# **Physiological** Reports

### ORIGINAL RESEARCH

# Six weeks of high-intensity interval training to exhaustion attenuates dynamic cerebral autoregulation without influencing resting cerebral blood velocity in young fit men

Audrey Drapeau<sup>1,2</sup>, Lawrence Labrecque<sup>1,2</sup>, Sarah Imhoff<sup>1,2</sup>, Myriam Paquette<sup>1,2</sup>, Olivier Le Blanc<sup>1,2</sup>, Simon Malenfant<sup>1,2</sup> & Patrice Brassard<sup>1,2</sup>

1 Department of Kinesiology, Faculty of Medicine, Université Laval, Québec, Canada

2 Research Center of the Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada

#### Keywords

Aerobic fitness, exercise intensity, cerebral blood flow, cerebral pressure-flow relationship, transfer function analysis.

#### Correspondence

Patrice Brassard, Department of Kinesiology, Faculty of Medicine, PEPS - Université Laval, 2300 rue de la Terrasse, room 0290-H, Québec (Qc) GIV 0A6, Canada. Tel: 418 656-2131 extension 405621 Fax: 418 656-4537 E-mail: patrice.brassard@kin.ulaval.ca

#### **Funding information**

Funding of the current project came from the Ministère de l'Éducation, du Loisir et du Sport du Québec and the Fundation of the Institut Universitaire de Cardiologie et Pneumologie de Québec. A scholarship was granted to Myriam Paquette from the Canadian Institutes of Health Research. The Société Québécoise d'Hypertension Artérielle supported LL with a doctoral scholarship and SI has her doctoral training supported by the Fonds de recherche du Québec - Santé.

Received: 27 June 2019; Revised: 12 June 2019; Accepted: 30 June 2019

doi: 10.14814/phy2.14185

Physiol Rep, 7 (15), 2019, e14185, https://doi.org/10.14814/phy2.14185

# Introduction

Established evidence show that cardiorespiratory fitness (CRF) is more cardioprotective when compared with overall physical activity levels (Lee et al., 2011). CRF-related benefits are not confided to the cardiovascular function and rather extend to the cerebrovascular system

#### 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 remains 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<sub>85</sub> (85% of maximal aerobic power, 1-7 min effort bouts, n = 8) and HIIT<sub>115</sub> (115% of maximal aerobic power, 30 sec 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 (MCAv<sub>mean</sub>) 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 MCAv<sub>mean</sub> (both P > 0.05). TFA phase during 0.10 Hz squat-stands decreased after HIIT irrespective of intensity (HIIT<sub>85</sub>:  $0.77 \pm 0.22$  vs.  $0.67 \pm 0.18$  radians; HIIT<sub>115</sub>: pre:  $0.62 \pm 0.19$  vs. post:  $0.59 \pm 0.13$  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 posttraining irrespective of intensity training in endurance-trained men.

> (Lucas et al., 2015; Tarumi and Zhang, 2018). For instance, aerobic exercise training alters favorably cerebrovascular health in varying clinical conditions ranging from chronic obstructive pulmonary disease (Lewis et al., 2019), cognitive impairments (Alfini et al., 2019), stroke (Ivey et al., 2011) and following cancer (Northey et al., 2019). Evidence show that life-long aerobic training

This is an open access article under the terms of the Creative Commons Attribution License.

<sup>© 2019</sup> The Authors. Physiological Reports published by Wiley Periodicals, Inc. on behalf of

The Physiological Society and the American Physiological Society.

which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

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 (MCAv<sub>mean</sub>) (Ainslie et al., 2008; Bailey et al., 2013), and in the posterior circulation (as indexed by arterial spin labeling in posterior cingular cortex/precuneus) (Thomas et al., 2013) and higher extracranial blood flow (as indexed by carotid Doppler) (Braz et al., 2017) 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 MCAvmean responses at rest (Murrell et al., 2013). 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 (Ainslie and Duffin, 2009; Willie et al., 2014; Smith and Ainslie, 2017). Among these regulatory mechanisms, dynamic cerebral autoregulation (dCA), that is, 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 (Aaslid et al., 1989). However, the influence of CRF on dCA remains equivocal. Indeed, while some investigators reported no noticeable differences in dCA between endurance-trained individuals (Ichikawa et al., 2013) or Masters athletes (Aengevaeren et al., 2013) with untrained individuals, our research group (Labrecque et al., 2017) and others (Lind-Holst et al., 2011) 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 (Lewis et al., 2019).

