Cognitive impairment during high-intensity exercise: influence of cerebral blood flow

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Running head: Cognitive performance during high-intensity exercise

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Abstract

Purpose: Cognitive performance appears to be impaired during high-intensity exercise, and this occurs concurrently with a reduction in cerebral blood flow (CBF). However, it is unclear whether cognitive impairment during high-intensity exercise is associated with reduced CBF. We tested the hypothesis that a reduction in CBF is responsible for impaired cognitive performance during high-intensity exercise. **Methods:** Using a randomized crossover design seventeen healthy males performed spatial delayed-response (DR) and Go/No-Go tasks in three conditions [Exercise (EX), Exercise+CO_2 (EX+CO_2), and a non-exercising Control (CON)]. In the EX and EX+CO_2, they performed cognitive tasks at rest and during 8-mins of moderate and high-intensity exercise. Exercise intensity corresponded to ~50% (moderate) and ~80% (high) of peak oxygen uptake. In the EX+CO_2, the participants inspired hypercapnic gas (2% CO_2) during high-intensity exercise. In the CON, they performed the cognitive tasks without exercise. **Results:** Middle cerebral artery mean velocity (MCAv) increased during high-intensity exercise in the EX+CO_2 relative to the EX [69.4 (10.6) $cm \cdot s^{-1}$, vs. 57.2 (7.7) $cm \cdot s^{-1}$, $P < 0.001$]. Accuracy of the cognitive tasks was impaired during high-intensity exercise in the EX [84.1 (13.3) %, $P < 0.05$] and the EX+CO_2 [85.7 (11.6) %, $P < 0.05$] relative to rest [EX: 95.1 (5.3) %, EX+CO_2: 95.1 (5.3) %]. However, no differences between the EX and the EX+CO_2 were observed ($P > 0.10$). These results demonstrate that restored CBF did not prevent cognitive impairment during high-intensity exercise. **Conclusion:** We conclude that a reduction in CBF is not responsible for impaired cognitive performance during high-intensity exercise.

Introduction

Cognitive function refers to a variety of processes that are linked to specific regions of the brain (1). It is widely accepted that cerebral blood flow (CBF) increases in response to regional neuronal activation to meet metabolic demands (2). The brain is primarily dependent on the aerobic metabolism (3) and the cardiovascular system supplies both oxygen and nutrients to the brain. Thus, a high level of metabolism, coupled with a lack of energy stores within the brain, necessitates that CBF is constantly maintained (4). Several studies suggests that a reduction in CBF is, at least in part, associated with poor cognitive function in both young and elderly individuals (5, 6). Collectively, these findings suggest that impaired cognitive function may be associated with a reduction in CBF.

It is well established that CBF is regulated via dynamic cerebral autoregulation over a wide range of cerebral perfusion pressures (7). During exercise, CBF is regulated by complex interactions between neuronal activity and metabolism, blood pressure, sympathetic nervous system activity, partial pressure of oxygen and carbon dioxide (CO_2), and cardiac output (7, 8). CBF during exercise is dependent on the intensity of the exercise (7, 8) and during mild to moderate intensity exercise CBF increases, in response to neuronal activity and metabolism (7). In contrast, CBF progressively decreases during maximal exercise primarily due to hyperventilation-induced hypocania constricts blood vessels (7, 8), which suggested that brain metabolic demand may be unfulfilled during high-intensity exercise. Moreover, extensive activation of motor and sensory systems during high-intensity exercise likely attenuates higher order functions of the prefrontal cortex because the brain has finite metabolic resources (9). It has therefore been postulated that a reduction in CBF may compromise cerebral metabolism in the prefrontal cortex during high-intensity exercise and ultimately impair cognitive performance.

Cognitive performance appears to be impaired during high-intensity exercise (10, 11). However, as it stands, there is no empirical evidence showing that reduced CBF is responsible for cognitive impairment during high-intensity exercise. A few previous studies reported that cognitive performance improved during mild to moderate exercise independently of increased CBF (6, 12), which suggested that CBF may not be directly associated with cognitive improvement during exercise. However, given that CBF supplies oxygen and nutrients to meet metabolic demands in brain regions associated with

cognitive performance (e.g. prefrontal cortex), CBF may have an important role in maintaining cognitive performance during high-intensity exercise.

It is well established that CO_2 is a potent cerebral, but not muscle, vasodilator (13, 14). Therefore, for the first time we sought to characterise the effects of restored CBF, via CO_2 inhalation, on cognitive performance during high-intensity exercise. The purpose of the present study was to test the hypothesis that restored CBF via CO_2 inhalation would attenuate cognitive impairment.

