Research article

Dynamic cerebral autoregulation of endurance-trained men following 6 weeks of high-intensity interval training to exhaustion

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Running head: High-intensity exercise training and the brain

Authors contribution

P.B. contributed to the original idea of the study; M.P., O.L.B., S.M. and P.B. contributed to data collection; A.D., L.L. contributed to data analyses; A.D., L.L., S.I. contributed to data interpretation; A.D. and P.B. drafted the article. All authors provided approval of the final article.

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NEW & NOTEWORTHY

The novel findings of this study are that 6 weeks of submaximal and supramaximal high-intensity interval exercise to exhaustion reduce dynamic cerebral autoregulation irrespective of training intensity in endurance-trained men. However, these HIIT protocols do not influence resting cerebral blood flow in these individuals. The results indicate the cerebrovasculature of endurance-trained men has an attenuated ability to react to large and rapid changes in blood pressure following HIIT.
ABSTRACT

Elevated cardiorespiratory fitness (CRF) is associated with reduced dynamic cerebral autoregulation (dCA), but the impact of exercise training per se on dCA remains equivocal. In addition, resting cerebral blood flow (CBF) and dCA after high-intensity interval training (HIIT) in individuals with already high CRF is unknown. We examined to what extent 6 weeks of HIIT affect resting CBF and dCA in cardiorespiratory fit men and explored if potential changes are intensity-dependent. Endurance-trained men were assigned to group HIIT_{85} (85% of maximal aerobic power, 1 to 7 min effort bouts, n = 8) and HIIT_{115} (115% of maximal aerobic power, 30 s to 1 min effort bouts, n = 9). Training sessions were completed until exhaustion 3 times/week over 6 weeks. Mean arterial pressure (MAP) and middle cerebral artery mean blood velocity (MCA_{mean}) were measured continuously at rest and during repeated squat-stands (0.05 and 0.10 Hz). Transfer function analysis (TFA) was used to characterize dCA on driven blood pressure oscillations during repeated squat-stands. Neither training nor intensity had an effect on resting MAP and MCA_{mean} (both P > 0.05). TFA phase during 0.10 Hz squat-stands decreased after HIIT irrespective of intensity (HIIT_{85}: 0.77 ± 0.22 vs. 0.67 ± 0.18 radians; HIIT_{115}: pre: 0.62 ± 0.19 vs. post: 0.59 ± 0.13 radians, time effect P = 0.048). These results suggest that HIIT over 6 weeks have no apparent benefits on resting CBF, but a subtle attenuation in dCA is seen post-training irrespective of intensity training in endurance-trained men.

Keywords: Exercise intensity, cerebral blood flow, transfer function analysis, cerebral pressure-flow relationship, aerobic fitness
INTRODUCTION

Established evidence show that cardiorespiratory fitness (CRF) is more cardioprotective when compared to overall physical activity levels (19). CRF-related benefits are not confined to the cardiovascular function and rather extend to the cerebrovascular system (23, 36). For instance, aerobic exercise training alters favorably cerebrovascular health in varying clinical conditions ranging from chronic obstructive pulmonary disease (21), cognitive impairments (6), stroke (14) and following cancer (27). Evidence show that life-long aerobic training individuals with elevated CRF have higher resting intracranial blood velocity in the anterior circulation, (as indexed by transcranial Doppler sonography of mean blood velocity in middle cerebral artery (MCA\textsubscript{mean}) (3, 7), and in the posterior circulation (as indexed by arterial spin labelling in posterior cingular cortex/precuneus) (37) and higher extracranial blood flow (as indexed by carotid Doppler) (9) than their sedentary counterparts. In inactive individuals, short-term aerobic training (12 weeks) longitudinally elevates CRF and cerebrovascular reactivity to carbon dioxide, whereas it induces equivocal MCA\textsubscript{mean} responses at rest (26). However, whether exercise training can elevate resting CBF in individuals with high CRF remains to be determined.

At rest or in response to challenges such as exercise, a myriad of mechanisms continuously interacts to maintain adequate CBF (4, 35, 40). Among these regulatory mechanisms, dynamic cerebral autoregulation (dCA), i.e. the ability of cerebral vessels to respond to rapid changes in blood pressure (BP), reacts rapidly even before baroreceptor reflex to modulate cerebrovascular resistance and minimize deviations in CBF (1).
However, the influence of CRF on dCA remains equivocal. Indeed, while some investigators reported no noticeable differences in dCA between endurance-trained individuals (13) or Masters athletes (2) with untrained individuals, our research group (17) and others (22) observed diminished dCA with elevated CRF. Nonetheless, training-induced effects on dCA in cardiorespiratory fit individuals remain unexplored while dCA seems not to be influenced by aerobic exercise training in older healthy sedentary participants and chronic obstructive pulmonary disease patients (20).