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) (Laursen and Jenkins, 2002). HIIT is defined as short bursts of exercise ≥80% of maximal heart rate (HR) alternating with periods of recovery or light exercise (Weston et al., 2014). 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) (Lucas et al., 2015; Ramos et al., 2015; Batacan et al., 2017; MacInnis and Gibala, 2017). Different HIIT protocols are used by athletes, such as submaximal training below maximal oxygen consumption (VO<sub>2max</sub>), training at VO<sub>2max</sub> and supramaximal training (power output above

 $VO_{2max}$ ). Our research group compared two of these HIIT protocols, and recently reported that endurancetrained men performing 6 weeks of submaximal (85% maximal aerobic power) and supramaximal (115% maximal aerobic power) HIIT to exhaustion improve significantly  $VO_{2max}$  and anaerobic power irrespective of training intensity (Paquette et al., 2017). However, the knowledge about concurrent cerebrovascular adaptations specific to HIIT conducted at different training intensities remains limited in healthy humans (Lucas et al., 2015).

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 extend 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 training history of 5–12 h/week for at least 2 years. All participants were free from any diagnosed medical conditions. They showed a normal ECG, did not take any medication and were free from any cardiovascular or cerebrovascular 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) (Paquette et al., 2017).

### **Experimental protocol**

This study was part of a larger study examining the influence of submaximal and supramaximal training on determinants of endurance performance (Paquette et al., 2017). 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 postvalues collected on three visits: (1) anthropometrics, resting systemic and cerebral hemodynamic measurements and the evaluation of dCA (2) incremental cycling test for determination of  $VO_{2max}$ , 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 pretraining  $VO_{2max}$ , they were randomly assigned to two different intensity training groups; 85% of maximal aerobic power (HIIT<sub>85</sub>) and 115% of maximal aerobic power (HIIT<sub>115</sub>). The posttraining 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<sub>85</sub> group performed repeated 1- to 7-min effort bouts. The intensity was set to 85% of maximal aerobic power. The other experimental group, HIIT<sub>115</sub>, repeated 30-sec 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 (Paquette et al., 2017). 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<sub>115</sub> group compared to HIIT<sub>85</sub> (19.3  $\pm$  4.7 vs. 36.6  $\pm$  14.4 min/session; P = 0.005) (Paquette et al., 2017). For further details on the training interventions, refer to (Paquette et al., 2017).

### 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 (MAP). 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 intraarterial BP recordings (Omboni et al., 1993; Sammons et al., 2007).

### Middle cerebral artery blood velocity

A transcranial Doppler ultrasound was used at a frequency of 2-MHz pulsed to monitor  $MCAv_{mean}$  (Doppler Box; Compumedics DWL USA, Inc. San Juan Capistrano, CA). A standardized procedure (Willie et al., 2011) 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 posttraining 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 ( $P_{ET}CO_2$ ) 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 (Powerlab 16/30 ML880; ADInstruments, Colorado Springs, CO, USA) converted and stored at 1 kHz 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 $\nu_{mean}$  (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 (CVCi; MCA $\nu_{mean}$ /MAP) and its reciprocal, resistance (CVRi; MAP/MCA $\nu_{mean}$ ) were then calculated. Baseline data were averaged over the last 3 min of the resting period, except

recordings of  $P_{ET}CO_2$  which were averaged over the last 2 min of the resting period.

### Assessment of dynamic cerebral autoregulation

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 MCAv signals (Smirl et al., 2015). 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 ~90° 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. Then, over a period of 5 min, squat-stand maneuvers were repeated at a frequency of 0.05 Hz (10 sec squat, 10 sec standing) and 0.10 Hz (5 sec squat, 5 sec standing) (Smirl et al., 2015; Labrecque et al., 2017; Labrecque et al., 2019). Large oscillations in MAP are extensively buffered by the cerebral vessels when performed at frequencies within the high-pass filter buffering range (<0.20 Hz) (Zhang et al., 1998). The repeated squat-stands increase the signal-to-noise ratio, which enhance the reproducibility and interpretability of results through a physiologically relevant MAP stimulus to cerebral vessels. 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<sub>mean</sub>, and P<sub>ET</sub>CO<sub>2</sub> 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 P<sub>ET</sub>CO<sub>2</sub>, an averaged P<sub>ET</sub>CO<sub>2</sub> of the first and last five breaths of each maneuver (0.05 and 0.10 Hz) were calculated (Labrecque et al., 2019).