Methods

Participants

A convenience sample of seventeen healthy men [mean (SD), age = 22.1 (1.7) years; height = 1.71 (0.07) m; body mass = 62.5 (7.0) kg; body mass index = 21.3 (2.2) $kg \cdot m^{-2}$; peak oxygen uptake ($\dot{V}O_{2peak}$) = 45.2 (7.2) $ml \cdot kg \cdot min^{-1}$] volunteered for this study. As estrogen levels are known to alter CBF (15) and cognition (16), only male participants were recruited. All participants were physically active (i.e., they engaged in moderate physical activity at least 2-3 days per a week within 3 month) and did not have any history of cardiovascular, cerebrovascular, or respiratory disease. They were asked to refrain from intense physical activity for 24 hours and not to consume any food or drink, except water, for 3 hours before each experimental session. The study was approved by the Fukuoka University Human Ethics Committee: (16-07-01). The study conformed to the standards set by the latest revision of the *Declaration of Helsinki*, except for registration in a database, with each participant providing written informed consent.

Experimental procedure

Participants attended the laboratory (ambient temperature 25°C and humidity 50%) on four occasions. During the initial visit, participants undertook a maximal exercise test on an electrically braked cycle ergometer (Aerobike 75XLIII; Combi, Tokyo, Japan) to assess their $\dot{V}O_{2peak}$. Following a warm-up at 10 watts (W) for 1 min, exercise workload was increased by $20W \cdot min^{-1}$ until exhaustion. Participants were instructed to maintain a cadence of 60 $r \cdot min^{-1}$ throughout and the test was terminated if the participants were unable to maintain a cadence of >40 $r \cdot min^{-1}$. During the maximal exercise test, ventilatory parameters were measured using a gas analysis system (ARCO-2000, ARCO System,

Chiba, Japan). During the maximal exercise tests, the peak $\dot{V}O_2$ ($\dot{V}O_{2peak}$) was recorded as the highest $\dot{V}O_2$ measured over the course of one minute. Exercise workloads at ~50% [moderate: 116 (16) W] and ~80% [high: 198 (27) W] $\dot{V}O_{2peak}$ were subsequently calculated (17). After the maximal test, the participants were familiarized with the experimental equipment and cognitive tasks (see cognitive tasks). The participants repeatedly performed the cognitive tasks until accuracy of ≥85% was achieved (18).

In the remaining three experimental sessions, the participants performed the cognitive tasks in the Exercise (EX), Exercise+CO_2 inhalation (EX+CO_2) and Control (CON) conditions in a single blinded randomized crossover design. Figure 1 illustrates the experimental protocol. At the beginning of the experiment, the participants performed the first cognitive task at rest while seated on the ergometer. One min after completing the cognitive tasks, participants started cycling at 50% $\dot{V}O_{2peak}$ for 8 min in both the EX and EX+CO_2 trials. Thereafter, participants cycled at 80% $\dot{V}O_{2peak}$ for an additional 8 min. They performed the second and third cognitive tasks 3 min after commencing each workload. During exercise at 80% $\dot{V}O_{2peak}$, the participants inspired either normal (room air [0.04% CO_2]: EX condition) or hypercapnic gas (2% CO_2: EX+CO_2 condition) (12) through a face mask attached to a one-way valve connected with 100-L Douglas bags. The inhalation of the gas mixture started 30-s before the cognitive tasks (12) during high-intensity exercise and participants were blinded to the respective conditions. In the CON condition, the participants performed the cognitive tasks at rest while seated on the ergometer.

Insert Figure 1 about here

Cognitive tasks

Cognitive function was assessed by a spatial delayed response (DR) task and a Go/No-Go task; both of which are considered to be executive function tasks (19). The tasks were completed on a laptop computer (Let's note CF-R4, Panasonic, Osaka, Japan) with the display placed 80cm from the participants. A portable numeric keypad and shift-key on the keyboard were used to perform the cognitive task. They were horizontally attached above both sides of the ergometer's handlebar (right side; numeric keypad for the spatial DR task, left side; key board for the Go/No-Go task).