In endurance-trained individuals with already elevated CRF, one option to optimize endurance performance or related physiological adaptations is through the addition of high-intensity interval training (HIIT) (18). HIIT is defined as short bursts of exercise ≥ 80% of maximal heart rate (HR) alternating with periods of recovery or light exercise (38). Requiring half the accumulated time at target intensity, metabolic and cardiovascular health are improved equally and often superiorly with HIIT compared to traditional moderate-intensity continuous training (MICT) (8, 23, 24, 31). Different HIIT protocols are used by athletes, such as submaximal training below maximal oxygen consumption (VO₂max), training at VO₂max and supramaximal training (power output above VO₂max). Our research group compared two of these HIIT protocols, and recently reported that endurance-trained men performing 6 weeks of submaximal (85% maximal aerobic power) and supramaximal (115% maximal aerobic power) HIIT to exhaustion improve significantly VO₂max and anaerobic power irrespective of training intensity (29). However,
the knowledge about concurrent cerebrovascular adaptations specific to HIIT conducted at different training intensities remains limited in healthy humans (23).

Therefore, the aim of this study was to examine the influence of submaximal and supramaximal HIIT on resting CBF and dCA in endurance-trained men. We hypothesized that resting CBF would be increased, while dCA would be diminished following HIIT, and the extent of these changes would be intensity-independent.

MATERIALS AND METHODS

Ethics and informed consent

The Comité d'éthique de la recherche de l'IUCPQ-Université Laval (CER: 20869) approved the study according to the principles established in the Declaration of Helsinki (except for registration in a database). Informed consent was obtained by all participants prior to the investigation.

Participants

We recruited nineteen endurance-trained men with a history of 5 to 12 h/week for at least 2 years. All participants were free from any diagnosed medical conditions. A variety of endurance sports were undertaken by the participants including road cycling \((n = 9)\), triathlon \((n = 7)\), mountain biking \((n = 2)\) and cross-country skiing \((n = 1)\) (29).

Experimental protocol
This study was part of a larger study examining the influence of submaximal and supramaximal training on determinants of endurance performance (29). However, the current question was determined *a priori* and was prospectively studied as a separate question. For the purpose of our study, we analyzed and compared pre and post-values collected on three visits: 1) anthropometrics, resting systemic and cerebral hemodynamic measurements and the evaluation of dCA 2) incremental cycling test for determination of VO$_{2\text{max}}$, and 3) maximal aerobic power evaluation for prescription of training session intensity. Prior to testing, all participants were asked to refrain from consuming alcohol and caffeine for 24 h and to avoid exercise training for at least 12 h. The data were collected in the same order for all participants and the visits were separated by at least 48 h. After being matched according to their age and pre-training VO$_{2\text{max}}$, they were randomly assigned to two different intensity training groups; 85% of maximal aerobic power (HIIT$_{85}$) and 115% of maximal aerobic power (HIIT$_{115}$). The post-training testing sessions were repeated 48-96 h following the end of the 6-week training program.

**Training interventions**

Over a period of 6 weeks, training consisted in three HIIT sessions per week with 48-72 h between sessions. On the remaining days, participants were allowed to maintain a similar low and/or moderate-intensity volume that they were typically performing prior to the study. Other than the ones already included in the study protocol, HIIT was strictly prohibited.
Specifically, the HIIT\textsubscript{85} group performed repeated 1- to 7-min efforts bouts. The intensity was set to 85\% of maximal aerobic power. The other experimental group, HIIT\textsubscript{115}, repeated 30-s to 1-min effort bouts at 115\% maximal aerobic power. Both groups interspaced their effort bout with active recovery (150 W or 50\% of maximal aerobic power if maximal aerobic power < 300 W). To avoid routine monotony and to keep the focus on exercise intensity rather than duration, both groups alternated exercise bout duration from one session to another throughout the 6-week period (29). The specificity of our protocol was that both groups had to perform each HIIT session until exhaustion, defined as the inability to complete an effort bout, in order to match the two intensity training protocols for total effort. As already reported, the total training volume was different between groups being 47 \% less in HIIT\textsubscript{115} group compared to HIIT\textsubscript{85} (19.3 ± 4.7 vs 36.6 ± 14.4 min/session; \(P = 0.005\)) (29). For further details on the training interventions, refer to (29).

**Measurements**

*Systemic hemodynamics*

A 5-lead ECG was used to measure HR. BP was measured beat-to-beat by the volume-clamp method using a finger cuff (Nexfin, Edwards Lifesciences, Ontario, Canada). For uniformity, the cuff was always placed on the right middle finger. BP was corrected by referencing the cuff to the level of the heart using a height correcting unit. The integration of the pressure curve divided by the duration of the cardiac cycle allowed to calculate mean arterial pressure. The dynamic relationship between the BP and cerebral blood
velocity is indexed reliably by the volume-clamp method which correlates the dynamic changes in beat-to-beat BP with the intra-arterial BP recordings (28, 32).

