A 10-min reduction in cerebral blood flow does not alter post-intervention executive function: Evidence from lower-body negative pressure

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Abstract

A single bout of exercise as well as exposure to a hypercapnic environment increases cerebral blood flow (CBF) and is an adaptation linked to a post-intervention executive function (EF) benefit. In the present investigation we sought to determine whether a transient reduction in CBF impairs EF. Accordingly, we employed 10-min -30 mmHg and -50 mmHg lower-body negative pressure (LBNP) interventions as well as a non-LBNP control condition. LBNP was employed because it sequesters blood in the lower legs and safely and reliably decreases CBF. Transcranial Doppler ultrasound was used to measure middle cerebral artery velocity (MCAv) to estimate CBF prior to and during LBNP conditions. As well, an assessment of the inhibitory control component of EF (i.e., antipointing) was completed prior to (pre-) and immediately after (i.e., post-) each condition. Antipointing requires that an individual reach mirror-symmetrical to an exogenously presented target and is a task providing the resolution to detect subtle EF changes. Results showed that LBNP produced a 14% reduction in MCAv; however, null hypothesis, equivalence and Bayesian contrasts indicated that antipointing metrics did not vary from pre- to post-intervention, and LBNP-based changes in MCAv magnitude were not reliably correlated with antipointing planning times. Hence, a 10-min reduction in CBF did not impact the efficiency or effectiveness of an inhibitory control measure of EF.

Introduction

Executive function (EF) is a high-level cognitive construct including the core components of inhibitory control, working memory and cognitive flexibility (for reviews see, Diamond 2013; Miyake et al. 2000). Extensive literature has shown that a single bout of exercise provides a postexercise EF benefit (Barella et al. 2010; Chang et al. 2012; Heath et al. 2018; Tari et al. 2020) that has – in part – been linked to an exercise-mediated increase in cerebral blood flow (CBF) (Kleinloog et al. 2019; Poels et al., 2008; Tari et al. 2020; but see Ogoh et al. 2014). In particular, a transient increase in CBF is thought to produce thermo-mechanical changes to the brain's glial and neural circuits that improve EF network efficiency (i.e., the hemo-neural hypothesis) (Moore and Cao 2008).

In demonstrating the role of CBF in mediating a single bout of exercise EF benefit, Tari et al. (2020) measured middle cerebral artery velocity (MCAv) via transcranial Doppler ultrasound (TCD) to estimate CBF in healthy young adults in conditions involving: (1) a 10 min single bout of moderate to heavy intensity aerobic exercise (via cycle ergometer) and (2) a 10 min non-exercise condition involving the inhalation of a higher-than-atmospheric concentration of CO_2 (i.e., hypercapnic environment). The hypercapnic condition was used because it increases CO_2 (i.e., PCO_2) and produces systematic vasodilation that in turn increases CBF (for review see, Ainslie and Duffin 2009). As expected, exercise and hypercapnic conditions produced an average 19% increase in peak systolic MCAv, and both conditions produced a pre- to post-intervention reduction in an inhibitory control measure of EF (see details of inhibitory control task below). Moreover, cortical hemodynamic changes in both conditions were related to the magnitude of a post-intervention EF benefit. Accordingly,

Tari et al. demonstrated a transient increase in CBF independent of the metabolic costs and intensity demands of exercise benefits EF (see also Shirzad et al. 2022).

A bi-directional link between CBF and EF has additionally been demonstrated in *chronic* exercise studies and work involving *chronic* disease-related hypoperfusion. On the one hand, older adults who engage in regular physical activity have increased CBF compared to sedentary controls (for recent systematic review see, Pavia Prudente et al. 2023) and Colcombe et al.'s (2004) classic work demonstrated that individuals in the former category have improved EF and increased task-based activity within frontoparietal EF networks. On the other hand, Jefferson et al. (2007) showed that reduced CBF arising from stable cardiovascular disease is linked to impaired EF (for review see, Norling et al. 2019). To our knowledge, however, no work has examined whether a *transient* decrease in CBF adversely impacts a post-intervention measure of EF. This represents an important line of inquiry given that it provides a potential framework to better understand the putative relationship between a transient exercise-based increase in CBF and improved EF in healthy adults, and because it provides a basis to understand how occupational environments eliciting transient reductions in CBF (i.e., military and space flight/exploration) may impact post-intervention EF.