148 The details of the cognitive task are described in detail elsewhere (19). Briefly, the
149 cognitive task was initiated by a target visual stimulus appearing on the screen (spatial
150 DR task). While the participants attempted to memorize the location of the target visual
151 stimulus, they performed a Go/No-Go task trial. In the Go/No-Go task, the participants
152 were required to either respond (Go trial) or not (No-Go trial) according to the stimulus.
153 After a trial in the Go/No-Go task, the visual stimulus was presented at all eight locations
154 and the participant attempted to recall the location of the target visual stimulus which was
155 presented in the preceding spatial DR task. These sequence was defined as one single trial
156 and was repeated for a total of 24 trials due to complete the cognitive tasks within 5 min.
157 The average time to complete the cognitive tasks was 236 (19) s.
158 Cognitive performance was evaluated by reaction time (RT) and accuracy of the cognitive
159 task. RT in the spatial DR task and Go trial in the Go/No-Go task were time elapsed from
160 the stimulus onset to the response. We excluded RT in the error trials from evaluating RT
161 in each cognitive tasks. In the spatial DR task, an incorrect response or omission was
162 regarded as an error trial. In the Go/No-Go task, there were some pairs of figure patterns
163 and the response association. After four / five /six correct trials, the response association
164 was reversed between the Go and No-Go stimulus and then different or new figure pattern
165 appeared. The first trial in each pattern were excluded from analysis. In the Go/No-Go
166 task, omitting a response in a Go-trial or performing an incorrect response in a No-Go
167 trial was regarded as an error trial. Accuracy of the cognitive performance was calculated
168 as number of correct response/total number of trials.
169
170 *Cerebral blood flow and cerebral oxygenation*
171 Middle cerebral artery mean velocity (MCAv) was measured using 2-MHz transcranial
172 Doppler ultrasonography (TCD-X; Atys Medical, Rhone, France) with a probe over the
173 right temporal window as previously described (20). The probe was fixed with an
174 adjustable headband and adhesive ultrasonic gel after position and angle of the probe were
175 adjusted to obtain an optimal signal-to-noise ratio. Cerebral oxygenation was assessed by
176 monitoring changes in oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) with
177 a near-infrared spectroscopy (NIRS) (BOM-L1 TRW, Omegawave, Tokyo, Japan) as
178 previously described (21). Total hemoglobin (total-Hb) was calculated as the sum of oxy-
179 Hb and deoxy Hb and cerebral oxygenation was expressed as oxy-Hb/total-Hb × 100 (%).

A probe holder was placed over the left prefrontal lobe, and source-detector distance of near-infrared light was set at 4 cm. Prior to the cognitive task at rest, oxy-Hb, deoxy-Hb, total-Hb, cerebral oxygenation were recorded for 30 s as a baseline while the participant rested on the ergometer. Cerebral oxygenation during the cognitive tasks were averaged and expressed relative to the baseline.

Physiological and psychological measures

Heart rate (HR) was recorded continuously using a heart rate monitor (RS800CX; Polar Electro Oy, Kempele, Finland). Minute ventilation ($\dot{V}_E$), $\dot{V}O_2$, fraction of end-tidal CO_2 ($F_{ET}CO_2$) and O_2 ($F_{ET}O_2$) were also recorded continuously (ARCO-2000, ARCO System, Chiba, Japan). End-tidal partial pressure of CO_2 ($P_{ET}CO_2$) and O_2 ($P_{ET}O_2$) was calculated from obtained $F_{ET}CO_2$ and $F_{ET}O_2$. Ratings of perceived exertion (RPE, 6-20 scale) (22) and blood lactate were collected immediately after each cognitive task. Blood lactate concentration from the left earlobe was determined by the lactate oxidase method using an automated analyzer (Lactate Pro 2 LT-1730; Arkray, Kyoto, Japan).

Data and statistical analysis

Accuracy of the cognitive performance was calculated as the number of correct responses in both cognitive tasks. HR, cerebral oxygenation and respiratory variables were averaged during the cognitive tasks. MCAv was averaged over final min of the cognitive task. MCAv data from one participant was removed due to technical issues, hence MCAv data for 16 participants was analyzed. A two-way repeated-measures ANOVA [condition (EX, EX+CO_2, and CON) × intensity (rest, moderate-, and high-intensity)] was performed. Where main or interaction effects were observed, post-hoc analyses was conducted using a multiple comparison with the Bonferroni correction. The degree of freedom was corrected using the Huynh Feldt Epsilon when the assumption of sphericity was violated. Effect size are presented as partial eta-squared (η_p^2) in the main effects and interactions. All data are expressed as mean (SD). The significance level was set at $P < 0.05$.

Results

Maximal exercise test

Following maximal exercise, data were as follow; W_{max} = 266.4 (33.8) W; HR_{max} = 188.6 (6.9) bpm; RPE = 18.8 (0.9); Blood lactate = 8.0 (2.1) $mmol \cdot L^{-1}$; respiratory exchange ratio = 1.24 (0.07).