**Middle cerebral artery blood velocity**

A transcranial Doppler ultrasound was used at a frequency of 2-MHz pulsed to monitor MCA$_{\text{mean}}$ (Doppler Box; Compumedics DWL USA, Inc. San Juan Capistrano, CA). A standardized procedure (39) was repeated for every participant to localize and identify the left MCA. After the optimal signal was attained, signal depth, gain and power were recorded for post-training evaluations. The probe was fixed to a head set that was placed over a custom-made headband. An adhesive conductive ultrasonic gel (Tensive, Parker Laboratory, Fairfield, NY, USA) was used to ensure a stable position and angle of the probe throughout testing.

**End-tidal partial pressure of carbon dioxide**

A breath-by-breath gas analyzer (Breezesuite, MedGraphics Corp., MN) was used to measure end-tidal partial pressure of carbon dioxide (P$_{\text{ET CO}}$2) during supine rest baseline and squat-stand maneuvers. Before each evaluation, the analyzer was calibrated to known gas concentrations following manufacturer instructions.

**Data acquisition**

An analog-to-digital converter (Power- lab 16/30 ML880; ADInstruments, Colorado Springs, CO, USA) converted and stored at 1kHz all signals. Subsequent analysis was
performed with a free version of a commercially software (LabChart version 8.1.8; ADInstruments).

**Visit 1**

*Anthropometric measurements and resting hemodynamics*

Upon arrival, each participant was measured and weighed. Resting hemodynamic measurements included MAP (volume-clamp method using a finger cuff), HR (electrocardiogram), and MCA\_\text{mean} (transcranial Doppler ultrasound), which were continuously monitored on a beat-by-beat basis in a supine position after 10 min of rest. Cerebrovascular conductance index (CVC\text{i}; MCA\_\text{mean}/MAP) and its reciprocal, resistance (CVR\text{i}; MAP/MCA\_\text{mean}) was then calculated. Baseline data were averaged over the last 3 min of the resting period, except recordings of $P_{\text{ETCO}_2}$ which were averaged over the last 2 min of the resting period.

*Assessment of dynamic cerebral autoregulation*

\text{dCA} was characterized by forcing MAP oscillations using repeated squat-stand maneuvers. It has been shown to be the best reproducible technique to be used and to elicit high interpretable linearity association between MAP and MCA\_v signals (34). A minimum of 10 min of standing rest was required before performing the squat-stand maneuvers to ensure all cardiovascular variables had returned to baseline. From the standing position, the participants repeatedly squatted down until the back of their legs attained a $\sim 90$ degrees angle. To achieve a specific frequency of forced oscillations, squat and standing
positions were sustained in alternation for a specific time period. In order to achieve the right pace, instructions were given, and participants were asked to practice 2 or 3 squats. Over a period of 5 min, squat-stand maneuvers were repeated at a frequency of 0.05 Hz (10 s squat, 10 s standing) and 0.10 Hz (5 s squat, 5 s standing) (16, 17, 34). Those frequencies were chosen because it has been shown that under the buffering range of 0.20 Hz, large oscillations in MAP are extensively buffered by the cerebral vessels (41). Because it optimizes the signal-to-noise ratio, the squat-stand maneuvers make the interpretations reliable to study cerebrovascular reactivity to BP through a physiologically relevant MAP stimulus. Each participant executed the squat-stand maneuvers at both frequencies (0.05 and 0.10 Hz) in a randomly fashion. A 5-min standing recovery period separated each sequence to assure cardiovascular variables returned to baseline. The breathing instructions to the participants included normal breathing and avoiding Valsalva maneuvers. During this evaluation, MAP, HR, MCAv_mean, and PETCO₂ were recorded in a continuous manner. TFA metrics characterizing the linear dynamic relationship between MAP and MCAv is described in more details in the following section.

To evaluate whether squats induced changes in PETCO₂, an averaged PETCO₂ of the first and last five breaths of each maneuver (0.05 and 0.10 Hz) were calculated (16).

Assessment of the dynamic relationship between MAP and MCAv

The recommendations of the Cerebral Autoregulation Research Network (CARNet) (11) were followed when analyzing data using the commercially available software Ensemble (Version 1.0.0.14, Elucimed, Wellington, New Zealand). The spectral analysis of beat-to-
beat MAP and MCAv signals was interpolated and re-sampled at 4 Hz. The Welch algorithm was used to do TFA. The analysis required a 5-min recording subdivided into five windows. The successive windows overlapped by 50%. Prior to discrete Fourier transform analysis, data within each subdivision were detrended linearly and passed through a Hanning window.

For TFA, the cross-spectrum between MAP and MCAv was determined and divided by the MAP auto-spectrum to derive the transfer function coherence (fraction of the MAP which is linearly related to MCAv), absolute gain (cm/sec/mmHg) (amplitude of MCAv change for a given oscillation in MAP), normalized gain (%/mmHg), and phase (radians) (difference of the timing of the MAP and MCAv waveforms).