Lower-body negative pressure (LBNP) is a technique frequently used to decrease CBF (for review see, Goswami 2023). LBNP entails positioning a participant supine in an airtight bore sealed at the level of the iliac crest (i.e., waist-level) and exerting sub-atmospheric pressure to the lower-limbs. The resulting vacuum produces a caudal fluid shift by sequestering blood in the venous system of the lower limbs (see Akselrod et al. 2001) and leads to a rapid (i.e., ~ 60 s) decrease in CBF that is reversed within seconds

following LBNP cessation (Little et al. 1995; Crystal and Salem 2015). Although extensive research has examined the cortical hemodynamic response to LBNP (Balldin, et al. 1996; Duracher et al. 2015; for review see Goswami et al. 2019), a paucity of work has examined the influence of LBNP on cognition and EF. In fact, Han et al. (2009) provide the only study to examine the link between a LBNP-based reduction in CBF and cognition. In their study, participants were exposed to 5 min -30 mmHg and -50 mmHg interventions while simultaneous event-related brain potentials (ERP) were measured in response to an oddball paradigm (i.e., attentional response to an infrequently presented visual cue). Results showed that a reduction in MCAv scaled to LBNP magnitude and that the amplitude of the P300 ERP was decreased in both LBNP conditions. As such, the authors proposed that a transient decrease in CBF impairs the attentional system's reactivity to a novel stimulus. It is, however, important to recognize that Han et al.'s oddball paradigm was assessed simultaneously with the LBNP protocol and did not provide a behavioural measure of EF. As such, it is unclear whether a transient reduction in CBF negatively impacts a *post-intervention* measure of EF.

Here, participants completed 10-min -30 mmHg and -50 mmHg LBNP interventions as well as a 10-min non-LBNP control. The LBNP magnitudes were selected because they produce a scalable presyncope reduction in CBF (Goswami et al. 2019). CBF was estimated via a TCD-based measure of MCAv and pre- and post-intervention EF was assessed via the pro- and antipointing task. Propointing requires a goal-directed limb movement to the veridical location of an exogenously presented target, whereas antipointing (i.e., a countermanding task) requires a response mirror-symmetrical to the target. Antipointing results in longer reaction times (RT) and less accurate endpoints

than propointing (Carey et al. 1996; Heath et al. 2009; Maraj and Heath 2010) and these behavioural 'costs' have been attributed to EF demands of suppressing a pre-potent propointing response (i.e., inhibitory control) (Heath et al., 2009; for review of antisaccades see, Munoz and Everling 2004). Moreover, neuroimaging and electroencephalographic work has shown that antipointing involves EF networks (Connolly et al. 2000; Heath et al. 2011) that show task-dependent changes following single- and chronic bouts of exercise (Colcombe et al. 2003). Thus, the inclusion of pro- and antipointing provides a framework for determining whether a transient reduction in CBF renders a post-intervention impairment in general information processing (i.e., an increase in pro- *and* antipointing reaction time (RT)) or a selective EF impairment (i.e., an increase in antipointing – but not propointing – RT). In terms of research predictions, if a transient reduction in CBF negatively impacts EF then -30 mmHg and -50 mmHg LBNP post-intervention antipointing RTs should be longer than their pre-intervention counterparts and the magnitude of this increase should scale in relation to the magnitude of the reduction in CBF. In turn, if a transient reduction in CBF does not negatively impact EF then post-intervention antipointing RTs should not differ from their pre-intervention counterparts.

Methods

Participants

Seventeen participants aged 19-26 years (6 females, 11 males) were recruited from the University of Western Ontario community. Sample size was determined *a priori* via G*Power (v. 3.1: Means: Difference between two dependent means) using an effect size specified in previous work examining pre- to postexercise changes in antipointing RTs (α

= 0.05, power = 0.80, d_z = 0.74) (Tari et al. 2021). All participants were naïve to the purpose of this study (i.e., had no previous experience with LBNP or the antipointing task). Inclusion criteria included, self-reported right-hand dominant (i.e., "What hand do you write with?"); normal or corrected-to-normal vision; self-report not having metabolic, neurological (including concussion), psychiatric, and musculoskeletal conditions; no history of blood pressure or cardiorespiratory conditions; not currently taking prescription or nonprescription medication(s) that alter metabolic, cardiovascular, respiratory, hemodynamic or neuropsychological states. Inclusion criteria also required that participants did not have history of using tobacco produces (i.e., smoking, vaping, chewing tobacco). It was requested that participants abstain from caffeine, recreational drugs and alcohol 12 hours prior to starting the study and that they get eight hours of sleep the night before data collection. Participants reported adhering to these recommendations. Prior to data collection, participants read a letter of information approved by the Health Sciences Research Ethics Board, University of Western Ontario (HSREB #119772) and provided informed written consent. This study was conducted according to the most recent iteration of the Declaration of Helsinki with the exception that participants were not registered with a database.

Participants obtained a full score on the 2020 Physical Activity Readiness Questionnaire (PAR - Q+). In addition, participants completed the Godin Leisure-Time Exercise Questionnaire (GLTEQ) to determine participant-specific recreational activity. The average GLTEQ score was 69 (SD = 19; range: 39 - 111) and indicated that participants were recreationally active. The GLETQ was used given work reporting that fitness level influences the relationship between CBF and EF (Chang et al. 2012).

