The acute effect of exercise intensity on peripheral and cerebral vascular function in healthy adults

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Running Head: Exercise intensity and vascular function

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Abstract:

The acute effect of exercise intensity on cerebrovascular reactivity, and whether this mirrors changes in peripheral vascular function, has not been investigated. The aim of this study was to explore the acute effect of exercise intensity on cerebrovascular reactivity (CVR) and peripheral vascular function in healthy young adults (n=10, 6 females, 22.7 ± 3.5 years). Participants completed four experimental conditions on separate days: high intensity interval exercise (HIIE) with intervals performed at 75% maximal oxygen uptake ($\dot{V}O_{2max}$; HIIE1), HIIE with intervals performed at 90% $\dot{V}O_{2max}$ (HIIE2), continuous moderate intensity exercise (MIE) at 60% $\dot{V}O_{2max}$ and a sedentary control condition (CON). All exercise conditions were completed on a cycle ergometer and matched for time (30 min) and average intensity (60% $\dot{V}O_{2max}$). Brachial artery flow-mediated dilation (FMD) and CVR of the middle cerebral artery were measured before exercise, and one- and three hours post-exercise. CVR was assessed using transcranial Doppler ultrasonography to both hypercapnia (6% carbon dioxide breathing) and hypocapnia (hyperventilation). FMD was significantly elevated above baseline one and three hours following both HIIE conditions ($P<0.05$), but FMD was unchanged following the MIE and CON trials ($P>0.33$). CVR to both hypercapnia and hypocapnia, and when expressed across the end-tidal CO_2 range, was unchanged in all conditions, at all time points (all $P>0.14$). In conclusion, these novel findings show that the acute increases in peripheral vascular function following HIIE, compared to MIE, were not mirrored by

changes in cerebrovascular reactivity, which was unaltered following all exercise conditions in healthy young adults.

Key Words: cerebrovascular reactivity, flow mediated dilation, endothelial function, HIIE

New & Noteworthy: This is the first study to identify that acute improvements in peripheral vascular function following high-intensity interval exercise are not mirrored by improvements in cerebrovascular reactivity in healthy young adults. High-intensity interval exercise completed at both 75% and 90% $\dot{V}O_{2max}$ increased brachial artery flow-mediated dilation one and three hours following exercise, compared to continuous moderate intensity exercise and a sedentary control condition. By contrast, cerebrovascular reactivity was unchanged following all four conditions.

Introduction

Atherosclerosis is a precursor to overt cardiovascular disease, and endothelial dysfunction is the first detectable manifestation of the atherosclerotic process (42). Aerobic exercise training is known to have beneficial effects on endothelial function (24), and this is mediated by exercise-induced increases in shear stress (53). Since the chronic benefits of exercise are likely related to the repeated acute responses following a single bout of exercise (17), it is important to investigate changes in endothelial function following a single bout of exercise (51). Increases in peripheral shear stress are greater with higher intensity exercise (23, 49), and might therefore confer acute intensity-dependent improvements in peripheral vascular function (18, 25). However, the acute effect of exercise intensity on cerebrovascular reactivity has received little investigation.

Cerebrovascular function plays an important role in the risk of cerebrovascular diseases such as stroke, dementia and cognitive decline (14, 38). Recently, Bliss et al., (6) highlighted the beneficial effects of exercise training on cerebrovascular health, including improved endothelial function and cerebral angiogenesis. High-intensity interval training is known to improve peripheral vascular function (41), and there is a growing interest in the effects of high-intensity interval exercise (HIIE) on cerebrovascular health (12, 36, 59). A commonly utilised measurement of cerebrovascular function is the ability of the cerebrovasculature to vasodilate or constrict in response to hypercapnia and hypocapnia, respectively, termed cerebrovascular reactivity (CVR). However, the acute effects of exercise on CVR are not well understood. In particular, it is not known whether acute changes in peripheral endothelial function (assessed through brachial artery flow-mediated dilation; FMD) are mirrored by changes in CVR. Initial evidence suggested the two may be related, since the overnight change in FMD and CVR were strongly,

74 positively correlated (2). However, more recently, no relationship has been observed
75 between resting cerebral and peripheral vascular function in healthy young adults,
76 suggesting the two may share different mechanistic pathways (13). Exploring whether
77 peripheral vascular function and CVR respond similarly following an acute challenge
78 (such as exercise) will provide further insight into whether they share a common
79 mechanism of change (56). Currently, it is unknown if the acute effects of exercise on
80 peripheral vascular function are mirrored by changes in CVR.

81 A recent systematic review explored the effect of HIIE on cerebrovascular function (59).
82 In total, only 7 eligible studies were found, which included a combination of acute and
83 exercise training studies, with data on CVR following acute HIIE limited to a single study
84 (11). In healthy adults, one bout of HIIE (completed at 85-90% heart rate reserve)
85 significantly lowered CVR to hypercapnia immediately and one hour following HIIE, but
86 was restored to baseline levels two hours following exercise (11). In contrast, moderate
87 intensity exercise and a sedentary control condition did not alter CVR. This was thought
88 to be a result of repeated exposure to hyperventilation-induced hypocapnia during HIIE
89 (39), impairing the dilatory capacity of the cerebrovasculature following exercise, which
90 may explain why CVR did not fall following moderate intensity exercise. However, the
91 exercise conditions were not equivalent for time or work performed, which is an
92 important consideration to isolate and understand the effects of exercise intensity (28).

93 Since shear stress appears to be the primary mechanism underlying acute (52) and chronic
94 (53) exercise-induced improvements in peripheral vascular function, exercise which
95 elicits the greatest increases in cerebral blood flow (CBF) may therefore result in the
96 greatest post-exercise improvements in CVR. During incremental cycling exercise, CBF
97 increases until ~75-90% of maximal oxygen uptake ($\dot{V}O_{2max}$) (8) but then decreases with

maximal-intensity exercise due to the role of hyperventilation-induced hypocapnia (47, 57). Prescribing HIIE at ~75% $\dot{V}O_{2max}$ may therefore result in greater acute increases in CVR than exercise performed at a greater intensity, but this has not been explored.

This study aimed to investigate the acute effect of exercise intensity on peripheral and cerebral vascular function in healthy adults. Specifically, this study compared continuous moderate intensity exercise (MIE, 60% VO_{2max}), HIIE performed at 75% $\dot{V}O_{2max}$ and HIIE performed at 90% $\dot{V}O_{2max}$, which were all matched for time (30 minutes) and average intensity (target: 60% $\dot{V}O_{2max}$). It was hypothesised that: 1) both HIIE protocols would increase brachial FMD compared to MIE and a resting control; 2) increases in middle cerebral artery blood velocity (MCAv) during exercise would be higher during HIIE completed at 75% $\dot{V}O_{2max}$ compared to MIE and HIIE completed at 90% $\dot{V}O_{2max}$; and 3) CVR would be unchanged following MIE, increased following HIIE completed at 75% $\dot{V}O_{2max}$ and decreased following HIIE completed at 90% $\dot{V}O_{2max}$.

Methods

Participants

An *a priori* sample size calculation was performed for this investigation. This study was powered to the intensity-dependent post-exercise (1h) changes in FMD, to detect an effect size of ~1.2 (7). This revealed a required sample size of 12 participants.

Following ethical approval from the University of Exeter ethics committee (180613/A/07), twelve healthy adults volunteered to take part in this study. Exclusion criteria included smoking, contraindications to exercise, cardiometabolic disease and the use of any medication or supplement known to influence vascular function. One participant did not complete the study due to an unrelated injury, and one participant was removed due to inadequate acquisition of vascular data. Consequently, data are presented as n=10 (6 females) throughout. Participant characteristics are described in Table 1.

Study design

Participants completed one preliminary visit and four subsequent experimental visits to the laboratory. The preliminary visit served to familiarise participants with all experimental procedures before participants completed an incremental (30 $W \cdot min^{-1}$) ramp test to exhaustion on an electronically braked cycle-ergometer (Lode Excalibur Sport, Groningen, the Netherlands). $\dot{V}O_{2max}$ was determined as the highest 10 s average (MedGraphics, UK). The mean $\dot{V}O_2$ response time from the incremental ramp test was accounted for when prescribing the power outputs for each exercise trial (58).