Physiological and psychological variables

Physiological and psychological variables are presented in Table 1. HR, RPE, $\dot{V}E$, $\dot{V}O_2$, and blood lactate concentration increased during exercise in the EX and EX+CO_2 as a function of exercise intensity (all $P < 0.001$). CO_2 inhalation did not alter these variables during high-intensity exercise (all $P > 0.2$). $P_{ET}O_2$ was greater during high-intensity exercise in the EX+CO_2 condition compared to the EX condition ($P < 0.01$). In the CON condition, all variables remained stable throughout the trial.

Insert Table 1 about here

Cerebral blood flow, $P_{ET}CO_2$, and cerebral oxygenation

Figure 2A illustrates MCAv at rest and during exercise. In the EX and EX+CO_2 conditions, MCAv increased during moderate intensity exercise compared to rest (both $P < 0.01$). However, MCAv decreased to the resting level during high-intensity exercise in the EX condition ($P < 0.01$, vs. Moderate). In the EX+CO_2 condition, MCAv remained elevated during high-intensity exercise ($P < 0.001$, vs. Rest). In the CON condition, MCAv remained stable throughout the experiment. MCAv was also greater in the EX+CO_2 condition compared to the EX and CON trials during high-intensity exercise (both $P < 0.01$).

Figure 2B displays $P_{ET}CO_2$ at rest and during exercise. In the EX and EX+CO_2 conditions, $P_{ET}CO_2$ increased during moderate intensity exercise compared to rest ($P < 0.001$, respectively). $P_{ET}CO_2$ decreased during high-intensity exercise to the resting level in the EX condition ($P < 0.001$, vs. Moderate), while it remained elevated in the EX+CO_2 condition ($P < 0.05$, vs. Rest). $P_{ET}CO_2$ in the EX+CO_2 condition was greater than the EX and CON conditions during high-intensity exercise ($P < 0.05$, respectively). These results indicate that CO_2 inhalation prevented a reduction in MCAv, probably via an increase in arterial pressure of CO_2 ($PaCO_2$). Cerebral oxygenation did not alter during exercise with or without CO_2 inhalation (Table 1).

Insert Figure 2 about here

Cognitive tasks

Figure 3A shows accuracy of the cognitive performance. Accuracy of the cognitive performance was impaired during high-intensity exercise in the EX condition and EX+CO_2 condition (both $P < 0.05$, vs. Rest). The impairment was not different between EX and EX+CO_2 condition ($P > 0.10$). These results show that accuracy of the cognitive performance was impaired during high-intensity exercise in both EX and EX+CO_2 conditions. Figure 3B and C shows RT in the spatial DR task and Go/No-Go task, respectively. RT in the spatial DR task and Go/No-Go task did not alter during exercise irrespective of CO_2 inhalation.

Insert Figure 3 about here

Discussion

This study tested the hypotheses that a reduction in MCAv (a surrogate for CBF) is directly associated with impairment in cognitive performance during high-intensity exercise. For the first time we provide empirical evidence that restoring MCAv did not prevent impaired cognitive performance during high-intensity exercise. These novel findings indicate that a reduction in CBF is not responsible for impairments in cognitive performance during high-intensity exercise.

In the EX condition, MCAv increased during moderate exercise, then reduced towards the resting level during high-intensity exercise. The reduction in MCAv during high-intensity exercise was comparable with values reported in the review article (8). MCAv was significantly greater (~21%) during high-intensity exercise in the EX+CO_2 condition compared with the EX condition, indicating that 2% CO_2 inhalation was adequate to restore reduction in CBF during high-intensity exercise. These findings suggest that a reduction in MCAv is primarily due to hyperventilation-induced decrease in $PaCO_2$ and subsequent vasoconstriction of small cerebral vessels (7, 8). In addition, sympathetic nervous activity might alter MCAv during high-intensity exercise by constricting large

cerebral vessels. Nevertheless, the role of sympathetic nervous activity on regulation of CBF are controversial (8, 23), and further studies are required to clarify the contribution of sympathetic nervous activity to regulation of MCAv during high-intensity exercise.

In contrast to MCAv, there were no differences in HR, RPE, $\dot{V}_E$, VO_2, blood lactate concentration and cerebral oxygenation between EX and EX+CO_2 conditions. These results indicate that we successfully increased CBF via CO_2 inhalation, with minimalizing the influence on other physiological variables. Despite multiple factors involved in the regulation of CBF, CBF is primarily regulated by $PaCO_2$ during exercise (7, 8). Hence, CO_2 inhalation has previously been used to test the hypothesis that a reduction in CBF and/or cerebral oxygenation is a limiting factor of exercise performance. In these studies, CO_2 inhalation did not have beneficial effects on exercise performance (24), which suggests that exercise performance is not limited by a reduction in CBF. Ogoh and colleagues (2014) indicated that an increase in CBF by CO_2 inhalation did not affect cognitive performance during prolonged exercise. However, cognitive performance was assessed using the Stroop color-word test and remained unaltered during prolonged moderate-intensity (Target HR 140 bpm) exercise (12). Therefore, until now the association between impaired cognitive performance and reductions in CBF during high-intensity exercise ($\geq$ 80% VO_{2peak}) has not been examined.