Apparatus and Procedures

Participants completed three experimental conditions: -30 mmHg and -50 mmHg LBNP conditions and a non-LBNP control condition. The conditions were ordered randomly and performed in a single session with each condition requiring approximately 30 min to complete with 10 min provided between successive conditions. The random ordering resulted in the control, -30 mmHg and -50 mmHg conditions being completed as the first condition for five, seven and five participants, respectively. Prior to the intervention an ECG monitor (ADInstruments Bio Amp FE132, Dunedin, New Zealand) was affixed to participants chest to record heart rate (HR), while systolic and diastolic blood pressure (BP) were recorded via finometer (FMS Finometer Model 1, Finapress Medical Systems, Enschede, The Netherlands). For each condition a TCD probe (Neurovision 500M, Neurovision TOC2M; Multigon Industries, Elmsford, CA, USA) was coated with an aqueous ultrasound gel (Aquasonic Clear, Parker Laboratories Inc., Farifield, NJ, USA) and secured via headset to the participant's left anterior temporal window to assess MCAv. TCD has been shown to be a valid proxy for direct measures of CBF (e.g., Xenon 133 tracing) (see Bishop et al. 1986). LBNP was achieved by having participants lie supine in the LBNP bore with their feet placed flat on an adjustable footrest (**Figure 1**). The footrest was adjusted according to the participant's height to ensure that the entrance to the bore was at the level of the participant's iliac crest. Once inside the bore, an adjustable nylon skirt was placed around the participant's waist and secured to the bore in an airtight fashion. Negative atmospheric pressure in the LBNP bore was achieved via vacuum.

For the duration of the protocol, participants lay supine with their lower body (i.e., below the iliac crest) placed in an airtight LBNP bore. All conditions consisted of three assessment timepoints (see **Figure 1** for timeline of experimental events). The first was a 10 min pre-intervention wherein HR, BP and MCAv were recorded for the last 2 min of this timepoint, and during which an EF assessment was completed (see EF function task details below). The second timepoint (i.e., intervention) consisted of the 10-min application of -30 mmHg or -50 mmHg LBNP, or the non-LBNP control. As per the pre-intervention timepoint, HR, BP and MCAv were recorded during the last 2 min of the intervention timepoint. In addition, at the 5- and 10-min intervals of this timepoint, a checklist was provided to participant allowing them to indicate the intensity of seven symptom that have been associated with LBNP (i.e., nausea, sweating, light-headed, shortness of breath, chest stiffness, stomach-ache, general discomfort). Participants verbally reported LBNP symptom intensity on a Likert scale ranging from 0-5 (i.e., "0" indicating an absence of symptomology and "5" indicating severe intensity and termination of the LBNP protocol). The symptomology checklist was delivered to determine whether possible changes in post-intervention EF was related to the adverse consequence of LBNP-induced symptomology. An assessment of EF was not completed during the intervention timepoint. To our knowledge, no studies have directly investigated whether an LBNP-induced reduction in CBF impacts EF, and as such, we elected to not measure EF during a time period that may be associated with LBNP-induced symptomology. The third timepoint (i.e., post-intervention) employed the same procedures as the pre-intervention; that is, a 10-min session wherein HR, BP and MCAv were collected for the last 2 min of the timepoint and following the EF task assessment.

Executive function

Pre- and post-intervention EF assessments were completed via pro- and antipointing trials completed on a custom-built iPad® app (XCode developed via Swift; v. 5.3 Apple Inc, Cupertino, CA, USA) operating at a native screen and touch resolution of 60 Hz (Tari and Heath 2022). Prior to data collection, participants were familiarized with the pro- and antipointing task via in-app tutorials. For all assessments, participants completed the task while supine in the LBNP bore with the iPad® (10.9" screen) equipped with the iOS v.15.0 operating system (Apple Inc., Cupertino, CA, USA) and secured above body midline (see **Figure 1**). Visual stimuli were presented on a grey (RGB code: 125, 125, 125) background and included a centrally located white (RGB code: 255, 255, 255) home location cross (i.e., 1 by 1 cm) and targets (i.e., open white circle; 1 cm in diameter) presented 6 cm (i.e., proximal target) and 9 cm (i.e., distal target) to the left and right of the home location and on the same horizontal plane. The onset of a trial was initiated by presentation of the home location which indicated where participants were to place their right index finger. Following contact with the home location, a uniformly distributed randomized foreperiod between 1000 and 2000 ms was introduced after which a target appeared for 50 ms in one of four locations (i.e., left 6 cm or 9 cm; right 6 cm or 9 cm) and cued participants to either pro- (i.e., point to veridical target location) or antipoint (i.e., point mirror-symmetrical to target location) "as quickly and accurately as possible". Additionally, participants were instructed to not slide their finger from the home location to the target; rather, the instruction was to lift and point to the target. Pro- and antipointing trials were completed in separate and pseudo-randomly ordered blocks requiring that at least one block of propointing, or antipointing, trials be completed as the

first trial block at each of the pre- and post-intervention sessions across each of the control, -30 mmHg and -50 mmHg conditions, For each pro- and antipointing block, 80 trials were pseudo-randomly presented at each target location (i.e., left and right field) and eccentricity (i.e., proximal or distal to screen's midline). The pseudo-random ordering target was set so that the same target location was not presented on more than three successive trials. Prior to a block of trials an instruction screen was provided that indicated that nature of the upcoming trial-type (i.e., pro- vs. antipointing). Upon completion of the pre-intervention EF task, the associated "intervention" timepoint was initiated. Post-intervention pro- and antipointing trials were completed ~2 minutes upon LBNP cessation to allow HR, BP and MCAv to return to pre-intervention values. Each EF assessment required approximately 8-min to complete.