The four subsequent experimental visits were completed in a different order for each participant to control for any potential order effect. At least 48 hours separated experimental visits, and the mean ± SD time to complete the 4 visits was 25 ± 7 days.

Participants were instructed to avoid vigorous exercise and alcohol consumption in the 24 hours preceding each visit. Following an overnight fast (including abstaining from caffeine), participants reported to the laboratory at 08:00 and were provided with a standardised cereal breakfast consisting of 50 g cornflakes and 150 mL semi-skimmed milk. The macronutrient content is unlikely to have influenced vascular function (30, 54). Peripheral and cerebral vascular function were assessed 30 min after breakfast, and then one and three hours after the completion of the experimental condition. Apart from the exercise trials, participants remained at rest in the laboratory throughout.

Experimental trials

Immediately following the assessment of baseline resting vascular measures, participants completed either seated rested in the laboratory (control trial; CON), or 30 min of cycling at 60% $\dot{V}O_{2max}$ (moderate-intensity exercise; MIE), or two different 30 min HIIE protocols, with the work rate of the active intervals corresponding to either 75% (HIIE1) or 90% (HIIE2) $\dot{V}O_{2max}$. Specifically, HIIE1 included a 2.5 min warm up and 2.5 min cool down at 45% $\dot{V}O_{2max}$ and five 3 min intervals at 75% $\dot{V}O_{2max}$, interspersed with four 2.5 min recovery intervals at 45% $\dot{V}O_{2max}$. HIIE2 included the same 2 min warm up and cool down, and five 2 min intervals at 90% $\dot{V}O_{2max}$, separated by four 4 min recovery intervals at 45% $\dot{V}O_{2max}$ (Figure 1). Each exercise protocol was completed using the same cycle-ergometer as the prior ramp test. The exercise conditions were matched for time (all trials were 30 min in duration) and average intensity (all trials were designed to have a target average intensity of 60% $\dot{V}O_{2max}$).

Breath by breath $\dot{V}O_2$ and end-tidal carbon dioxide ($P_{ET}CO_2$) during exercise was measured throughout (MedGraphics, UK) and averaged into 10 s time bins. Given the

158 interval nature of HIIE1 and HIIE2, $P_{ET}CO_2$ data was also expressed as the highest (peak)
159 and lowest (minimum) 10 s average during exercise. The velocity of blood in the middle
160 cerebral artery (MCAv) was quantified via transcranial Doppler (TCD) sonography
161 (MultiDop, DWL, Germany) using a 2 MHz probe placed over the temporal window and
162 held in place using a customisable headset (DiaMon, DWL, Germany). MCAv data were
163 sampled at a frequency of 200 Hz (PowerLab 8/30 ML880, ADInstruments) and then
164 exported into 10 s time bins (LabChart version 8, ADInstruments), and 95% confidence
165 intervals were calculated. The total area under the mean MCAv versus time (30 min)
166 curve was calculated for each trial using the trapezoidal rule.

167 *Peripheral vascular function*

168 Peripheral vascular function was quantified via FMD using high resolution duplex
169 ultrasonography (Apogee 1000, SIUI, China) with a 13 MHz linear array transducer, in
170 accordance with current guidelines (50). Briefly, participants rested in a darkened,
171 temperature controlled (~23°C) room for 10 min prior to each assessment. Baseline
172 diameter was determined over a 1 minute period, which immediately preceded rapid (<
173 0.3 s) forearm cuff inflation (Hokanson, Bellevue, USA) to 220 mmHg for 5 min. The
174 brachial artery was continuously imaged for 3 min post rapid deflation, and endothelial
175 dependent (19, 50) vasodilation was calculated using the peak increase in arterial
176 diameter. All images were assessed during end diastole using validated software (Brachial
177 Analyzer for Research, MIA, USA) (37) and analyses was performed blinded to the
178 experimental condition. The area under the curve for shear rate was calculated from the
179 point of cuff deflation until the time of peak dilation (SR_{AUC}) (40). FMD was not
180 normalised to SR_{AUC} as these were not consistently related, which is in line with other
181 observations post exercise (35). The FMD statistic was allometrically scaled to address

182 the observed changes in baseline diameter post exercise and the concerns regarding ratio
183 scaling of this outcome (4). The within (pre- and post-CON) and between day (baseline
184 of all four visits) coefficient of variation for the FMD statistic was 5.2% and 13.8%,
185 respectively.

186 *Cerebrovascular Reactivity*

187 Participants remained supine after the FMD protocol for approximately 5 minutes before
188 the assessment of cerebrovascular reactivity. MCAv was measured throughout using
189 TCD (DWL, Germany), and end-tidal CO_2 ($P_{ET}CO_2$) using a gas analyser (ADInstruments
190 ML206). The depth and position of the probe was noted for each participant in order to
191 standardise the insonation of the MCA for each participant within- and between- day (31).
192 The within and between-day coefficient of variation for baseline MCAv was 5.3%
193 (95%CI: 3.8-8.8%) and 9.3% (95%CI: 7.4-13.2%), respectively. Following a 1 minute
194 recorded baseline, participants breathed 6% CO_2, 21% O_2 and balance nitrogen for 4
195 minutes. After 5 minutes of re-acclimatisation, participants were then instructed to
196 perform deep hyperventilation at a frequency of 25 breaths per minute for 1 minute (CVR
197 Hypocapnia) (44). In order to address recent concerns regarding the variability of changes
198 in MCAv during open-circuit hypercapnic challenges (10, 31), CVR was quantified as
199 the highest rolling 30 s average absolute change in MCAv per 1 mmHg increase in
200 $P_{ET}CO_2$ (31). CVR to hypocapnia was quantified as the absolute change in MCAv from
201 rest per 1 mmHg change in $P_{ET}CO_2$ in the final 10 s of hyperventilation. To account for
202 the influence of potential changes in mean arterial pressure on CVR outcomes within-
203 and between-day, beat-by-beat blood pressure was non-invasively measured via finger
204 plethysmography (Human NIBP Nano, ADInstruments) during assessments of CVR. The
205 ratio between resting mean arterial pressure and MCAv was expressed as the

cerebrovascular conductance index (CVC = MCAv/mean arterial pressure). All MCAv, mean arterial pressure and $P_{ET}CO_2$ data were integrated (Powerlab; model - 8/30, ADInstruments) and stored at 200 Hz using an analogue-to-digital converter interfaced with a laptop computer (Lab Chart version 8, ADInstruments).

Statistical analyses

Data are presented as mean ± standard deviation (SD). All analyses were performed using SPSS version 26 (IBM, USA). Differences in the physiological responses during each of the experimental trials were explored using a one-way ANOVA. All vascular responses were analysed using a mixed model ANOVA, with trial (CON, MIE, HIIE1, HIIE2) and time (Pre, 1 hour post, 3 hours post) as the main effects. Statistical significance was accepted when $P<0.05$, and effect sizes were calculated to demonstrate the magnitude of any difference. Effect sizes for the ANOVA main and interaction effect were interpreted using partial eta squared (ηp^2) values of ≤0.06 = small, 0.06 to 0.14 = moderate and >0.14 = large (15). Follow up pairwise comparisons were interpreted using standardised effect sizes (*d*); small <0.5, moderate = 0.5-0.8 and large ≥0.8 (15).

Results

Physiological responses during experimental trials

The group responses to each experimental trial are presented in Table 2 and Figure 2. The power output for each exercise intensity was as follows: 45% $\dot{V}O_{2\ max}$ 72 ± 19 W, 60% $\dot{V}O_{2\ max}$ 118 ± 25 W, 75% $\dot{V}O_{2\ max}$ 161 ± 29 W, 90% $\dot{V}O_{2\ max}$ 211 ± 39 W. By design, mean $\dot{V}O_2$ was not different between exercise trials (P=0.44, ηp^2=0.08), although the highest $\dot{V}O_2$ achieved was greatest in HIIE2 compared to HIIE 1 (P<0.001, d=0.58) and MIE (P<0.001, d=1.33), whilst HIIE1 was greater than MIE (P<0.001, d=0.87). Mean $P_{ET}CO_2$ was lower in HIIE2 compared to MIE (P=0.007, d=0.75) and HIIE1 (P=0.028, d=0.54). $P_{ET}CO_2$ minimum was lower in HIIE2 compared to MIE (P<0.001, d=1.16) and in HIIE1 compared to MIE (P=0.045, d=0.46). Average MCAv mean *(*P=0.03, d=0.92), MCAv peak *(*P=0.04, d=0.77) and area under the MCAv mean curve versus time *(*P=0.02, d=1.11) was greater in HIIE1 compared to CON.