Specific point of estimate of driven frequency (0.05 and 0.10 Hz) were chosen to sample TFA values. They were selected in the very low (0.02-0.07 Hz) and low (0.07-0.20 Hz) frequency ranges where dCA is believed to be the most operant (34). A threshold of 0.50 of coherence was necessary to ensure robustness of the phase and gain subsequent analysis (41). When coherence exceeded the threshold, phase wrap-around was not present.

Visit 2

*Maximal oxygen consumption (VO₂max)*

VO₂max was determined during a progressive ramp exercise test executed on an electromagnetically braked upright cycle ergometer (Corival, Lode, the Netherlands) (29).
Briefly, the exercise protocol included 3 min of resting period followed by a warm-up of 1 min of unloaded cycling, then by an individualized incremental ramp protocol to volitional exhaustion. The highest 30 s averaged VO$_2$, concurrent with a respiratory exchange ratio $\geq 1.15$ was used to define VO$_{2\text{max}}$ (29).

**Visit 3**

*Maximal aerobic power*

Maximal aerobic power was measured for the determination of training intensities (85 and 115% maximal aerobic power) as previously described (29).

**Statistical analysis**

The Shapiro-Wilk test was used to confirm normal distribution of data. Data were analyzed by a two-way repeated-measures analysis of variance when normal distribution was confirmed otherwise data were log transformed before analysis. If data were missing, they were analyzed by fitting a mixed effects model. Following detection of an interaction effect (Time x Intensity), differences were identified using within groups paired and between groups independent samples t-tests, with Bonferroni correction. Statistical significance was established *a priori* at $P < 0.05$ for all tests. All values are expressed as mean $\pm$ standard deviation. Statistical analyses were performed using a commercially available software (Prism for macOS, version 8, GraphPad software, CA, USA).
RESULTS

Participant compliance

A total of 17 out of 19 participants completed the study; HIIT$_{85}$: 26 ± 6 years, 1.77 ± 0.08 m, 72.1 ± 12 kg, $n = 8$ and HIIT$_{115}$: 28 ± 6 y., 1.77 ± 0.09 m, 73.1 ± 7.5 kg, $n = 9$. We excluded two participants from our final analysis; one participant in HIIT$_{85}$ was ill and absent > 3 training sessions and the other participant in HIIT$_{115}$ complained from excessive fatigue during training regime. Excessive noise/artifact in the recordings of two participants (HIIT$_{85}$, $n = 1$; HIIT$_{115}$, $n = 1$), did not allow for TFA measurements, therefore a total of 15 participants were included in the dCA analysis. Of note, we excluded pre-training values of MCAv, CVCi and CVRi of one participant due velocity that did not identify with certainty the MCAv pattern as compared to reference values (39). Also, due to technical reasons (malfunction of the gas exchange analyzer), $P_{E\text{t}}CO_2$ recordings of only 11 participants were completed during baseline rest, 12 participants during pre-training squat-stands and 6 participants post-training.

Anthropometric measurements and resting hemodynamics

As previously reported by our research group, six weeks of submaximal and supramaximal HIIT did not modify body mass (intensity effect $P = 0.84$; time effect $P = 0.16$; interaction effect $P = 0.85$). However, HIIT protocols significantly increased VO$_{2\text{max}}$ in both groups after 6 weeks, demonstrating that the selected training program effectively increased CRF irrespective of intensity (HIIT$_{85}$ pre: 56.0 ± 6.0 vs post: 59.3 ± 4.7 mL/kg/min; HIIT$_{115}$ pre: 55.9 ± 4.0 vs post 59.2 ± 1.1 mL/kg/min, time effect $P = 0.002$) (29).
Concurrently, resting heart rate significantly decreased after training irrespective of intensity (by 8% in HIIT85 and 5% in HIIT115, time effect $P = 0.02$). However, despite an improvement in CRF, neither training nor intensity resulted in any change in MAP (intensity effect $P = 0.09$, time effect $P = 0.51$; interaction effect $P = 0.44$) and MCAv$_{\text{mean}}$ (intensity effect $P = 0.55$, time effect $P = 0.93$; interaction effect $P = 0.40$). CVCi and CVRi were neither influenced by training nor intensity (Table 1).

**TFA of forced oscillations in MAP and MCAv**

The power spectrum densities of MAP and MCAv during repeated squat-stands at 0.05 and 0.10 Hz did not differ between groups or across time (pre- and post-training) (all $P > 0.05$; Table 2). HIIT decreased TFA phase during 0.10 Hz squat-stands irrespective of training intensity (effect of time $P = 0.048$; Figure 1). TFA gain and coherence were unaffected by training or intensity during repeated squat-stands at both frequencies (all $P > 0.05$). There were no significant changes in $P_{\text{ET}}$CO$_2$ during repeated squat-stands at 0.05 Hz and 0.10 Hz (all $P > 0.05$) and were comparable between groups and time (pre-vs. post-training; Table 2).