Data reduction

TCD data corrupted by signal aliasing or loss (e.g., sudden head shift) were omitted (Terslev et al., 2017) and peak systolic MCAv were analyzed given Rosengarten and Kaps' (2002) demonstration that they provide a valid TCD-based measure of CBF. As in previous pro- and antipointing work (e.g., Maraj and Heath 2010), RTs less than 150 ms or greater than 2.5 standard deviations of a participant- and task-specific mean were excluded from data analysis (< 3% of trials). Further, movement times (MT) less than 100 ms or greater than 2.5 standard deviations of a participant- and task-specific mean were removed from analysis (<2 % of trials). Pro- and antipointing trials resulting in a directional error (i.e., propointing instead of antipointing and vice versa) were excluded from RT and MT analyses (<1 % of trials). The low error rate is attributed to the completion of pro- and antipointing trials in separate blocks (Heath et al. 2011).

Dependent variables and statistical analyses

MCAv, HR and systolic (BP_{sys}) and diastolic (BP_{dia}) BP were analyzed via 3 (condition: control, -30mmHg LBNP, -50mmHg LBNP) by 3 (time: pre-intervention, intervention, post-intervention) fully repeated measures ANOVA ($\alpha = 0.05$). Dependent variables for the pro- and antipointing tasks included RT (i.e., time from target onset to release of pressure from the iPad screen [i.e., movement onset]), movement time (MT) (i.e., time from movement onset to subsequent contact with the iPad screen), and gain (i.e., movement amplitude/veridical target location). Reaction time was the primary behavioural metric and served to determine whether the LBNP intervention influenced general information processing (i.e., pro- and antipointing) or more specifically influenced high-level EF associated with an manual-motor measure of inhibitory control (i.e., antipointing). In turn, MT and gain were used as secondary measures to determine whether any potential changes in pre- to post-intervention RT resulted from a strategy designed to decrease movement planning times at the cost of longer MTs or decreased endpoint accuracy (i.e., speed-accuracy trade-off) (Fitts, 1954). RT, MT, and gain were analyzed via 3 (condition: control, -30 mmHg LBNP, and -50 mmHg LBNP) by 2 (time: pre-intervention, post-intervention) by 2 (task: propointing, antipointing) fully repeated measures ANOVA (alpha = 0.05). Where appropriate, the two one-sided test (TOST) statistic is reported to determine whether results were within an equivalence boundary (Lakens et al., 2016). The effect size used to compute the TOST statistic (d_z =0.62) was derived from previous work contrasting pre- and postexercise changes in antipointing RTs (Tari and Heath, 2022). In addition, given that frequentist statistics cannot provide explicit evidence for the null hypothesis, we computed Bayesian single-sample t-test

contrasts of pro- and antipointing RT difference scores (i.e., post-intervention minus pre-intervention) across control, -30 mmHg and -50 mmHg LBNP. In particular, we used JASP (v. 0.18.3) (JASP Team, 2024) to compute Bayes factors for a test of the null hypothesis (i.e., H_{01}) with a standard Cauchy distribution of 0.707. In interpreting H_{01}, Jeffreys' (1981) nomenclature of "anecdotal" (i.e., 1 to <3), "moderate" (i.e., 3 to <10), "strong" (i.e., 10 to <100) and "very strong" (i.e., >100) was used to contextualize Bayes factor robustness.

Results

Heart rate (HR) and blood pressure (BP)

HR and BP_{sys} produced main effects of **condition**, $Fs(2,32) = 27.13$ and 6.75 for HR and BP_{sys}, respectively, $ps < 0.001$ and <0.01, $\eta_p^2 = 0.63$ and 0.29, **time**, $Fs(2,32) = 87.56$ and 79.47, $ps < 0.001$, $\eta_p^2 = 0.85$ and 0.83, and **condition by time** interactions, $Fs(4,64) =$ 75.36 and 17.73, $ps < 0.001$, $\eta_p^2 = 0.83$ and 0.53. The interactions were decomposed via HR and BP_{sys} difference scores (intervention minus pre-intervention, post-intervention minus pre-intervention) computed separately for each condition and contrasted to a value of zero via single-samples t-tests. **Figure 2** shows that control condition intervention ($ts(16) = 1.43$ and 1.50 for HR and BP_{sys}, respectively, $ps > 0.15$, $d_z = 0.35$ and 0.36) and post-intervention ($ts(16) = 1.17$ and 1.00, $ps > 0.33$, $d_z = 0.35$ and 0.24) HR and BP_{sys} did not reliably differ from pre-intervention. In contrast, intervention HR and BP_{sys} for -30 mmHg ($ts(16) = 7.62$ and -3.84 for HR and BP_{sys}, respectively, $ps < 0.001$, $d_z = 1.85$ and -0.93) and -50 mmHg ($ts(16) = 10.84$ and -9.25 $ps < 0.001$, $d_z = 2.62$ and -2.23) LBNP conditions were increased and decreased, respectively, compared to pre-intervention. In turn, post-intervention HR and BP_{sys} for -30 mmHg ($ts(16) = 0.37$ and 0.60, $ps > 0.72$, d_z