# Assessment of the dynamic relationship between MAP and MCAv

The recommendations of the Cerebral Autoregulation Research Network (CARNet) (Claassen et al., 2016) were followed when analyzing data using the commercially available software Ensemble (Version 1.0.0.14, Elucimed, Wellington, New Zealand). The spectral analysis of beatto-beat MAP and MCAv signals was interpolated and resampled 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 per 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 estimates 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 (Smirl et al., 2015). A threshold of 0.50 of coherence was necessary to ensure robustness of the phase and gain subsequent analysis (Zhang et al., 1998). When coherence exceeded the threshold, phase wraparound was not present.

### Visit 2

#### Maximal oxygen consumption (VO<sub>2max</sub>)

 $VO_{2max}$  was determined during a progressive ramp exercise test executed on an electromagnetically braked upright cycle ergometer (Corival, Lode, the Netherlands) (Paquette et al., 2017). 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 sec averaged  $VO_2$ , concurrent with a respiratory exchange ratio  $\geq 1.15$  was used to define  $VO_{2max}$  (Paquette et al., 2017).

### 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 (Paquette et al., 2017).

### **Statistical analysis**

The Shapiro–Wilk test was used to confirm normal distribution of data. When normal distribution was confirmed, differences (within-subject factor: Time: Pre vs. Posttraining; between subject factor: Group:  $HIIT_{85}$  vs.  $HIIT_{115}$ ) were analyzed using a two-way repeated measure analysis of variance (ANOVA). 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 Group), 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 of 19 participants completed the study; HIIT<sub>85</sub>: 26  $\pm$  6 years, 1.77  $\pm$  0.08 m, 72.1  $\pm$  12.0 kg, n = 8 and HIIT<sub>115</sub>: 28 ± 6 years, 1.77 ± 0.09 m,  $73.1 \pm 7.5$  kg, n = 9. We excluded two participants from our final analysis; one participant in HIIT<sub>85</sub> was ill and absent >3 training sessions and the other participant in HIIT<sub>115</sub> complained from excessive fatigue during training regime. Excessive noise/artifact in the recordings of two participants (HIIT<sub>85</sub>, n = 1; HIIT<sub>115</sub>, n = 1), did not allow for TFA measurements, therefore a total of 15 participants were included in the dCA analysis. Of note, we excluded pretraining values of MCAv, CVCi, and CVRi of one participant because blood velocity could not be identified with certainty as a MCAv as compared to reference values (Willie et al., 2011). Also, due to technical reasons (malfunction of the gas exchange analyzer),  $P_{ET}CO_2$ recordings of only 11 participants were completed during

baseline rest, 12 participants during pretraining squat-stands and six participants posttraining.

# Anthropometric measurements and resting hemodynamics

As previously reported by our research group, 6 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  $VO_{2max}$  in both groups after 6 weeks, demonstrating that the selected training program effectively increased CRF irrespective of intensity (HIIT<sub>85</sub> pre:  $56.0 \pm 6.0$  vs. post:  $59.3 \pm 4.7$  mL/kg per min; HIIT<sub>115</sub> pre:  $55.9 \pm 4.0$  vs. post  $59.2 \pm 1.1$  mL/kg per min, time effect P = 0.002) (Paquette et al., 2017).