Peripheral vascular outcomes

There was a time by trial interaction effect for brachial baseline diameter (P=0.002, η^2 =0.305, Fig 3A). Baseline diameter was never different from PRE within a trial, however baseline diameter was lower 1 hour post HIIE1 compared to 1 hour post CON (P=0.029, d=0.20) and HIIE2 (P=0.003, d=0.40).

There was a time by trial interaction for the absolute change in brachial artery diameter post occlusion (P=0.025, η^2=0.321 Fig 3B). Within trial: The change in brachial artery diameter was greater 1 hour (P=0.001, d=1.09) after HIIE1 compared to PRE. In the HIIE2 trial, the change in brachial artery diameter was greater 1 hour (P<0.001, d=0.97) and 3 hours (P=0.032, d=0.74) after HIIE2 compared to PRE. Between trials: There were

no differences between trials at the PRE timepoint (P>0.368, d<0.16). One hour after exercise, the change in brachial artery diameter post occlusion was greater in the HIIE1 trial than CON (P=0.002, d=1.15) and MIIE (P=0.006, d=0.76) but not different compared to HIIE2 (P=0.442, d=0.23). The change in brachial diameter post occlusion was only different between HIIE2 and CON at the 3 hour time point (P=0.033, d=0.53).

There was no main effect of trial (P=0.996, η^2=0.002), time (P=0.707, η^2=0.038) or trial by time interaction (P=0.382, η^2=0.108) for the time taken to achieve peak dilation post occlusion.

There was a time by trial interaction for allometrically-adjusted FMD (P=0.014, Fig 3C). Within trial: FMD was never different from PRE values at any time points in the CON (P>0.325) or MIE (P>0.521) trials. In the HIIE1 trial, FMD was elevated 1 hour (P<0.001, d=1.13) and 3 hours (P=0.023, d=0.54) after HIIE1 compared to PRE. In the HIIE2 trial, FMD was elevated 1 hour (P<0.001, d=0.91) and 3 hours (P=0.043, d=0.48) after HIIE2 compared to PRE.

Between trials: There were no differences in FMD between trials at the PRE timepoint (P>0.322, d<0.26). One hour after exercise, FMD in the HIIE1 trial was greater than in CON (P<0.001, d=1.01) and greater than in MIIE (P=0.002, d=0.77) but not different compared to HIIE2 (P=0.544, d=0.14). FMD was also greater one hour post HIIE2 compared to the same time point in CON (P<0.001, d=0.88), and greater than MIE (P=0.010, d=0.62). No differences between trials were observed at the 3 hour timepoint (P>0.210, d<0.30 for all).

Mean SR_{AUC} data are presented in Fig 3D (n=9 due to signal loss). There was no effect of trial (P=0.466, η^2 = 0.099), time (P=0.592, η^2 =0.046 or trial by time interaction effect (P=0.312, η^2 = 0.132) for SR_{AUC}.

Cerebrovascular outcomes

There was no trial by time interaction for resting MCAv (P=0.713, η^2=0.064, Fig 4A), however there was a main effect of time (P=0.02, η^2=0.379). Resting MCAv was higher at the PRE timepoint compared to 1 hour post (P=0.01, d=0.39) and 3 hours post (P=0.01, d=0.51) across the experimental trials.

There was no main effect of trial (P=0.789, η^2=0.042), time (P=0.093, η^2=0.257) or trial by time interaction (P=0.379, η^2=0.118) for resting mean arterial pressure. There was no main effect of trial (P=0.712, η^2=0.054), time (P=0.170, η^2=0.217) or trial by time interaction for resting CVC (P=0.207, η^2 = 0.175).

Cerebrovascular reactivity

The responses to the hypercapnic stimulus are presented in Figure 4. A mean increase in $P_{ET}CO_2$ of 10.1 ± 3.0 mmHg was observed at the time of peak MCAv, which was never different across observations (P=0.722, η^2=0.063). There was no time by trial interaction for the increase in MCAv during the hypercapnic challenge (P=0.820, η^2=0.051). There was no main effect of trial (P=0.135, η^2 = 0.183), time (P=0.145, η^2 = 0.193) or trial by time interaction (P=0.605, η^2 = 0.078) for CVR-hypercapnia.

Figure 5 presents the physiological responses during the hyperventilation challenge. This stimulus caused a mean reduction in $P_{ET}CO_2$ of 13.5 ± 5.5 mmHg, which was never different across observations (time by trial interaction P=0.594, η^2=0.060). There was no time by trial interaction for the fall in MCAv during hyperventilation (P=0.763,

289 η^2=0.053). There was no main effect of trial (*P*=0.157, η^2 = 0.173), time (*P*=0.688, η^2 =

290 0.041) or trial by time interaction (*P*=0.595, η^2 = 0.079) for CVR-hypocapnia.

Discussion

This study found that HIIE (with exercise intervals performed at both 75% and 90% $\dot{V}O_{2max}$) acutely improved brachial artery FMD in healthy young adults, compared to MIE and a sedentary control condition. However, the present study found no effect of exercise intensity on CVR, with CVR to both hyper- and hypocapnia remaining unchanged following the exercise and sedentary control conditions. Finally, the present study found no significant differences in the overall MCAv response to exercise between exercise conditions (expressed as MCAv AUC), although the profile of MCAv during exercise differed between protocols.

The effect of exercise intensity on peripheral vascular function

The present study found that allometrically adjusted brachial artery FMD was significantly elevated above baseline one and three hours following both HIIE conditions, but continuous MIE did not alter FMD in healthy adults. These findings are in agreement with previous work in healthy adults comparing high and moderate intensity constant work-rate exercise (25). These findings are also consistent with previous data in healthy adolescents, where HIIE performed at 90% peak power significantly elevated brachial artery FMD compared to work-matched MIE one hour following exercise (7). The present study develops these findings and shows that elevations in FMD extend for three hours post-HIIE in healthy adults. Exercise-induced elevations in shear-stress have been shown to mediate post-exercise improvements in brachial artery FMD (52, 53). Given this, the superior improvement in post-exercise FMD during the HIIE trials, compared to MIE, is likely a consequence of greater brachial artery shear stress during higher exercise intensities (23, 49), or an important role of the interval pattern of exercise (33).

Interestingly, the present study found no further benefit of work-matched HIIE performed at 90% $\dot{V}O_{2max}$, compared to 75% $\dot{V}O_{2max}$, but this may be a consequence of matching the exercise conditions (i.e. greater intensity at 90% $\dot{V}O_{2max}$, but shorter interval duration). It is possible this may have resulted in a similar shear stress stimulus between the two HIIE trials, where the same number of intervals were also performed. However, it was not possible to measure brachial artery shear stress during the exercise conditions, and technical challenges limit the ability to measure limb shear rates at such high intensities. Furthermore, other factors have previously been shown to influence post-exercise changes in FMD (18), such as differences in redox state between exercise conditions (28) alongside participant characteristics, such as cardiorespiratory fitness (5). Nevertheless, the present data show acute beneficial effects of HIIE on peripheral vascular function in healthy adults, compared to equivalent continuous moderate intensity exercise.