= 0.09 and 0.14) and -50 mmHg (*ts*(16) = 0.55 and 0.29, *ps* > 0.33, d_z = 0.13 and 0.07) LBNP conditions did not reliably differ from pre-intervention. In addition, we contrasted HR and BP_{sys} difference scores (i.e., intervention minus pre-intervention) between -30 and -50 mmHg LBNP conditions and observed that the magnitude of a pre-intervention to intervention increase in HR (*t*(16) = 9.47, *p* < 0.001, d_z = 2.29) and decrease in BP_{sys} (*t*(16) = 4.30, *p* < 0.01, d_z = 1.04) was larger in the -50 mmHg (HR: 20 bpm, SD = 7, BP_{sys}: -16 mmHg, SD = 7) than the -30 mmHg (HR: 7 bpm, SD = 4, BP_{sys}: -8 mmHg, SD = 5) LBNP condition

BP_{dia} did not produce main effects of **condition**, *F*(2,32) = 1.10, *p* = 0.35, η_p^2 = 0.06, **time**, *F*(2,32) = 3.09, *p* = 0.07, η_p^2 = 0.16, nor a **condition** by **time** interaction, *F*(2,32) = 1.81, *p* = 0.139, η_p^2 = 0.10 (**Figure 2**).

Middle cerebral artery velocity (MCAv)

Figure 3 presents an exemplar participant's MCAv at pre-intervention, intervention and post-intervention for control, -30 mmHg and -50 mmHg conditions. The figure demonstrates that MCAv in the -30 mmHg and -50 mmHg LBNP – but not the control – conditions decreased at LBNP onset and remained decreased throughout the intervention and then increased to pre-intervention levels within ~10 s following LBNP cessation (i.e., at post-intervention). In terms of quantitative results, MCAv produced a main effect for **time**, *F*(2,32)= 57.42, *p*< 0.001, η_p^2 = 0.76, and a **condition** by **time** interaction, *F*(2,32) = 26.56, *p*< 0.001, η_p^2 = 0.59. The same post hoc technique used for HR and BP_{sys} was used here and the right panels of **Figure 4** shows that control condition MCAv values at intervention and post-intervention did not reliably differ from pre-intervention (*ts*(16) = 0.19 and -0.67, *ps* > 0.51, d_z = 0.05 and -0.16). In contrast, -30 mmHg and -50 mmHg

LBNP conditions produced a pre-intervention to intervention decrease in MCAv (*ts*(16) = 4.16 and 4.69, *ps* < 0.001, d_z = 1.02 and 1.14); however, at post-intervention -30 mmHg and -50 mmHg condition values did not reliably differ from pre-intervention (*ts*(16) = 0.90 and -0.46, *ps* > 0.38, d_z = 0.22 and -0.11). A paired-samples t-test contrasting intervention minus pre-intervention difference scores between -30 mmHg (-13 cm/s, SD = 7) and -50 mmHg (-15 cm/s, SD = 7) LBNP conditions did not yield a reliable difference (*t*(16)=0.35, *p* = 0.36, d_z = 0.09), however, a TOST statistic indicated that this difference was outside an equivalence boundary (*t*(17)=1.54, *p* = 0.072).

Executive function: Reaction time (RT), movement time (MT) and gain

RT produced a main effect of **task**, *F*(1,16) = 34.07, *p*< 0.001, η_p^2 = 0.68, such that values for propointing (296 ms, SD = 39) were less than antipointing (335 ms, SD = 55) – a finding independent of condition and time of assessment. RT did not produce main effects for **condition**, *F*(2,32) = 1.61, *p* = 0.22, η_p^2 = 0.08, **time**, *F*(1,16) = 1.37, p = 0.26, η_p^2 = 0.07, nor any higher-order interactions, *Fs*(2,32) < 0.52, *ps* > 0.61, η_p^2 < 0.03 (**Figure 5**). Moreover, and given the nature of our research hypothesis, we computed participant-specific RT differences scores (pre- minus post-intervention) separately for pro- and antipointing across control, -30 mmHg LBNP and -50 mmHg LBNP conditions. Pro- and antipointing difference scores for each condition were contrasted to zero via single-sample TOST statistics and results indicated that values for all conditions were within an equivalence boundary (*ts*(16) > 2.56, *ps* < 0.01). As well, **Table 1** provides Bayesian single-sample t-tests contrasts of pro- and antipointing RT difference scores and demonstrates anecdotal to moderate support for the null hypothesis. Thus, frequentist

and Bayesian statistics support the assertion that the LBNP protocol did not influence an inhibitory control measure of EF.