Cognitive function involves executive function that consists of basic components of inhibition, working memory, and cognitive flexibility (25). In the present study a combination of spatial DR and Go/No-Go tasks was employed. Spatial DR task requires working memory and the Go/No-Go task requires selective attention, response inhibition, and interference control and hence; both are considered executive function tasks. Given that the prefrontal cortex is involved in executive function (26), it is likely to have played a key role in cognitive performance in the present study. By contrast, acute exercise activates brain regions including motor and sensory cortices, insular cortex, and cerebellum (27-29). Since the participants performed multiple cognitive tasks, we can assume that multiple brain regions were activated when the participants performed cognitive tasks during high-intensity exercise (30). To account for the effects of acute exercise on cognitive performance, Dietrich and Audiffren (2011) proposed a reticular-activating hypofrontality model. This model proposed that extensive activation of motor

and sensory systems during high-intensity exercise attenuates higher order functions of the prefrontal cortex because the brain has finite metabolic resources. Based on the assumption, cognitive performance would be impaired during high-intensity exercise due to the limited metabolic resources in the brain. However, this assumption has also been challenged in the literature.

Despite observing an impairment in cognitive performance during high-intensity exercise, cognitive performance was not impaired in the same cognitive tasks during moderate-intensity exercise in the present study. This possibly suggests that that competition for limited metabolic resources occurred among different brain regions, and that more metabolic resources were allocated to the motor and sensory cortices at the expense of the prefrontal cortex during high-intensity exercise. However, the present study demonstrates that restoration of CBF did not prevent impaired cognitive performance during high-intensity exercise. Given that restoration of CBF provides additional metabolic resources for extensive brain regions including the prefrontal cortex, the present results suggest that a reduction in CBF and consequent limited metabolic resources are not the primary factors that impaired cognitive performance during high-intensity exercise. Rather, the absence of attenuated cognitive performance following CBF restoration suggests a limited capacity of the brain to simultaneously activate multiple regions involved in cognitive performance and high-intensity exercise. However, further research is required to confirm this hypothesis.

Alternatively, exercise affects brain circuits involving a number of neurotransmitters including dopamine and noradrenaline (31). Dopaminergic system, originating from the ventral tegmental area, has projection to the prefrontal cortex (32). Noradrenergic system, originating from the locus coeruleus, also has vast projections to the prefrontal cortex (32). Dopamine and noradrenaline mediate the strength of the prefrontal cortex network connections, and regulation of dopamine and noradrenaline is required for appropriate prefrontal cognitive function (33). Notably, excess noradrenaline and dopamine are thought to weaken the signal to noise ratio and impairs the prefrontal cortex function (33). These findings imply that there exists an optimal activation level in noradrenergic and dopaminergic systems. In the present study, accuracy of cognitive performance was

impaired during high-intensity exercise in both EX and EX+CO_2 conditions, which may suggest that increased neuronal noise impaired the accuracy of the cognitive performance during high-intensity exercise. Hence, another possible interpretation of the present results is that increases noradrenergic and dopaminergic system activity impaired cognitive performance during high-intensity exercise, irrespective of CBF restoration. The absence of restored cognitive performance by CBF restoration might suggest that additional metabolic resources are not effective to optimize noradrenergic and dopaminergic systems during high-intensity exercise.

It has been suggested that acute exercise at moderate intensity is beneficial to cognitive performance (31, 34). However, we did not observe cognitive improvement during moderate-intensity exercise. Exercise duration longer than 20 min is prone to induce positive effects (34). In the present study, cognitive task was performed 3 min after the start of moderate-intensity exercise. Thus, lack of cognitive improvement during moderate-intensity exercise suggests that exercise duration was not sufficient to improve cognitive performance. Indeed, McMorris and colleagues also reported no improvement in cognitive performance during moderate-intensity exercise, where cognitive performance was assessed during incremental exercise at 50% and 80% maximum aerobic power (35).