The effect of exercise intensity on cerebrovascular reactivity

Contrary to the hypothesis, the present study found that CVR was unaltered following any exercise condition in healthy adults. Given that peripheral endothelial function was increased by HIIE, these data could indicate that the baseline cerebrovascular vasodilatory capacity in healthy young adults cannot be acutely improved by such exercise. This inference is supported by recent evidence that habitual endurance or resistance training in young adults was also not associated with elevated CVR compared to untrained young, healthy adults (aged ~28 years) (16). It remains to be explored if acute exercise can have a positive effect on cerebrovascular function in populations with impaired CVR, such as older adults or individuals with cerebrovascular disease. Exercise training has been shown to improve CVR in stroke patients (27), and a recent systematic review found that exercise training tended to improve CVR in older adults, although data

are limited to just four studies (46). Collectively, these data suggest that exercise does not acutely or chronically elevate CVR in a sample of healthy young adults, where benefits may be observed in older or at-risk populations.

The data from the present study are in contrast to the only previous study investigating CVR following acute HIIE, where Burma et al., (11) observed a 37% decrease in CVR to hypercapnia immediately and one hour following exercise (ten 1-minute intervals at ~85% heart rate reserve), also in young adults. This was suggested to be a consequence of repeated and prolonged cerebral vasoconstriction that occurred during HIIE, as a result of hyperventilation-induced hypocapnia (39), subsequently altering vessel tone and limiting the capacity of the cerebrovasculature to maximally dilate. However, the present study suggests that the vasodilatory capacity of the cerebrovasculature is preserved following both HIIE protocols. The differences between the findings from Burma et al., and those of the present study may be attributed to the HIIE protocol utilised (i.e. a different intensity and number of intervals utilised) or in the technique used to assess CVR. The present study delivered a steady-state increase in $P_{ET}CO_2$ through fixed concentration CO_2 breathing, whereas Burma et al. used a re-breathing protocol, which elevates $P_{ET}CO_2$ breath-by-breath and elicits much larger increases in $P_{ET}CO_2$ (~30 mmHg) compared to the current study (~10 mmHg). This is an important consideration given the different limitations of different methods used to assess CVR (21). As highlighted by a recent systematic review, the effects of HIIE on cerebrovascular function are poorly understood (59), and are likely influenced by protocol, assessment method and population.

It was hypothesised that HIIE performed at 75% $\dot{V}O_{2max}$ would elicit the greatest increases in MCAv during exercise, compared to HIIE performed at 90% VO_{2max} and

MIE at 60% $\dot{V}O_{2max}$, as this is the intensity that is thought to elicit the greatest increases in MCAv during incremental exercise (47). It was also hypothesised that this would result in the greatest post-exercise improvements in CVR, as shear stress and elevations in cerebral blood follow during exercise are thought to be important mechanisms for exercise-induced improvements in cerebrovascular reactivity (12, 52). However, only HIIE performed at 75% $\dot{V}O_{2max}$ elicited an MCAv AUC response greater than the seated control condition, and this could be underpinning the absence of change in post-exercise CVR observed in the present study. Consequently, the exercise protocols utilised in the present study may not have provided a sufficient stimulus to mediate post-exercise improvements in CVR. However, cerebral blood velocity is not the same as shear stress, and without a measure of shear during exercise, this remains speculative. Some pilot data suggests that exercise-induced elevations in shear stress in the internal carotid artery (ICA) are almost double during HIIE compared to work-matched MIE (12), but these data are very limited and likely protocol-dependent. Furthermore, resting shear stress of the ICA is very high in young adults (over 4-fold that of the brachial artery) (13). Therefore, it is also possible that resting characteristics of the cerebrovasculature in this population, particularly the high levels of baseline shear, limit the capacity for exercise to further elevate shear stress, and thus improve cerebrovascular reactivity via this mechanism. Nevertheless, future research is needed to firstly understand the CBF and shear stress responses to different exercise conditions, and then to investigate the subsequent effects on cerebrovascular function.

A key observation from the present study was that HIIE improved peripheral vascular function, but that this was not mirrored by changes in cerebrovascular reactivity in healthy young adults. Initial evidence suggested that the overnight changes in the two were related

(2), but more recently Carr et al., (13) observed no significant correlation between resting peripheral and cerebral shear-mediated endothelial function at rest. The present study provides further evidence that the peripheral and cerebral vascular systems may share a different mechanism of change, building on previous data from our laboratory, where sugar sweetened-beverage consumption increased brachial artery FMD but did not change CVR in adolescents (30). Collectively, these data provide further support that findings from the periphery cannot be extrapolated to cerebrovascular reactivity. Nevertheless, the present study provides valuable and novel data that further contributes to a growing discussion around HIIE and cerebrovascular health (12, 36, 59).

Study considerations

The present study has a number of methodological strengths. These include the time- and average intensity-matching of the three exercise conditions and the inclusion of a control condition, allowing thorough investigation into the effect of exercise intensity. Furthermore, all data were analysed according to published guidelines, with FMD data scaled allometrically (3) and CVR analysed using a reliable approach from open circuit CO_2 breathing tests (31).

However, the present study is not without its limitations. This study had six female participants, and menstrual cycle phase was not controlled for in this study. Whether or not the menstrual cycle should be controlled for in cardiovascular research has been debated (48, 55). Although there is some evidence to suggest that cardiovascular outcomes are influenced by menstrual cycle phase (55), recent research has found no effect of menstrual cycle phase on allometrically-scaled brachial artery FMD (45) nor

cerebral autoregulation in heathy, young females (20, 32). Nevertheless, whether the menstrual cycle alters the acute FMD response to exercise is unknown.

This study used TCD to measure MCAv, which is only a valid surrogate measure of cerebral blood flow if MCA diameter remains unchanged (1). Although debated (9, 26), TCD is considered an appropriate and practical measurement technique to assess CBF during exercise and CO_2 breathing challenges (1), although there is a lack of standardisation for TCD-measured CVR regarding protocol and data handling, which introduces conflict in the existing literature (10). Furthermore, assessing CVR in this way introduces greater variability, compared to targeting $P_{ET}CO_2$ levels using end-tidal forcing (22). Future studies utilising end-tidal forcing and MR techniques are therefore warranted. Nevertheless, open circuit CO_2 breathing remains a commonly used method to assess CVR, and data have been analysed using the most reliable approach to minimise the potentially confounding effects of differences in ventilation and $P_{ET}CO_2$ within- and between-day (31).

An additional consideration is the timing of post-exercise assessments of vascular function, with measurements completed at one and three hours post exercise. This means the time-course of potential post-exercise changes in CVR cannot be fully determined, which is an important consideration given that Burma et al., (11) observed a significant decrease in CVR immediately following HIIE. However, we can confirm that any post exercise changes in CVR do not coincide with alterations in FMD, so the possibility that changes in CVR were missed in our study is unlikely.

An additional limitation is the inclusion of intracranial measures of the MCA only. Marked regional differences have been observed in the CBF response to incremental

exercise, with ICA and MCA blood flow decreasing after ~70-75% $\dot{V}O_{2max}$, whilst blood flow in the vertebral and posterior cerebral artery continues to increase with greater exercise intensity (43, 47). It has therefore been suggested that HIIE may elicit greater positive effects on the posterior circulation (12), which is more susceptible to deterioration than the anterior circulation (29). However, Labrecque et al., (34) observed similar responses of the middle and posterior cerebral arteries during and following a single bout of HIIE, performed at 100% $\dot{V}O_{2max}$ in young, fit women. Furthermore, Burma et al., (11) found similar post-HIIE CVR responses in the middle and posterior cerebral arteries. Collectively, existing data suggest more research is needed on the regional cerebrovascular responses during and following acute HIIE (59). Finally, CVR measured in the MCA is not the same as ICA shear-mediated function (13), which may show differential responses following HIIE, particularly if shear stress is a primary mechanism, and therefore requires further investigation.

Conclusions

This study found that acute HIIE performed with intervals at 75% and 90% $\dot{V}O_{2max}$ improved peripheral vascular function one and three hours following exercise in healthy adults, which was unaltered by MIE. However, CVR of the MCA was not altered following either HIIE conditions, nor following MIE. These novel data show distinctly different responses of the peripheral and cerebral vasculature following HIIE, and provides valuable data on the effect of HIIE on cerebrovascular reactivity. These data contribute to a growing discussion surrounding high intensity exercise and the brain (12, 36), with future research needed to explore potentially important considerations surrounding the exercise dose (intensity, duration), measurement technique and timing, and sample used.