Concurrently, resting heart rate significantly decreased after training irrespective of intensity (by 8% in HIIT<sub>85</sub> and 5% in HIIT<sub>115</sub>, 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<sub>mean</sub> (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 posttraining) (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; Fig. 1). TFA gain and coherence

Group Time	HIIT <sub>85</sub>		HIIT <sub>115</sub>		P values		
	Pre	Post	Pre	Post	Group	Time	Interaction
Systemic measurements							
Ν	8	8	9	9			
HR (bpm)	$59 \pm 9$	$54 \pm 8$	$55 \pm 8$	$53 \pm 7$	0.51	0.02	0.17
MAP (mmHg)	$76 \pm 8$	$76 \pm 14$	$80 \pm 10$	$85 \pm 9$	0.08	0.51	0.44
Ν	6	6	5	5			
P <sub>ET</sub> CO <sub>2</sub> (mmHg)	$44 \pm 5$	46 ± 3	$45 \pm 3$	47 ± 2	0.45	0.12	0.92
Cerebral measurements							
Ν	7	8	9	9			
MCAv <sub>mean</sub> (cm/sec)	68 ± 9	66 ± 10	63 ± 10	66 ± 11	0.55	0.93	0.40
CVCi (cm/sec per mmHg)	0.86 ± 0.20	$0.89 \pm 0.16$	$0.80 \pm 0.15$	0.78 ± 0.16	0.10	0.56	0.87
CVRi (cm/sec per mmHg)	$1.12 \pm 0.20$	$1.17 \pm 0.20$	1.30 ± 0.24	$1.34 \pm 0.28$	0.09	0.50	0.87

Values are mean  $\pm$  standard deviation. HR, heart rate; MAP, mean arterial pressure;  $P_{ET}CO_2$ , end-tidal partial pressure of carbon dioxide; MCAv<sub>mean</sub>, middle cerebral artery 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

Group Time	HIIT <sub>85</sub>		HIIT <sub>115</sub>		P values		
	Pre	Post	Pre	Post	Group	Time	Interaction
Squats 0.05 Hz							
N	8	8	9	9			
MAP power (mmHg <sup>2</sup> )	$19424 \pm 19255$	18644 ± 19614	$10814 \pm 7845$	14325 ± 13938	0.41	0.65	0.48
MCAv power (cm/s <sup>2</sup> )	$9217 \pm 13070$	8936 ± 13572	$5203 \pm 3539$	$6488 \pm 9749$	0.55	0.76	0.63
Ν	6	3	6	3			
$P_{ET}CO_2$ ( $\Delta$ mmHg)	$-2 \pm 3$	$-2 \pm 4$	2 ± 1	$1 \pm 2$	0.26	0.16	0.31
Squats 0.10 Hz							
Ν	8	8	9	9			
MAP power (mmHg <sup>2</sup> )	$16130 \pm 13640$	$15895 \pm 15144$	$14281 \pm 10764$	$14510 \pm 12134$	0.80	1.00	0.91
MCAv power (cm/s <sup>2</sup> )	$9715 \pm 8263$	$8682 \pm 8416$	$7966 \pm 5059$	$9208\pm8806$	0.88	0.94	0.39
Ν	6	3	6	3			
$P_{ET}CO_2$ ( $\Delta$ mmHg)	1 ± 4	1 ± 2	$3 \pm 2$	$3 \pm 4$	0.18	0.99	0.77

Values are mean  $\pm$  standard deviation. MAP, mean arterial pressure; MCAv, middle cerebral artery blood velocity;  $P_{ET}CO_2$ , end-tidal partial pressure of carbon dioxide.

were unaffected by training or intensity during repeated squat-stands at both frequencies (all P > 0.05). Averaged P<sub>FT</sub>CO<sub>2</sub> over the whole period of each repeated squat-stands did not vary significantly when compared between pre and posttraining states at 0.05 Hz (HIIT<sub>85</sub> 43  $\pm$ 7 mmHg (n = 6) vs. 44 ± 0.2 mmHg (n = 2) and HIIT<sub>115</sub>:  $44 \pm 4 \text{ mmHg}$  (*n* = 5) vs.  $46 \pm 3 \text{ mmHg}$ (n = 3); group effect P = 0.630, time effect P = 0.284, interaction effect P = 0.920) and at 0.10 Hz (HIIT<sub>85</sub> 43  $\pm$ 8 mmHg (n = 6) vs. 46 ± 2 mmHg (n = 2) and HIIT<sub>115</sub>:  $45 \pm 4 \text{ mmHg} (n = 6) \text{ vs. } 46 \pm 3 \text{ mmHg} (n = 3); \text{ group}$ effect P = 0.644, time effect P = 0.422, interaction effect P = 0.778). Furthermore, there were no significant changes in P<sub>ET</sub>CO<sub>2</sub> from the beginning of repeated squats-stands at both frequencies and were comparable between groups and time (pre vs. posttraining; 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  $MCAv_{mean}$  remained unchanged following 6 weeks of submaximal or supramaximal HIIT to