Methodological consideration

First, we assessed MCAv as a surrogate for CBF based on the assumption that MCA diameter does not change during exercise. Recent studies suggest that MCA diameter may constrict in response to a reduction in $PaCO_2$ (36, 37). Since $P_{ET}CO_2$ was reduced during high-intensity exercise, a reduction in MCA diameter possibly underestimated CBF in the EX condition. However, in the EX condition, the degree of alternation in $P_{ET}CO_2$ was within the range where MCA diameter is unlikely to be affected (38). Furthermore, restoration of $P_{ET}CO_2$ and MCAv in the EX+CO_2 condition clearly indicate that CBF was restored during high-intensity exercise. It is unlikely that effect of changes in MCA diameter have profound effects on the present results.

Second, we only measured MCAv, and observed changes were limited to the territory of the MCA. Hence, changes in MCAv would not directly reflect variations in regional CBF, particularly to the prefrontal cortex. Furthermore, regional CBF distribution might be affected by changes in $PaCO_2$ during exercise (39). Hence, it is still unclear to what extent blood flow and additional metabolic resources were restored to the prefrontal cortex during high-intensity exercise with hypercapnic gas. Further studies are necessary to evaluate regional CBF distribution during high-intensity exercise with or without CO_2 inhalation.

Third, in the present study, cognitive performance was assessed using manual responses. One may argue that high-intensity exercise impaired motor response and not cognitive function. A recent study demonstrated that a reduction in CBF is associated with sub-optimal voluntary output from the motor cortex independent of changes in $P_{ET}CO_2$ (40). This led us to speculate that restoration of CBF by CO_2 inhalation appears to recover the optimal voluntary output from the motor cortex. However, we observed that cognitive performance was impaired in both EX and EX+CO_2 conditions despite differences in CBF. Hence, it is less likely that impaired cognitive performance was primarily due to impaired motor output during high-intensity exercise. Nevertheless, we cannot completely rule out the possibility that impaired motor output contributed to impaired cognitive performance during high-intensity exercise. Furthermore, it is also possible that cognitive performance was sufficiently impaired to mask the potential improvements with CO_2 inhalation. Perhaps, this is an inherent limitation with all cognitive performance tests assessed using manual responses. Future studies are needed to isolate the factors that impair motor output and cognition to elucidate how high intensity exercise impairs cognitive performance.

Conclusions

In summary, the present study indicated that cognitive performance was impaired during high-intensity exercise. In an attempt to prevent cognitive impairment, CBF was restored by hypercapnic gas inhalation during high-intensity exercise. However, restoration of CBF did not prevent the decline in cognitive performance. This suggests that the additional metabolic resources created by the CBF restoration did not maintain cognitive

403 performance during high-intensity exercise. This is the first study to demonstrate that a
404 reduction in CBF is not responsible for impaired cognitive performance during high-
405 intensity exercise. Future studies are therefore warranted to increase our understanding
406 of the physiological mechanism(s) responsible for impaired cognitive performance during
407 high-intensity exercise.
408
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415
416 **Conflict of interest**
417 The authors have no conflicts of interest to disclose. The results of the present study do
418 not constitute endorsement by the American College of Sports Medicine. The results of
419 this study are presented clearly, honestly, and without fabrication, falsification, or
420 inappropriate data manipulation.
421
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Figure Captions