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The authors declared no potential conflicts of interest, financial or otherwise.

Author contributions

MEW - data collection, data and statistical analysis, data interpretation, drafted and finalised the manuscript

JLK - data collection, data and statistical analysis, data interpretation, critical review of the manuscript

ABL - data collection, data and statistical analysis, data interpretation, critical review of the manuscript

ARB - study conceptualisation and design, data interpretation, critical review of the manuscript

BB - study conceptualisation and design, , data and statistical analysis, data interpretation, critical review of the manuscript

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Figure Captions

Figure 1. Experimental conditions. CON, resting control trial; MIE, moderate-intensity exercise; HIIE, high-intensity interval exercise. The numbers refer to cycling intervals at a percentage of maximal oxygen uptake for each individual. The average intensity of each exercise trial was designed to be 60% maximal oxygen uptake, and all exercise trials were 30 minutes in duration.

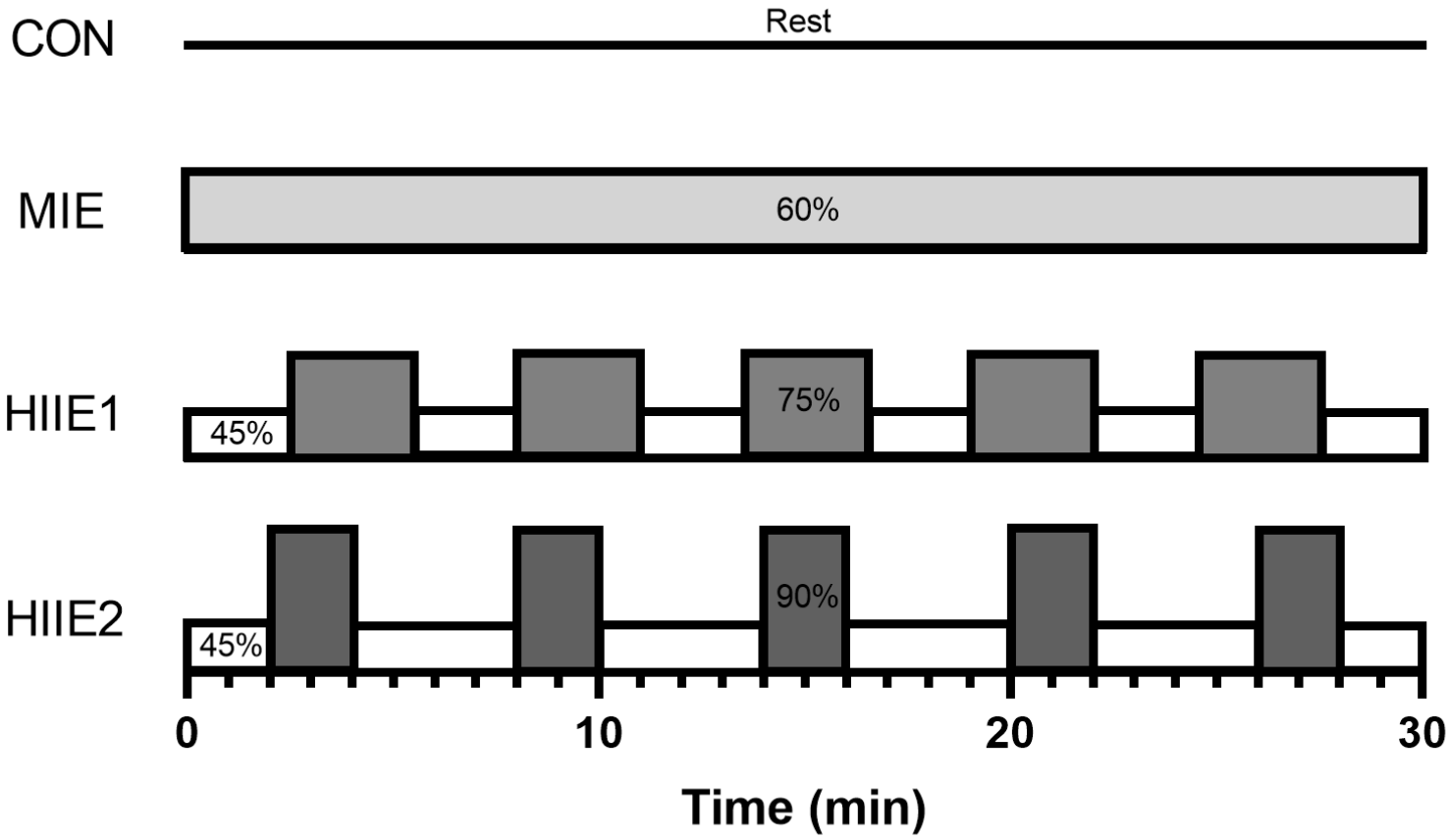
Figure 2. Mean ± 95% CI (shaded) middle cerebral artery blood velocity (MCAv) across the four experimental trials (A: control, B: moderate intensity exercise, C: high intensity interval exercise 1, D: high intensity interval exercise 2). The shading shows the pattern of the exercise stimulus. n = 9 (5 female) due to signal loss in 1 participant. Analysis of between trial differences are presented in Table 2.

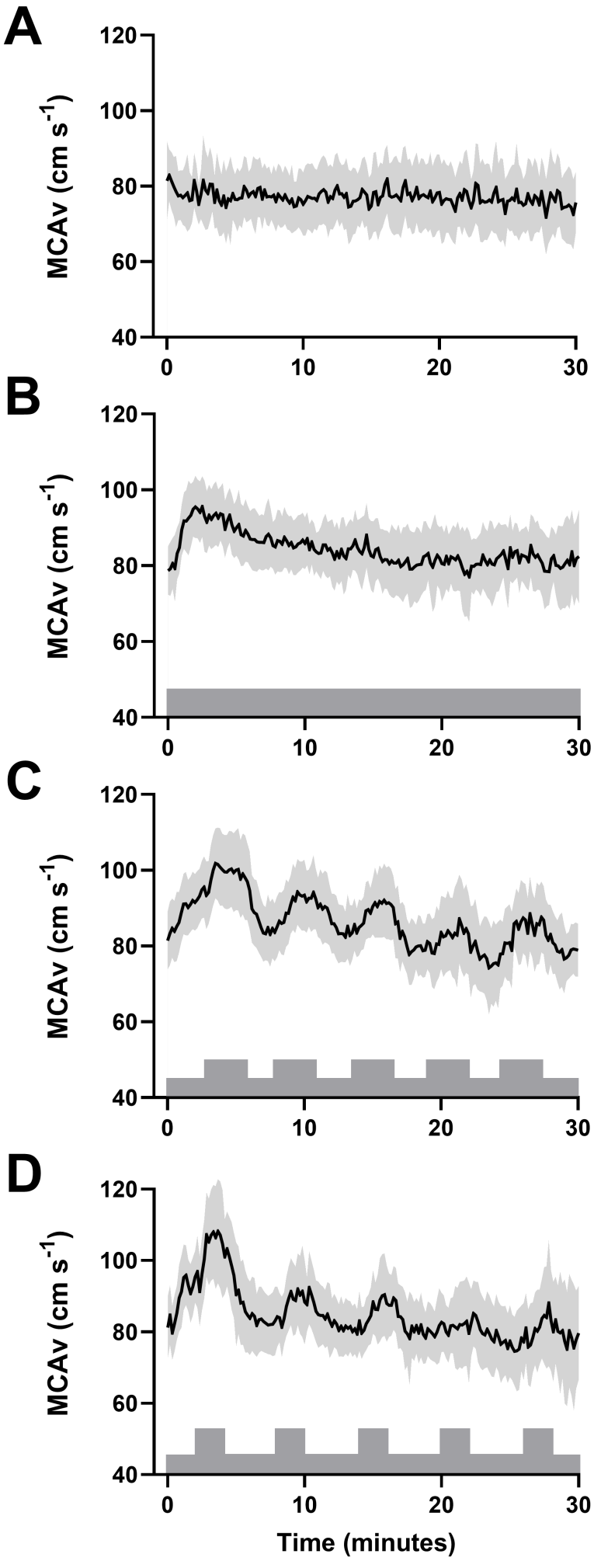
Figure 3. Peripheral vascular outcomes before (Pre), one and three hours after the four experimental trials (n=10, 6 female). CON, control; MIE, moderate intensity exercise; HIIE, high intensity interval exercise. FMD, flow mediated dilation allometrically adjusted to baseline diameter; SR_{AUC}, are under the shear rate curve until time of peak dilation. A repeated measures ANOVA revealed a significant time by trial interaction effect for the change in brachial artery diameter post occlusion (P=0.025; panel B) and the allometrically adjusted flow mediated dilation statistic (P=0.014; panel C). Only the within-trial significant differences are denoted. * = different from Pre within the high-intensity interval trial 1. # = significantly different from Pre within the high-intensity interval trial 2.