Movement time and gain produced main effects of **task**, *Fs*(1,16) = 11.26 and 6.88, for MT and gain, respectively, *ps* = 0.01 and = 0.02, η_p^2 = 0.41 and 0.31, such that propointing response has shorter durations (213 ms, SD = 69) and amplitudes closer to veridical (0.90, SD = 0.37) than antipointing (MT: 227 ms, SD = 77; gain: 0.86, SD = 0.35)

Relationship between MCAv and antipointing difference scores

We computed Pearson r correlation coefficients relating MCAv difference scores (i.e., intervention minus pre-intervention) and antipointing RT difference scores (i.e., pre-intervention minus post-intervention) separately for -30 mmHg and -50 mmHg conditions. Results indicated that the variables were not reliably related across any condition (*ps*>0.38).

Lower body negative pressure (LBNP) and symptomology

Participant-specific symptomology was reported at the 5- and 10-min marks during the intervention for all conditions (i.e., control, -30 mmHg LBNP and -50 mmHg LBNP). All symptomology reported during the control intervention produced Likert ratings of zero. For the -30 mmHg LBNP condition, the total Likert scores (i.e., summed across all symptoms and all participants) at the 5- and 10-min were 5 and 4, respectively (maximum possible score = 85), and for the -50 mmHg condition values at the 5-min and 10-min assessments were 8 and 7, respectively. In other words, symptomology was *very* low and was reported by few participants.

Discussion

We sought to determine whether a transient LBNP-based reduction in CBF negatively impacts a post-intervention inhibitory control measure of EF. Below, we first outline the physiological changes associated with the -30 mmHg and -50 mmHg LBNP conditions used here before turning our discussion to pre- and post-intervention measures of EF.

Heart rate (HR), blood pressure (BP), middle cerebral artery velocity (MCAv) and symptomology in LBNP

The control condition did not elicit changes in HR, BP_{sys}, BP_{dia}, or MCAv, whereas LBNP conditions produced an intervention-based increase in HR and a decrease in BP_{sys}, and MCAv. Previous work has shown that an LBNP-induced decrease in BP_{sys} reflects reduced peripheral vascular resistance fostering a systemic hypotensive state leading aortic and carotid body baroreceptors to increase HR via parasympathetic vagal nerve inhibition (Bennett 1987; Blomqvist and Stone 1991). Moreover, although autonomic mechanisms work to counteract LBNP-induced central hypotension, cerebral perfusion is not adequately maintained and renders a decrease in MCAv (Guo et al. 2006, Han et al. 2009). At the post-intervention timepoint, HR, BP_{sys}, and MCAv in LBNP conditions rapidly returned to pre-intervention values (i.e., < 8 s) and is a result linked to shift to homeostatic blood volume levels (Guo et al. 2006). It is also worth noting that the intervention-based changes in HR and BP_{sys} were smaller in the -30 mmHg than -50 mmHg LBNP condition, whereas the decrease in MCAv did not reliably scale to LBNP magnitude. In accounting for the fact that MCAv did not scale to LBNP magnitude we note that CBF changes to LBNP are not homogenous given documented participant-specific differences in cerebral blood volume and sympathoexcitatory reflex activation (Wilson et al. 2006; for review see, Goswamiet al. 2019). In spite of this, the combined

cardiovascular and cortical hemodynamics measures reported here evince a framework for determining whether a transient CBF reduction impacts a post-intervention inhibitory control measure of EF.

The LBNP intensities used here did not increase symptomology (e.g., syncope, general discomfort) and is in line with the view that -30 mmHg and -50 mmHg interventions are "mild" protocols (for review see, Goswami et al. 2019). This represents a salient finding because it allows the post-intervention EF findings outlined below to be interpreted independent of any LBNP-induced symptom(s) burden.

LBNP does not impact post-intervention executive function (EF)

Antipointing produced longer RTs, MTs and less accurate endpoints than propointing – results consistent across each condition (i.e., control, -30 mmHg, and -50 mmHg LBNP) and assessment timepoint (i.e., pre-intervention and post-intervention). The longer antipointing RTs (i.e., 40 ms, SD = 25) reflect the time-consuming EF demands of planning and implementing a countermanding task; that is, inhibiting a pre-potent response and decoupling the normally direct spatial relations between stimulus and response (Carey et al. 1996; Heath et al. 2009). As well, neuroimaging work has reported that antipointing is linked to increased task-based activity within frontal EF networks (i.e., dorsolateral prefrontal cortex) supporting inhibitory control (Connolly et al. 2000; Heath et al. 2011). In turn, that antipointing produced longer MTs and less accurate endpoints has been shown to reflect increased uncertainty related to visuomotor control (Edelman and Goldberg 2001) and a decrease in motor excitability due to the high-level EF demands of inhibiting a prepotent response (Heath et al. 2012).

Some previous work has shown that a single bout of exercise for as brief as 10-min – and across a continuum of intensities – *increases* CBF and is linked to a post-intervention inhibitory control benefit (Shirzad et al. 2022; Tari et al. 2020; Tari et al. 2023). The present work evaluated a potential bi-directional relationship between a transient *decrease* in CBF and a post-intervention impairment in inhibitory control. To that end, the control condition produced an expected null pre- to post-intervention change in pro- and antipointing RTs. This is a salient finding because it demonstrates that the task was immune to a practice-related performance benefit. More notably, the -30 mmHg and -50 mmHg LBNP conditions similarly demonstrated that pro- and antipointing RTs did not vary from pre- to post-intervention – a conclusion supported by null hypothesis and equivalence tests as well as Bayesian contrasts. Additionally, that pre- and post-intervention MT and gain for pro- and antipointing did not vary across control and LBNP conditions indicates that participants did not adopt an explicit or implicit strategy designed to decrease movement planning times at the cost of reduced movement accuracy (i.e., a speed-accuracy trade-off) (Fitts 1954). Thus, although the LBNP protocol decreased CBF, such a change did not alter post-intervention pro- or antipointing RTs and is a conclusion supported by the absence of a reliable correlation between intervention-based changes in MCAv and antipointing RT difference scores.