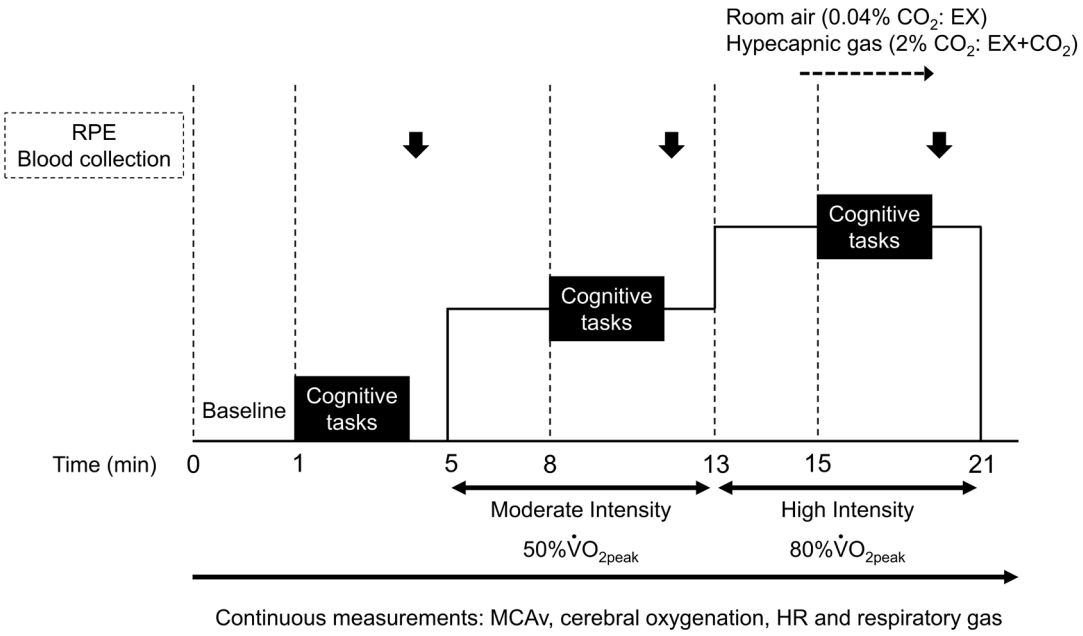

Figure 1: Experimental protocol. Black arrows indicate the timing of blood collection and RPE measurement. CO_2 inhalation started 30 s before the cognitive task during high-intensity exercise.

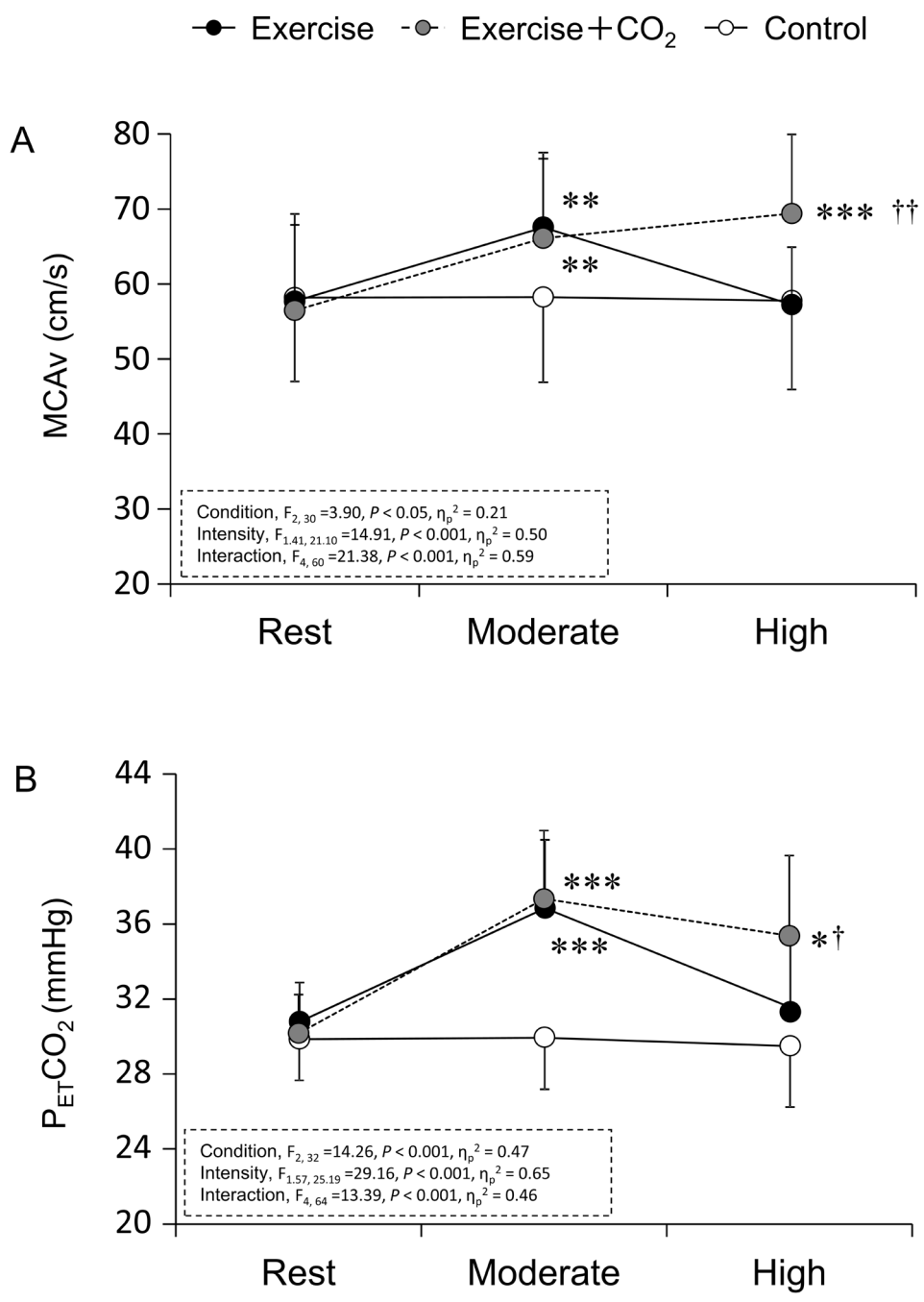

Figure 2: Middle cerebral artery mean velocity (MCAv) (A) and $P_{ET}CO_2$ (B) during the cognitive task. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. Rest. †$P < 0.05$, ††$P < 0.01$, vs. EX and CON.