exhaustion. Our results differ from cross-sectional studies assessing life-long training effect that reported elevated resting MCAv<sub>mean</sub> (Ainslie et al., 2008; Bailey et al., 2013) and regional CBF in the posterior cingular cortex (Thomas et al., 2013) in elderly trained participants. Longitudinally, short-term aerobic exercise of varied nature (continuous or interval training), intensity and duration [12 weeks (Murrell et al., 2013; Alfini et al., 2019) and 8 weeks (Lewis et al., 2019)] 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 MCAvmean following a 12-week program (Murrell et al., 2013), whereas others did not observe any change in MCAv<sub>mean</sub> (Lewis et al., 2019) or whole-brain CBF (Alfini et al., 2019) 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 (Lucas et al., 2015). Considering that it has been argued that the brain vasculature needs to be challenged in order to witness adaptive changes in cerebral hemodynamics (Brugniaux et al., 2014), our results do not rule out a potential influence of HIIT on CBF changes during aerobic exercise.



Figure 1. Transfer function analysis of forced oscillations 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.

# Effect of HIIT on dynamic cerebral autoregulation

We have previously demonstrated cross-sectionally that dCA is impaired in endurance-trained men with elevated CRF when compared with untrained controls (Labrecque et al., 2017). In that report, we showed that elevated CRF was associated with increased TFA gain during 0.10 Hz squat-stands, suggesting a subtle attenuation in dCA. In this 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 posttraining P > 0.05), but rather decreased TFA phase during repeated squat-stands at 0.10 Hz, irrespective of training intensity.

Therefore, these results suggest that when endurancetrained men with already elevated  $VO_{2max}$  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 (Labrecque et al., 2017)] through a reduction in TFA phase. It is possible that training did not affect dCA variables when forced oscillations of MAP and cerebral blood velocity were slower (0.05 Hz), but rather only had an impact when forced oscillations were faster at 0.10 Hz. Considering this study was not designed to examine specific mechanisms, 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 (Lewis et al., 2019). 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 (26-28 years). These results support that elevated CRF is associated with diminished dCA, whereas dCA is maintained in individuals with lower CRF (Lewis et al., 2019). 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 (Phillips et al., 2018). Unfortunately, we did not monitor BP changes during our HIIT sessions. 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 coupled with a lack of time control and a possible influence of training volume. 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 in MAP and P<sub>ET</sub>CO<sub>2</sub> that could impact on the diameter of the artery (Ainslie and Hoiland, 2014). The use of transcranial Doppler remains recognized to provide excellent temporal resolution and has been validated as an indirect surrogate marker of CBF (Serrador et al., 2000). We had technical issues when collecting data, which prevented us from quantifying P<sub>ET</sub>CO<sub>2</sub> in all participants. However, P<sub>ET</sub>CO<sub>2</sub> was monitored in several participants at rest before and following exercise training and no changes in P<sub>ET</sub>CO<sub>2</sub> were observed. Although further research is needed including more participants, these observations suggest that  $P_{ET}CO_2$ does not explain subtle dCA changes reported after exercise training. Finally, considering that sex (Labrecque et al., 2019; Favre and Serrador, 2019) and various clinical conditions such as type 2 diabetes and pulmonary arterial hypertension (Kim et al., 2008; Malenfant et al., 2017) 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.

# Acknowledgments

A special thank you to all the participants that agreed to perform our exhaustive training protocol. Without them,

the research could not have been done. We received special assistance from Louis-Charles B. Lacroix and Andrée-Anne Clément, who supervised the training sessions. We are grateful for Cycle Lambert who generously lended us the home trainers Tacx Bushido.