A priori we predicted that the LBNP-induced decrease in CBF would impair post-intervention EF. Hence, we were surprised by the equivalent pre- and post-intervention antipointing RTs. In accounting for this null result, we note that some work has shown that a transient reduction in CBF and/or oxygen availability elicits a compensatory mechanism improving oxygen extraction. For example, Lewis et al. (2014) employed a

pharmacological (i.e., indomethacin) reduction in CBF (34% decrease from baseline) in healthy young adults and concurrently observed improved efficiency of oxygen extraction (via invasive measure of arterial-to-venous difference) (see also McHenry et al. 1961). Moreover, Wang et al. (2020) examined the impact of intermittent hypoxia training (IHT) on cognitive function in older adults with amnestic mild cognitive impairment. Participants alternated between breathing hypoxic (10% O_2) and normoxic air every 5-min for eight cycles and pre- and post-intervention measures of cognition were assessed via the digit span task and California Verbal Learning Test. Exposure to the IHT protocol resulted in a 30% decrease in arterial O_2 saturation; however, immediately following this exposure cerebral tissue oxygenation was increased and was linked to a reliable improvement in cognitive measures. The authors proposed that such results reflect accommodation for decreased oxygen availability via enhanced efficiency of oxygen extraction that leads to a short-term improvement in information processing. Thus, one possible account for the null post-intervention change in EF is that the LBNP-induced reduction in CBF was accommodated by a compensatory improvement in oxygen extraction. A second explanation is that EF was assessed post-intervention and not concurrent with the LBNP-based CBF reduction. Thus, any EF deficit associated with a reduction in CBF may have been evanescent and ameliorated by the rapid return of CBF to baseline levels following LBNP cessation. In addressing this issue, we note that a selective post-intervention EF assessment was used for two reasons. First, we were unclear as to whether presyncope or other LBNP symptoms might manifest during the intervention and serve as a stressor precluding the assessment of a transient reduction in CBF on EF. Second, a significant literature has reported that EF is improved

immediately following a single bout of exercise (but not concurrent with exercise) and some work has tied this change to an exercise-mediated increase in CBF (for reviews see Chang et al. 2012; Ludyga et al. 2016; Zheng et al. 2021). Thus, the current protocol was designed to provide a corollary to the exercise neuroscience literature and establish whether a transient reduction in CBF negatively impacts a post-intervention measure of EF. A third explanation for the current findings is that a transient change in CBF (i.e., increase or decrease) is unrelated to EF. Indeed, although some work reported a link between an exercise-mediated increase in CBF and improved postexercise EF (e.g., Lucas et al. 2012; Tari et al. 2020; Shirzad et al. 2022) other work has not (Ogoh et al. 2014). Moreover, Washio and Ogoh (2023) proposed that an exercise-mediated pressor response plays a more salient role in a postexercise EF benefit than CBF. Regardless of the explanation, we believe the present results add importantly to the literature insomuch as they demonstrate that a 10-min reduction in CBF does not impair the efficiency of an inhibitory control measure of EF. Further, the present results provide a basis to understand EF abilities for occupational environments requiring exposure to transient reductions in CBF (i.e., military and space flight/exploration).

Study limitations

We recognize that the present work is limited by several methodological constraints. First, our TCD-based measure of MCAv did not quantify vessel diameter and thus does not provide an absolute measure of CBF. That said, although vessel diameter increases during exposure to a hypercapnic environment (i.e., 5% CO_2) (Coverdale 2014), LBNP is not linked to an increase in arterial CO_2 (Ahn et al. 1989) and has been reported as a valid proxy for CBF under such an environment (for review see, Tymkoet al. 2018). Second,

we employed single 10-min bouts of LBNP at -30 and -50 mmHg. As a result, it is unknown whether a longer duration protocol (e.g., 20-min) would negatively impact EF. Thus, future work should establish whether a dose-response relationship characterizes the magnitude and duration of an LBNP-based CBF reductions and any associated changes in EF. Third, we did not quantify participants cardiorespiratory fitness (i.e., VO_{2peak}) and did not include a sufficient sample size to determine whether participants' biological sex might have influenced post-LBNP EF. These are salient considerations given some research showing that high-fit individuals demonstrate better performance on EF tasks (Ludyga et al. 2016) and because biologically male participants show increased peripheral resistance to LBNP than biologically female counterparts (Frey and Hoffler 1985). Fourth, only healthy young adults were recruited for this work and as result it is unclear whether older adults, individuals with limited mobility, or persons with chronic reductions in CBF (i.e., hypoperfusion) would show a similar persistence of high-level EF following a transient LBNP protocol. Last, although the TOST and Bayesian statistics used here provide a basis to assert that a transient reduction in CBF does not impact the inhibitory control component of EF, it is possible that our sample did not provide sufficient power to detect a subtle EF deficit and/or did not address the EF component (i.e., working memory, cognitive flexibility) most susceptible to a reduction in CBF.