**DISCUSSION**

To our knowledge, our study is the first to assess the longitudinal effects of submaximal and supramaximal HIIT to exhaustion on resting cerebral hemodynamics and dCA in endurance-trained men. The main findings of this study are threefold: 1) resting CBF remained unchanged after 6 weeks of HIIT; 2) TFA phase during 0.10 Hz repeated squat-
stand maneuvers was reduced following training irrespective of intensity; 3) training intensity did not have any effect on our main outcome variables.

Effect of HIIT on resting cerebral blood flow

We found resting MCAv\text{mean} remained unchanged following 6 weeks of submaximal or supramaximal HIIT to exhaustion. Our results differ from cross-sectionnal studies assessing life-long training effect that reported elevated resting MCAv\text{mean} (3, 7) and regional CBF in the posterior cingular cortex (37) in elderly trained participants. Longitudinally, short-term aerobic exercise of varied nature (continuous or interval training), intensity and duration [12 weeks (6, 26) and 8 weeks (20)] has been associated with improved CRF in healthy individuals. In association with this training-induced CRF improvement, some investigators reported a small but significant increase in MCAv\text{mean} following a 12-week program (26), whereas others did not observe any change in MCAv\text{mean} (20) or whole-brain CBF (6) after respectively 8 and 12 weeks of training.

Nevertheless, the effect of exercise training using solely HIIT to exhaustion had not yet been documented in young endurance-trained men with already high CRF. In light of our results, it is possible that training duration might explain discrepancies. Indeed, 6 weeks of exercise training may not be a long enough stimulus to instigate noteworthy and clear beneficial adaptations (i.e. elevation in resting CBF) in young individuals, although HIIT is assumed to provide enough stimulus for cerebrovascular adaptation to occur (23). Considering that it has been argued that the brain vasculature needs to be challenged in
order to witness adaptive changes in cerebral hemodynamics (10), our results do not rule out a potential influence of HIIT on CBF changes during aerobic exercise.

**Effect of HIIT on dynamic cerebral autoregulation**

We have previously demonstrated cross-sectionally that dCA is impaired in endurance-trained men with elevated CRF (17). In that report, we showed that elevated CRF was associated with increased TFA gain during 0.10 Hz squat-stands compared to sedentary individuals, suggesting a subtle attenuation in dCA. In the present study, we trained a sample of the men included in that cross-sectional study by Labrecque et al. (2017) over 6 weeks with HIIT to exhaustion and investigated whether dCA would be further impaired, and whether these potential changes would be influenced by training intensity. The current findings revealed that irrespective of training intensity, 6 weeks of HIIT did not further impair TFA gain in these participants (unchanged TFA gain post-training \( P > 0.05 \)), but rather decreased TFA phase during repeated squat-stands at 0.10 Hz, irrespective of training intensity. These results suggest that when endurance-trained men with already elevated \( VO_2_{\text{max}} \) further improve CRF with HIIT, they also aggravate their attenuated dCA [TFA gain during 0.10 Hz squat-stands previously known to be higher in these endurance-trained men vs. sedentary controls (17)] through a reduction in TFA phase. The clinical and physiological implications of this subtle attenuation in dCA following HIIT in endurance-trained individuals remain to be elucidated.
To our knowledge, only one other longitudinal study assessed dCA following aerobic exercise training of varied nature and intensity (20). These authors reported no training effect on dCA in healthy older sedentary participants. One possible explanation might be that despite an ~18% increase in CRF, the sedentary older participants (>64 years) studied by Lewis et al. (2019) had significantly lower CRF levels at baseline than our young endurance-trained men (26 to 28 years). These results support that elevated CRF is associated with diminished dCA, whereas dCA is maintained in individuals with lower CRF (20). Further research is required to elucidate whether a threshold exists above which CRF will be associated with an attenuated dCA. In addition, Phillips et al. (2018) have recently reported that 4 weeks of repeated transient hypertension induced by colorectal distension in rats after spinal cord injury lead to impairments of the brain vasculature such as cerebrovascular endothelial dysfunction and profibrotic cerebrovascular stiffness (30). Unfortunately, we did not monitor BP changes during HIIT sessions to exhaustion performed 3 times/week for 6 weeks. We could speculate the subtle attenuation in dCA observed following HIIT in our participants is related to subclinical cerebrovascular impairments induced by the repetitive and rapid surges in BP during each HIIT session performed over 6 weeks.

Limitations

The findings from our present work should be interpreted in view of limitations. We acknowledge the uniqueness of our exhaustive HIIT training protocols limited the number of endurance-trained participants which resulted in a small sample size. Nonetheless, it
allowed us to explore the particularities, feasibility and longitudinal effects of training in this specific population. We relied on transcranial Doppler ultrasonography to measure cerebral blood velocity. This method is only valid if the insonated artery diameter remains constant. It is likely that our study protocol induced negligible physiological range of variation of MAP and $P_{ET}$CO$_2$ that could impact on the diameter of the artery (5). The use of transcranial Doppler remains recognized to provide excellent temporal resolution and has been validated as an indirect surrogate marker of CBF (33). Finally, considering that sex (12, 16) and various clinical conditions such as type 2 diabetes and pulmonary arterial hypertension (15, 25) have an influence on dCA, our findings cannot be generalized to healthy women or patients.