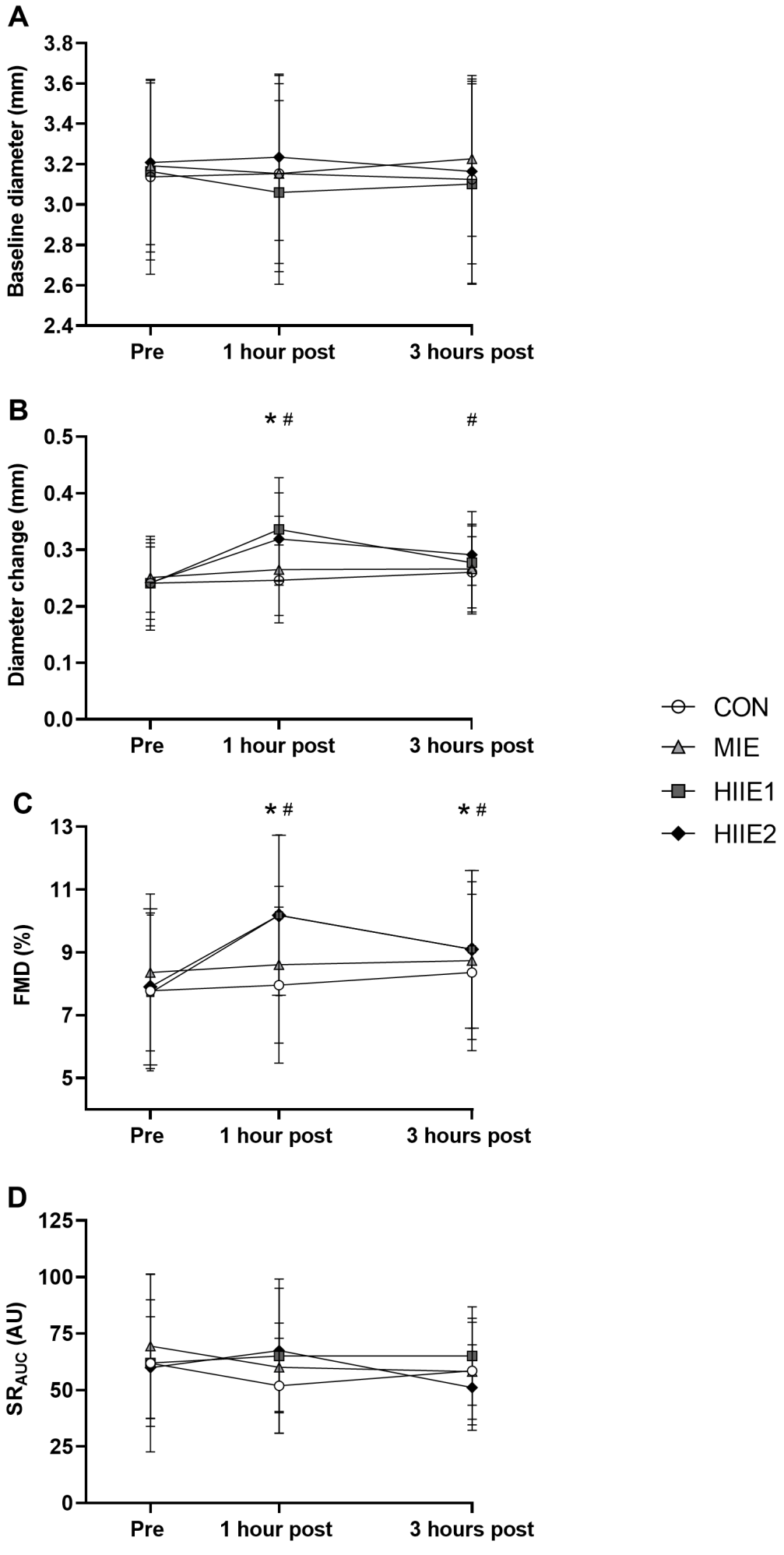
Figure 4. Physiological responses to 5 minutes of 5% carbon dioxide inhalation (n=10, 6 female). CON, control; MIE, moderate intensity exercise; HIIE, high intensity interval

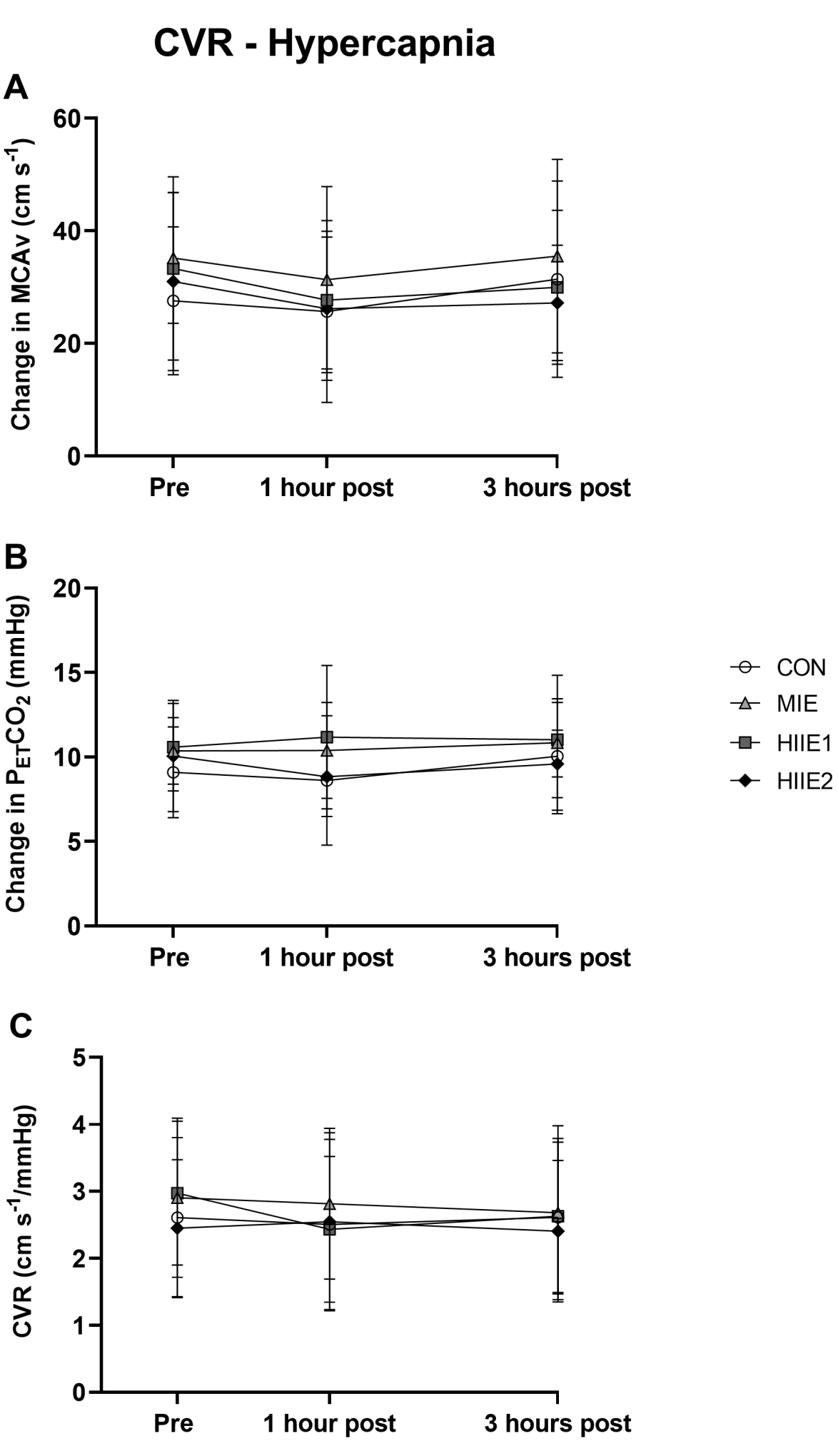
exercise. MCAv, middle cerebral artery blood velocity; $P_{ET}CO_2$, end tidal partial pressure of carbon dioxide; CVR, cerebrovascular reactivity. MCAv change reflects the difference between resting baseline and the highest 30 s rolling average during the hypercapnic stimulus. The $P_{ET}CO_2$ change is calculated as the difference between baseline and this time point. A repeated measures ANOVA revealed no significant time by trial interaction for any of these outcomes (P>0.605, η^2<0.078).

