

Intervention	Absolute V	$O_2 (ml \cdot min^{-1})$	Relative VO ₂ (ml·kg·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		

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

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 wheth measured for upitor 80 minutes post (interventionJune 16, 2022.