CONCLUSION

Collectively, these findings suggest that 6 weeks of HIIT to exhaustion does not influence resting CBF but is associated with a subtle attenuation in dCA irrespective of training intensity in endurance-trained men.

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**DISCLOSURE**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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REFERENCES

1. Aaslid R, Lindegaard KF, Sorteberg W, and Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 20: 45-52, 1989.

2. Aengevaeren VL, Claassen JA, Levine BD, and Zhang R. Cardiac baroreflex function and dynamic cerebral autoregulation in elderly Masters athletes. *J Appl Physiol (1985)* 114: 195-202, 2013.

3. Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, Thomas KN, Williams MJ, and Atkinson G. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *J Physiol* 586: 4005-4010, 2008.

4. Ainslie PN, and Duffin J. Integration of cerebrovascular CO2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol* 296: R1473-1495, 2009.

5. Ainslie PN, and Hoiland RL. Transcranial Doppler ultrasound: valid, invalid, or both? *J Appl Physiol (1985)* 117: 1081-1083, 2014.

6. Alfini AJ, Weiss LR, Nielson KA, Verber MD, and Smith JC. Resting Cerebral Blood Flow After Exercise Training in Mild Cognitive Impairment. *J Alzheimers Dis* 67: 671-684, 2019.

7. Bailey DM, Marley CJ, Brugniaux JV, Hodson D, New KJ, Ogho S, and Ainslie PN. Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. *Stroke* 44: 3235-3238, 2013.
8. **Batacan RB, Jr., Duncan MJ, Dalbo VJ, Tucker PS, and Fenning AS.** Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med* 51: 494-503, 2017.

9. **Braz ID, Fluck D, Lip GYH, Lundby C, and Fisher JP.** Impact of aerobic fitness on cerebral blood flow and cerebral vascular responsiveness to CO2 in young and older men. *Scand J Med Sci Sports* 27: 634-642, 2017.

10. **Brugniaux JV, Marley CJ, Hodson DA, New KJ, and Bailey DM.** Acute exercise stress reveals cerebrovascular benefits associated with moderate gains in cardiorespiratory fitness. *J Cereb Blood Flow Metab* 34: 1873-1876, 2014.

11. **Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB, and international Cerebral Autoregulation Research N.** Transfer function analysis of dynamic cerebral autoregulation: A white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab* 36: 665-680, 2016.

12. **Favre ME, and Serrador JM.** Sex differences in cerebral autoregulation are unaffected by menstrual cycle phase in young, healthy women. *Am J Physiol Heart Circ Physiol* 316: H920-H933, 2019.

13. **Ichikawa D, Miyazawa T, Horiuchi M, Kitama T, Fisher JP, and Ogoh S.** Relationship between aerobic endurance training and dynamic cerebral blood flow regulation in humans. *Scand J Med Sci Sports* 23: e320-329, 2013.

14. **Ivey FM, Ryan AS, Hafer-Macko CE, and Macko RF.** Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. *Stroke* 42: 1994-2000, 2011.
15. Kim YS, Immink RV, Stok WJ, Karemaker JM, Secher NH, and van Lieshout JJ. Dynamic cerebral autoregulatory capacity is affected early in Type 2 diabetes. *Clin Sci (Lond)* 115: 255-262, 2008.

16. Labrecque L, Rahimaly K, Imhoff S, Paquette M, Le Blanc O, Malenfant S, Drapeau A, Smirl JD, Bailey DM, and Brassard P. Dynamic cerebral autoregulation is attenuated in young fit women. *Physiol Rep* 7: e13984, 2019.

17. Labrecque L, Rahimaly K, Imhoff S, Paquette M, Le Blanc O, Malenfant S, Lucas SJE, Bailey DM, Smirl JD, and Brassard P. Diminished dynamic cerebral autoregulatory capacity with forced oscillations in mean arterial pressure with elevated cardiorespiratory fitness. *Physiol Rep* 5: 2017.

18. Laursen PB, and Jenkins DG. The scientific basis for high-intensity interval training: optimising training programmes and maximising performance in highly trained endurance athletes. *Sports Med* 32: 53-73, 2002.

19. Lee DC, Sui X, Ortega FB, Kim YS, Church TS, Winett RA, Ekelund U, Katzmarzyk PT, and Blair SN. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *Br J Sports Med* 45: 504-510, 2011.