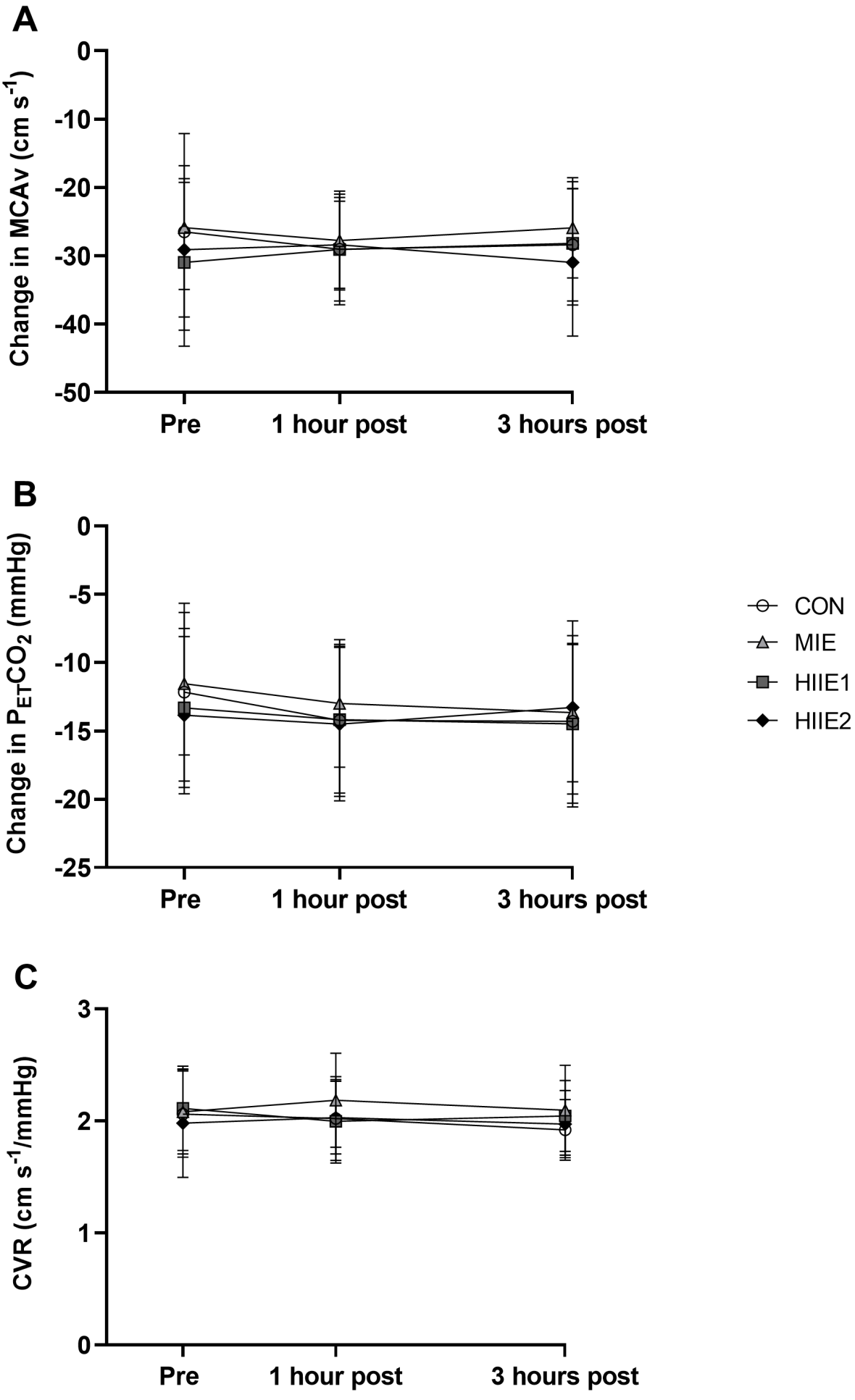
Figure 5. Physiological responses to 1 minute of deep hyperventilation (n=10, 6 female). CON, control; MIE, moderate intensity exercise; HIIE, high intensity interval exercise. MCAv, middle cerebral artery blood velocity; $P_{ET}CO_2$, end tidal partial pressure of carbon dioxide; CVR, cerebrovascular reactivity. The change in MCAv (panel A) and $P_{ET}CO_2$ (panel B) reflects the difference between resting baseline and the final 10 s of the hyperventilation stimulus. A repeated measures ANOVA revealed no significant time by trial interaction for any of these outcomes (P>0.594, η^2<0.079).


CON
Rest
MIE
60%
HIIE1
45%
75%
HIIE2
45%
90%
0
10
20
30
Time (min)


A
B
C
D
MCAv (cm s-1)
120
100
80
60
40
0
10
20
30
Time (minutes)


A
Baseline diameter (mm)
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
Pre
1 hour post
3 hours post
B
Diameter change (mm)
0.5
0.4
0.3
0.2
0.1
0.0
* #
#
Pre
1 hour post
3 hours post
C
FMD (%)
13
11
9
7
5
* #
* #
Pre
1 hour post
3 hours post
D
SRAUC (AU)
125
100
75
50
25
0
Pre
1 hour post
3 hours post
CON
MIE
HIIE1
HIIE2


CVR - Hypercapnia
A
Change in MCAv (cm s-1)
60
40
20
0
Pre
1 hour post
3 hours post
B
Change in PETCO2 (mmHg)
20
15
10
5
0
Pre
1 hour post
3 hours post
CON
MIE
HIIE1
HIIE2
C
CVR (cm s-1/mmHg)
5
4
3
2
1
0
Pre
1 hour post
3 hours post


CVR - Hypocapnia
A
Change in MCAv (cm s-1)
0
-10
-20
-30
-40
-50
Pre
1 hour post
3 hours post
B
Change in PETCO2 (mmHg)
0
-5
-10
-15
-20
-25
Pre
1 hour post
3 hours post
CON
MIE
HIIE1
HIIE2
C
CVR (cm s-1/mmHg)
3
2
1
0
Pre
1 hour post
3 hours post

Tables

Table 1: Participant characteristics.

Parameter	n=10	Males (n=4)	Females (n=6)
Age (y)	22.7 ± 3.5	24.8 ± 5.1	21.3 ± 0.8
Body mass (kg)	67.4 ± 9.7	73.8 ± 6.5	63.1 ± 9.4
Stature (m)	1.70 ± 0.08	1.77 ± 0.08	1.66 ± 0.06
BMI ($kg \cdot m^{-2}$)	23.3 ± 2.1	23.7 ± 1.0	23.0 ± 2.7
$\dot{V}O_{2\ max}$ ($L \cdot min^{-1}$)	2.65 ± 0.50	3.18 ± 0.28	2.30 ± 0.19
$\dot{V}O_{2\ max}$ ($ml \cdot kg \cdot min^{-1}$)	39 ± 5	43 ± 5	37 ± 4
$\dot{V}O_{2\ max}$ range ($ml \cdot kg \cdot min^{-1}$)	30 - 46	-	-
Peak power (W)	267 ± 40	309 ± 27	239 ± 13

BMI, body mass index; $VO_{2\ max}$, maximal oxygen consumption. Data are presented as the mean ± standard deviation.