# **Author Contributions**

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

# **Conflict of interest**

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

### References

- Aaslid, R., K. F. Lindegaard, W. Sorteberg, and H. Nornes. 1989. Cerebral autoregulation dynamics in humans. Stroke 20:45–52.
- Aengevaeren, V. L., J. A. Claassen, B. D. Levine, and R. Zhang. 2013. Cardiac baroreflex function and dynamic cerebral autoregulation in elderly Masters athletes. J. Appl. Physiol. 114:195–202.
- Ainslie, P. N., and J. Duffin. 2009. 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.
- Ainslie, P. N., and R. L. Hoiland. 2014. Transcranial Doppler ultrasound: valid, invalid, or both? J. Appl. Physiol. 117:1081–1083.
- Ainslie, P. N., J. D. Cotter, K. P. George, S. Lucas, C. Murrell, R. Shave, et al. 2008. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. J. Physiol. 586:4005–4010.
- Alfini, A. J., L. R. Weiss, K. A. Nielson, M. D. Verber, and J. C. Smith.2019. Resting cerebral blood flow after exercise training in mild cognitive impairment. J. Alzheimers Dis. 67:671–684.

Bailey, D. M., C. J. Marley, J. V. Brugniaux, D. Hodson, K. J. New, S. Ogoh, and P. N. Ainslie. 2013. Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. Stroke 44:3235– 3238.

Batacan, R. B. Jr, M. J. Duncan, V. J. Dalbo, P. S. Tucker, and A. S. Fenning. 2017. 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.

- Braz, I. D., D. Fluck, G. Y. H. Lip, C. Lundby, and J. P. Fisher. 2017. 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.
- Brugniaux, J. V., C. J. Marley, D. A. Hodson, K. J. New, and D. M. Bailey. 2014. Acute exercise stress reveals cerebrovascular benefits associated with moderate gains in cardiorespiratory fitness. J. Cereb. Blood Flow. Metab. 34:1873–1876.
- Claassen, J. A., A. S. Meel-van den Abeelen, D. M. Simpson, R. B. Panerai, and International Cerebral Autoregulation Research Network (CARNet). 2016. 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.
- Favre, M. E., and J. M. Serrador.2019. Sex differences in cerebral autoregulation are unaffected by menstrual cycle phase in young, healthy women. Am. J. Physiol. Heart Circ. Physiol. 316:H920–H933.
- Ichikawa, D., T. Miyazawa, M. Horiuchi, T. Kitama, J. P. Fisher, and S. Ogoh. 2013. Relationship between aerobic endurance training and dynamic cerebral blood flow regulation in humans. Scand. J. Med. Sci. Sports 23:e320–e329.
- Ivey, F. M., A. S. Ryan, C. E. Hafer-Macko, and R. F. Macko. 2011. Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. Stroke 42:1994– 2000.
- Kim, Y. S., R. V. Immink, W. J. Stok, J. M. Karemaker, N. H. Secher, and J. J. van Lieshout. 2008. Dynamic cerebral autoregulatory capacity is affected early in Type 2 diabetes. Clin. Sci. (Lond) 115:255–262.
- Labrecque, L., K. Rahimaly, S. Imhoff, M. Paquette, O. Le Blanc, S. Malenfant, S. J. E. Lucas, D. M. Bailey, J. D. Smirl, and P. Brassard. 2017 Diminished dynamic cerebral autoregulatory capacity with forced oscillations in mean arterial pressure with elevated cardiorespiratory fitness. Physiol. Rep. 5: pii: e13486.
- Labrecque, L., K. Rahimaly, S. Imhoff, M. Paquette, O. Le Blanc, S. Malenfant, et al. 2019. Dynamic cerebral autoregulation is attenuated in young fit women. Physiol. Rep. 7:e13984.
- Laursen, P. B., and D. G. Jenkins. 2002. The scientific basis for high-intensity interval training: optimising training programmes and maximising performance in highly trained endurance athletes. Sports Med. 32:53–73.
- Lee, D. C., X. Sui, F. B. Ortega, Y. S. Kim, T. S. Church, R. A. Winett, et al. 2011. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of allcause mortality in men and women. Br. J. Sports Med. 45:504–510.

Lewis, N., J. C. M. Gelinas, P. N. Ainslie, J. D. Smirl, G. Agar, B. Melzer, et al. 2019. Cerebrovascular function in patients with chronic obstructive pulmonary disease: the impact of exercise training. Am. J. Physiol. Heart Circ. Physiol. 316: H380–H391.