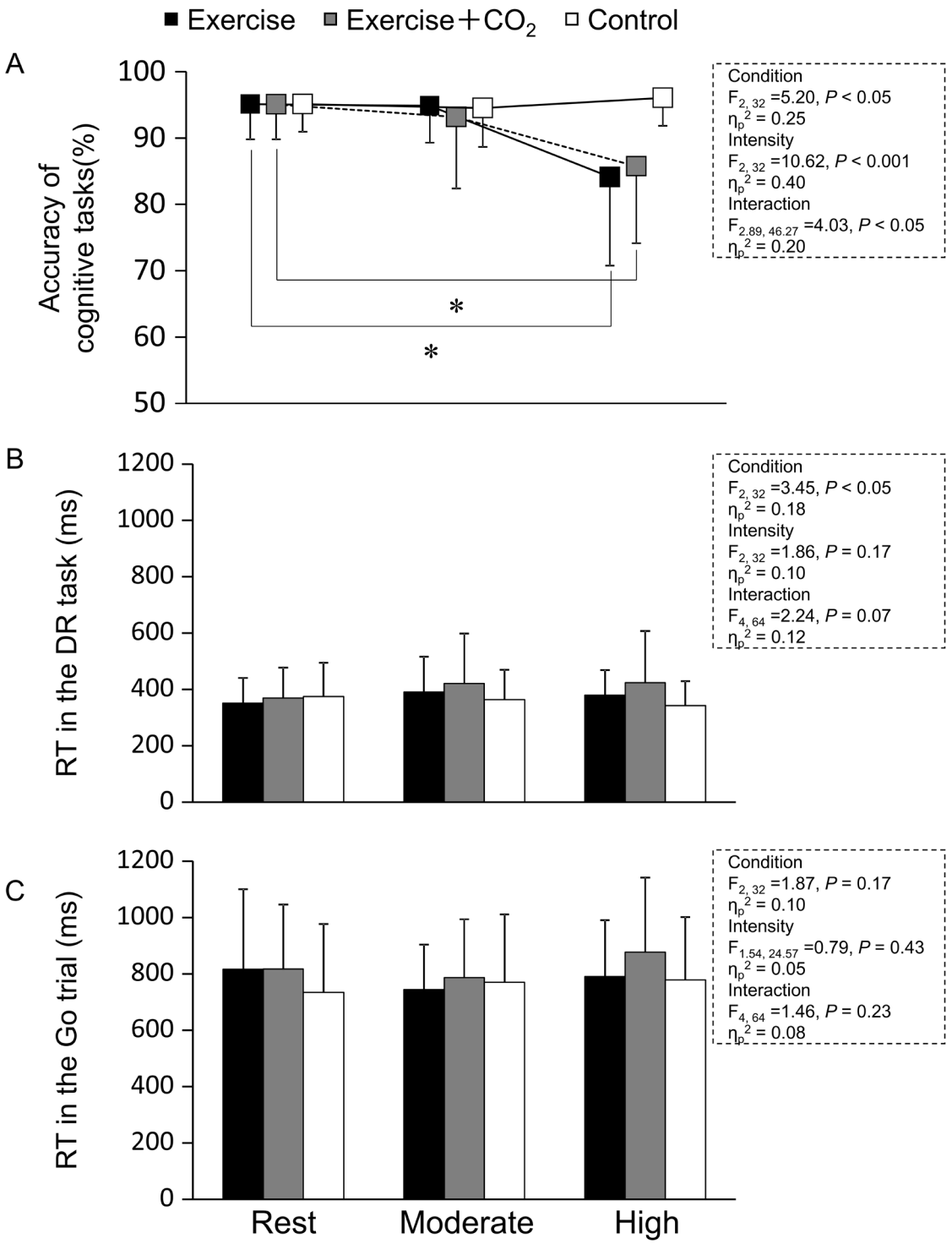

Figure 3: Accuracy of the cognitive performance (A). RT in the spatial DR task (B) and Go/No-Go task (C). *$P < 0.05$.