20. Lewis N, Gelinas JCM, Ainslie PN, Smirl JD, Agar G, Melzer B, Rolf JD, and Eves ND. Cerebrovascular function in patients with chronic obstructive pulmonary disease: the impact of exercise training. *Am J Physiol Heart Circ Physiol* 316: H380-H391, 2019.
21. Lewis NC, Smith KJ, Bain AR, Wildfong KW, Numan T, and Ainslie PN. Impact of transient hypotension on regional cerebral blood flow in humans. *Clin Sci (Lond)* 129: 169-178, 2015.

22. Lind-Holst M, Cotter JD, Helge JW, Boushel R, Augustesen H, Van Lieshout JJ, and Pott FC. Cerebral autoregulation dynamics in endurance-trained individuals. *J Appl Physiol (1985)* 110: 1327-1333, 2011.

23. Lucas SJ, Cotter JD, Brassard P, and Bailey DM. High-intensity interval exercise and cerebrovascular health: curiosity, cause, and consequence. *J Cereb Blood Flow Metab* 35: 902-911, 2015.

24. MacInnis MJ, and Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *J Physiol* 595: 2915-2930, 2017.

25. Malenfant S, Brassard P, Paquette M, Le Blanc O, Chouinard A, Nadeau V, Allan PD, Tzeng YC, Simard S, Bonnet S, and Provencher S. Compromised Cerebrovascular Regulation and Cerebral Oxygenation in Pulmonary Arterial Hypertension. *J Am Heart Assoc* 6: 2017.

26. Murrell CJ, Cotter JD, Thomas KN, Lucas SJ, Williams MJ, and Ainslie PN. Cerebral blood flow and cerebrovascular reactivity at rest and during sub-maximal exercise: effect of age and 12-week exercise training. *Age (Dordr)* 35: 905-920, 2013.

27. Northey JM, Pumpa KL, Quinlan C, Ikin A, Toohey K, Smee DJ, and Rattray B. Cognition in breast cancer survivors: A pilot study of interval and continuous exercise. *J Sci Med Sport* 2018.
28. **Omboni S, Parati G, Frattola A, Mutti E, Di Rienzo M, Castiglioni P, and Mancia G.** Spectral and sequence analysis of finger blood pressure variability. Comparison with analysis of intra-arterial recordings. *Hypertension* 22: 26-33, 1993.

29. **Paquette M, Le Blanc O, Lucas SJ, Thibault G, Bailey DM, and Brassard P.** Effects of submaximal and supramaximal interval training on determinants of endurance performance in endurance athletes. *Scand J Med Sci Sports* 27: 318-326, 2017.

30. **Phillips AA, Matin N, Jia M, Squair JW, Monga A, Zheng MMZ, Sachdeva R, Yung A, Hocaloski S, Elliott S, Kozlowski P, Dorrance AM, Laher I, Ainslie PN, and Krassioukov AV.** Transient Hypertension after Spinal Cord Injury Leads to Cerebrovascular Endothelial Dysfunction and Fibrosis. *J Neurotrauma* 35: 573-581, 2018.

31. **Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, and Coombes JS.** The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med* 45: 679-692, 2015.

32. **Sammons EL, Samani NJ, Smith SM, Rathbone WE, Bentley S, Potter JF, and Panerai RB.** Influence of noninvasive peripheral arterial blood pressure measurements on assessment of dynamic cerebral autoregulation. *J Appl Physiol (1985)* 103: 369-375, 2007.

33. **Serrador JM, Picot PA, Rutt BK, Shoemaker JK, and Bondar RL.** MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* 31: 1672-1678, 2000.

34. **Smirl JD, Hoffman K, Tzeng YC, Hansen A, and Ainslie PN.** Methodological comparison of active- and passive-driven oscillations in blood pressure; implications for
the assessment of cerebral pressure-flow relationships. *J Appl Physiol (1985)* 119: 487-501, 2015.

35. **Smith KJ, and Ainslie PN.** Regulation of cerebral blood flow and metabolism during exercise. *Exp Physiol* 102: 1356-1371, 2017.

36. **Tarumi T, and Zhang R.** Cerebral blood flow in normal aging adults: cardiovascular determinants, clinical implications, and aerobic fitness. *J Neurochem* 144: 595-608, 2018.

37. **Thomas BP, Yezhuvath US, Tseng BY, Liu P, Levine BD, Zhang R, and Lu H.** Life-long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO2. *J Magn Reson Imaging* 38: 1177-1183, 2013.

38. **Weston M, Taylor KL, Batterham AM, and Hopkins WG.** Effects of low-volume high-intensity interval training (HIT) on fitness in adults: a meta-analysis of controlled and non-controlled trials. *Sports Med* 44: 1005-1017, 2014.

39. **Willie CK, Colino FL, Bailey DM, Tzeng YC, Binsted G, Jones LW, Haykowsky MJ, Bellapart J, Ogoh S, Smith KJ, Smirl JD, Day TA, Lucas SJ, Eller LK, and Ainslie PN.** Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. *J Neurosci Methods* 196: 221-237, 2011.