Lind-Holst, M., J. D. Cotter, J. W. Helge, R. Boushel, H. Augustesen, J. J. Van Lieshout, et al. 2011. Cerebral autoregulation dynamics in endurance-trained individuals. J. Appl. Physiol. 110:1327–1333.

Lucas, S. J., J. D. Cotter, P. Brassard, and D. M. Bailey. 2015. High-intensity interval exercise and cerebrovascular health: curiosity, cause, and consequence. J. Cereb. Blood Flow. Metab. 35:902–911.

MacInnis, M. J., and M. J. Gibala. 2017. Physiological adaptations to interval training and the role of exercise intensity. J. Physiol. 595:2915–2930.

Malenfant, S., P. Brassard, M. Paquette, O. Le Blanc, A.Chouinard, V. Nadeau, P. D. Allan, Y. C. Tzeng, S. Simard,S. Bonnet, and Provencher S. 2017. Compromisedcerebrovascular regulation and cerebral oxygenation inpulmonary arterial hypertension. J. Am. Heart Assoc. 6:pii:e006126.

Murrell, C. J., J. D. Cotter, K. N. Thomas, S. J. Lucas, M. J. Williams, and P. N. Ainslie. 2013. 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.

Northey, J. M., K. L. Pumpa, C. Quinlan, A. Ikin, K. Toohey, D. J. Smee, et al. 2019. Cognition in breast cancer survivors: a pilot study of interval and continuous exercise. J. Sci. Med. Sport 22:580–585.

Omboni, S., G. Parati, A. Frattola, E. Mutti, M. Di Rienzo, P. Castiglioni, et al. 1993. Spectral and sequence analysis of finger blood pressure variability. Comparison with analysis of intra-arterial recordings. Hypertension 22:26–33.

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

Phillips, A. A., N. Matin, M. Jia, J. W. Squair, A. Monga, M. M. Z. Zheng, et al. 2018. Transient hypertension after spinal cord injury leads to cerebrovascular endothelial dysfunction and fibrosis. J. Neurotrauma. 35:573–581.

Ramos, J. S., L. C. Dalleck, A. E. Tjonna, K. S. Beetham, and J. S. Coombes. 2015. 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.

Sammons, E. L., N. J. Samani, S. M. Smith, W. E. Rathbone, S. Bentley, J. F. Potter, et al. 2007. Influence of noninvasive peripheral arterial blood pressure measurements on assessment of dynamic cerebral autoregulation. J. Appl. Physiol. 103:369–375.

Serrador, J. M., P. A. Picot, B. K. Rutt, J. K. Shoemaker, and R. L. Bondar. 2000. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. Stroke 31:1672–1678.

Smirl, J. D., K. Hoffman, Y. C. Tzeng, A. Hansen, and P. N. Ainslie. 2015. Methodological comparison of active- and passive-driven oscillations in blood pressure; implications for the assessment of cerebral pressure-flow relationships. J. Appl. Physiol. 119:487–501.

Smith, K. J., and P. N. Ainslie. 2017. Regulation of cerebral blood flow and metabolism during exercise. Exp. Physiol. 102:1356–1371.

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

Thomas, B. P., U. S. Yezhuvath, B. Y. Tseng, P. Liu, B. D. Levine, R. Zhang, et al. 2013. Life-long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO2. J. Magn. Reson. Imaging. 38:1177–1183.

Weston, M., K. L. Taylor, A. M. Batterham, and W. G. Hopkins. 2014. 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.

Willie, C. K., F. L. Colino, D. M. Bailey, Y. C. Tzeng, G. Binsted, L. W. Jones, et al. 2011. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. J. Neurosci. Methods 196:221–237.

Willie, C. K., Y. C. Tzeng, J. A. Fisher, and P. N. Ainslie. 2014. Integrative regulation of human brain blood flow. J. Physiol. 592:841–859.

Zhang, R., J. H. Zuckerman, C. A. Giller, B. D. Levine. 1998. Transfer function analysis of dynamic cerebral autoregulation in humans. Am. J. Physiol. 274:H233–H241.