Conclusions

The present study demonstrates that a 10-min LBNP-based reduction in CBF decreases CBF; however, this change did not impact a post-intervention measure of general information processing (i.e., propointing) or EF (i.e., antipointing).

Statements and Declarations

Author Contributions

JVR, MS, BT and MH conceived and designed the research, JVR, MS, CE and BT performed experiments; JVR, BT and MH analyzed data; JVR and MH interpreted results of experiments; JVR and MH prepared figures; JVR and MH drafted the manuscript; JVR, MS, CE and MH edited and revised the manuscript; JVR, MS, CE and MH approved the final version of the manuscript.

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Conflict of Interest

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

This work was approved by the Health Sciences Research Ethics Board, University of Western Ontario (HSREB #119772) and was conducted according to the most recent iteration of the Declaration of Helsinki.

Data Availability Statement

Data will be made available on reasonable request.

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Table 1. BF_{10} (i.e., test of alternative hypothesis) and BF_{01} (i.e., test of null hypothesis) values for single-samples t-statistics contrasting pro- and antipointing difference score (post-intervention minus pre-intervention) metrics as a function of control (con), -30 mmHg (-30) and -50 mmHg (-50) LBNP conditions.

	Propointing		Antipointing	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}
RT_{con}	0.33	3.08	0.25	4.01
RT_{-30}	0.29	3.44	0.25	4.00
RT_{-50}	1.01	0.99	0.28	3.56
MT_{con}	0.90	1.11	0.26	3.84
MT_{-30}	0.34	2.94	0.29	3.39
MT_{-50}	0.25	4.01	0.26	3.92
$Gain_{con}$	0.26	3.87	0.26	3.89
$Gain_{-30}$	0.46	2.16	0.26	3.91
$Gain_{-50}$	0.27	3.76	1.15	0.87

Note: RT and MT represent reaction time and movement time, respectively, and Gain represents movement amplitude in the primary movement axis divided by veridical target amplitude.

Figure Captions

1. Image **(A)** of experimental setup including lower-body negative pressure (LBNP) bore and placement of iPad® for the executive function (EF) task. Schematic **(B)** depicting the pre-intervention, intervention and post-intervention timelines for experimental events in each of the control, -30 mmHg and -50 mmHg LBNP conditions. The schematic shows that heart rate (HR) and blood pressure (BP) were measured during the last 2-min of the pre-intervention and intervention timelines and the first 2-min of the post-intervention time. Transcranial Doppler ultrasound was continuously measured throughout each timeline to provide an estimate of cerebral blood flow. Vertical black lines indicate when participants verbally reported LBNP-induced symptomology. The dashed horizontal lines indicated when the EF assessment took place during pre- and post-intervention timepoints.
2. The left panels depict group mean (and associated between-participant 95% confidence intervals) and participant-specific mean heart rate (HR: in beats/min [bpm]), systolic (BP_{sys}) and diastolic (BP_{dia}) blood pressure (in mmHg) for control, -30 mmHg and -50 mmHg LBNP conditions at pre-intervention (Pre), intervention (I) and post-intervention (Ps-I) timepoints. The right panels show group mean difference scores at intervention (intervention minus pre-intervention) and post-intervention (post-intervention minus pre-intervention) with associated 95% between-participant confidence intervals. The dotted horizontal line represents zero and error bar overlap with zero represents a reliable difference inclusive to a test of the null hypothesis.

3. Exemplar participant's middle cerebral artery velocity (MCAv: in cm/s) as a function of control, -30 mmHg and -50 mmHg LBNP conditions at pre-intervention, intervention and post-intervention timepoints. Note: for this figure data are not presented continuously, rather, MCAv at pre-intervention and intervention are depicted at the last 2-min of each timepoint, whereas post-intervention MCAv are presented at the first 2-min of this timepoint.
4. The left panel depicts group mean (and associated between-participant 95% confidence intervals) and participant-specific mean middle cerebral artery velocity (MCAv: in cm/s) for control, -30 mmHg and -50 mmHg LBNP conditions at pre-intervention (Pre), intervention (I) and post-intervention (Ps-I) timepoints. The right panels show group mean difference scores at intervention (intervention minus pre-intervention) and post-intervention (post-intervention minus pre-intervention) with associated 95% between-participant confidence intervals.
5. The left panels show group and participant-specific (and associated 95% between-participant confidence intervals) pro- and antipointing reaction time (in ms) for control, -30 mmHg and -50 mmHg LBNP conditions at pre-intervention (Pre), and post-intervention (Ps-I) timepoints. The right panels show group mean difference scores (pre-intervention minus post-intervention) with associated 95% between-participant confidence intervals.