40. **Willie CK, Tzeng YC, Fisher JA, and Ainslie PN.** Integrative regulation of human brain blood flow. *J Physiol* 592: 841-859, 2014.

41. **Zhang RZ, J. H.; Giller, C.A.; Levine, B. D.** Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol* 274: H233-H241, 1998.
### Table 1: Resting systemic and cerebral hemodynamics at baseline and post-training

| Group | HIIT$_{85}$ | HIIT$_{115}$ | P values |
|-------|-------------|--------------|----------|
|       | Pre         | Post         | Pre      | Post      | Intensity | Time | Interaction |
| Time  |             |              |          |           |           |      |             |
| **Systemic measurements** |             |              |          |           |           |      |             |
|       | 8           | 8            | 9        | 9         |           |      |             |
| HR (bpm) | 59 ± 9      | 54 ± 8       | 55 ± 8   | 53 ± 7    | 0.51      | 0.02 | 0.17        |
| MAP (mmHg) | 76 ± 8      | 76 ± 14      | 80 ± 10  | 85 ± 9    | 0.08      | 0.51 | 0.44        |
| **Cerebral measurements** |             |              |          |           |           |      |             |
|       | 6           | 6            | 5        | 5         |           |      |             |
| $P_{ETCO_2}$ (mmHg) | 44 ± 5      | 46 ± 3       | 45 ± 3   | 47 ± 2    | 0.45      | 0.12 | 0.92        |
| **Cerebrovascular conductance index** (cm/sec/mmHg) | 0.86 ± 0.20 | 0.89 ± 0.16 | 0.80 ± 0.15 | 0.78 ± 0.16 | 0.10 | 0.56 | 0.87 |
| **Cerebrovascular resistance index** (cm/sec/mmHg) | 1.12 ± 0.20 | 1.17 ± 0.20 | 1.30 ± 0.24 | 1.34 ± 0.28 | 0.09 | 0.50 | 0.87 |

Values are mean ± standard deviation
HR: Heart rate; MAP: Mean arterial pressure; $P_{ETCO_2}$: end-tidal partial pressure of carbon dioxide; MCAv$_{mean}$: Middle cerebral arterial mean blood velocity; CVCi: Cerebrovascular conductance index; CVRi: Cerebrovascular resistance index
Table 2: Power spectrum densities and change in end-tidal partial pressure of carbon dioxide during forced oscillations in mean arterial pressure and middle cerebral artery blood velocity during squat-stand maneuvers

| Groupe     | HIIT<sub>85</sub> | HIIT<sub>115</sub> |     |     |     |     |     |
|------------|------------------|------------------|-----|-----|-----|-----|-----|
| Time       | Pre   | Post  | Pre | Post | Intensity | Time | Interaction |
| Squats 0.05 Hz |       |       |     |      |     |     |     |
| N          | 8     | 8     | 9   | 9    |     |     |     |
| MAP power (mmHg<sup>2</sup>) | 19424 ± 19255 | 18644 ± 19614 | 10814 ± 7845 | 14325 ± 13938 | 0.41 | 0.65 | 0.48 |
| MCAv power (cm/s<sup>2</sup>) | 9217 ± 13070 | 8936 ± 13572 | 5203 ± 3539 | 6488 ± 9749 | 0.55 | 0.76 | 0.63 |
| N          | 6     | 3     | 6   | 3    |     |     |     |
| P<sub>eTP</sub>CO<sub>2</sub> (Δ mmHg) | -2 ± 3 | -2 ± 4 | 2 ± 1 | 1 ± 2 | 0.26 | 0.16 | 0.31 |
| Squats 0.10 Hz |       |       |     |      |     |     |     |
| N          | 8     | 8     | 9   | 9    |     |     |     |
| MAP power (mmHg<sup>2</sup>) | 16130 ± 13640 | 15895 ± 15144 | 14281 ± 10764 | 14510 ± 12134 | 0.80 | 1.00 | 0.91 |
| MCAv power (cm/s<sup>2</sup>) | 9715 ± 8263 | 8682 ± 8416 | 7966 ± 5059 | 9208 ± 8806 | 0.88 | 0.94 | 0.39 |
| N          | 6     | 3     | 6   | 3    |     |     |     |
| P<sub>eTP</sub>CO<sub>2</sub> (Δ mmHg) | 1 ± 4 | 1 ± 2 | 3 ± 2 | 3 ± 4 | 0.18 | 0.99 | 0.77 |

Values are mean ± standard deviation
HR: Heart rate; MAP: Mean arterial pressure; MCAv: Middle cerebral artery blood velocity; P<sub>eTP</sub>CO<sub>2</sub>: end-tidal partial pressure of carbon dioxide
FIGURE CAPTIONS

Figure 1  Transfer function analysis of forced oscillation in mean arterial pressure and middle cerebral artery blood velocity. Group averaged coherence, gain, normalized gain (nGain) and phase for 0.05 and 0.10 Hz repeated squat-stands.
Figure 1