Table 2 Physiological responses to the experimental trials.

	CON	MIE	HIIE1	HIIE2
$\dot{V}O_2$ mean (L min^{-1})	-	1.71 ± 0.35	1.69 ± 0.30	1.68 ± 0.34
$\dot{V}O_2$ mean (% $VO_{2\ max}$)	-	65 ± 4	65 ± 3	64 ± 3
$\dot{V}O_2$ peak (L min^{-1})	-	1.96 ± 0.35	2.27 ± 0.37 [b]	2.52 ± 0.47 [b, c]
$\dot{V}O_2$ peak (% $VO_{2\ max}$)	-	75 ± 5	88 ± 8 [b]	97 ± 5 [b, c]
$P_{ET}CO_2$ mean (mmHg)	-	39.4 ± 3.5	38.7 ± 3.6	36.9 ± 2.9 [b, c]
$P_{ET}CO_2$ peak (mmHg)	-	43.8 ± 4.1	44.7 ± 4.4	44.8 ± 3.9
$P_{ET}CO_2$ minimum (mmHg)	-	35.4 ± 3.0	33.7 ± 4.2 [b]	31.5 ± 3.6 [b]
MCAv mean (cm s^{-1})	79.3 ± 12.0	85.5 ± 11.6	89.1 ± 9.1 [a]	84.8 ± 13.1
MCAv peak (cm s^{-1})	90.9 ± 13.4	105.1 ± 11.3	110.1 ± 10.6 [a]	113.4 ± 20.4
MCAv AUC (cm s^{-1} • 30 min)	2382 ± 413	2516 ± 405	2757 ± 235 [a]	2590 ± 441

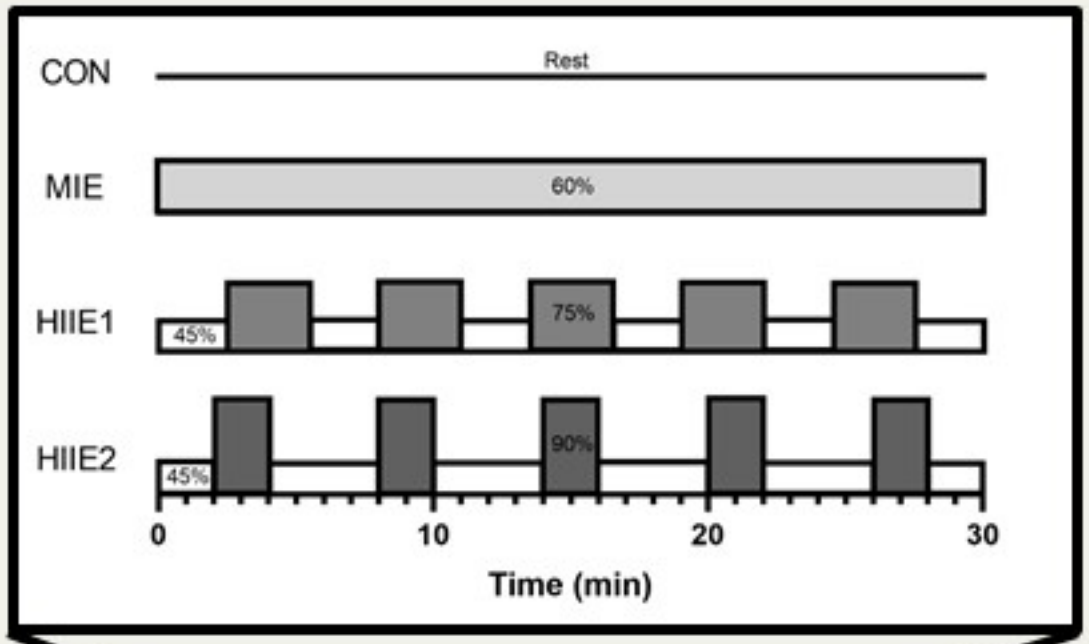
CON, control; MIE, moderate-intensity exercise; HIIE, high-intensity interval exercise; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_{2\ max}$, maximum oxygen uptake from prior incremental test; $P_{ET}CO_2$, partial pressure of end tidal carbon dioxide; MCAv, blood velocity in the middle cerebral artery; AUC, are under the blood flow versus time (30 min) curve. $\dot{V}O_{2\ peak}$ and $P_{ET}CO_{2\ peak}$, and $P_{ET}CO_2$ minimum reflect the highest and lowest 10 second averages, respectively. Due to signal loss in 1 participant, n=9 for MCAv outcomes. [a] = significantly different from CON, [b] = significantly different from MIE, [c] = significantly different from HIIE1.

15

The acute effect of exercise intensity on peripheral and cerebral vascular function in healthy adults

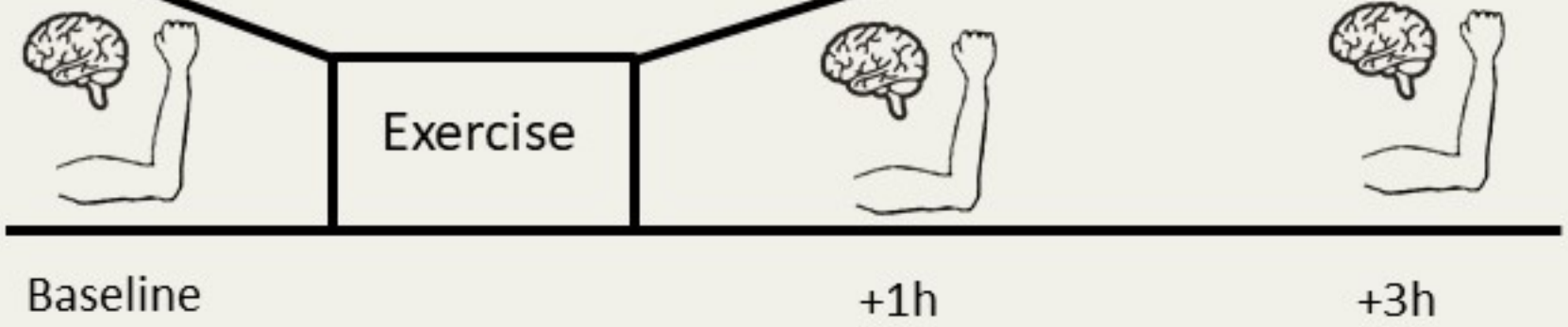
METHODS

10 adults (6 females, 22.7±3.5 years) completed 4 visits:



Brachial artery FMD

Middle cerebral artery cerebrovascular reactivity



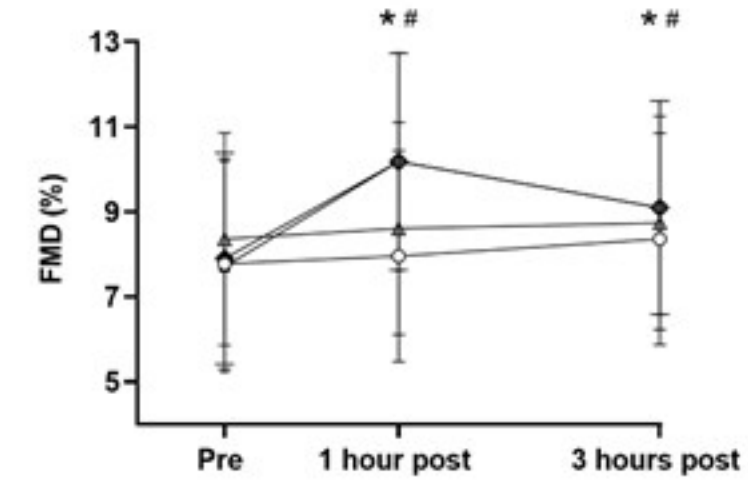
CONCLUSION

High-intensity interval exercise completed at both 75% and 90% $\dot{V}O_{2max}$ increased FMD 1 and 3 hours following exercise.

Cerebrovascular reactivity was unchanged following all four conditions.

OUTCOME

FMD:



CVR: