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Conflicts of interest: None

Running Title: Dynamic cerebral autoregulation and habitual exercise

What is the central question of this study?

Does habitual resistance and endurance exercise modify dynamic cerebral autoregulation?

What is the main finding and its importance?

To the authors' knowledge, this is the first study to directly assess dynamic cerebral autoregulation in resistance-trained individuals, and potential differences between exercise training modalities. Forced oscillations in blood pressure were induced by repeated squat-stands, from which dynamic cerebral autoregulation was assessed using transfer function analysis. These data indicate that dynamic cerebral autoregulatory function is largely unaffected by habitual exercise type, and further document the systemic circulatory effects of regular exercise.

Abstract

Regular endurance and resistance exercise produce differential but desirable physiological adaptations in both healthy and clinical populations. The chronic effect of these different exercise modalities on cerebral vessels' ability to respond to rapid changes in blood pressure (BP) had not been examined. We examined dynamic cerebral autoregulation (dCA) in 12 resistance-trained (mean±SD, 25±6 y), 12 endurance-trained (28±9 y), and 12 sedentary (26±6 y) volunteers. The dCA was assessed using transfer function analysis of forced oscillations in BP versus middle cerebral artery blood velocity (MCAv), induced via repeated squat-stands at 0.05 and 0.10 Hz. Resting BP and MCAv were similar between groups (interaction: both $P \geq 0.544$). The partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was unchanged ($P=0.561$) across squat-stand manoeuvres (grouped mean for absolute change +0.6±2.3 mm Hg). Gain and normalised gain were similar between groups across all frequencies (both $P \geq 0.261$). Phase showed a frequency-specific effect between groups ($P=0.043$), tending to be lower in resistance trained (0.63±0.21 radians) than in endurance trained (0.90±0.41, $P=0.052$) and untrained (0.85±0.38, $P=0.081$) at slower frequency (0.05 Hz) oscillations. Squat-stands induced MAP perturbations differed between groups (interaction: $P=0.031$), with greater changes in resistance ($P<0.001$) and endurance ($P=0.001$) compared with sedentary at 0.05 Hz (56±13 and 49±11 vs. 35±11 mm Hg, respectively). The differences persisted at 0.1 Hz between resistance and sedentary (49±12 vs. 33±7 mmHg, $P<0.001$). These results indicate that dCA remains largely unaltered by habitual endurance and resistance exercise with a trend for phase to be lower in the resistance exercise group at lower fequencies.

Introduction

The benefits of regular exercise have been documented extensively and the preventive medicinal capacity firmly established. It is now apparent that to maximise the potential benefits, a combination of exercise types should be undertaken (Garber et al., 2011). The physiological adaptations are type specific, with resistance exercise increasing muscular strength and mass (Kraemer, Deschenes, & Fleck, 1988), and endurance exercise exerting more influence on the heart, micro and macro vasculature, blood component volumes, and ultimately the maximal volume of oxygen consumption (Tomoto, Sugawara, Nogami, Aonuma, & Maeda, 2015). These alterations are driven in part by the acute haemodynamic response during exercise. Exercise has a complex and wide-ranging impact on the cardiovascular system, with adaptation in the regulation of many organ-specific circulations, including that of the brain (Ainslie et al., 2008; Murrell et al., 2013; Portugal et al., 2015).

Continuous aerobic exercise such as running and cycling, elicits minor elevations in mean arterial blood pressure (Palatini et al., 1989). This type of exercise is associated with increased central arterial compliance (Cameron & Dart, 1994; Tanaka et al., 2000), reductions in resting arterial blood pressure (Whelton, Chin, Xin, & He, 2002) and improved left ventricular function (Goodman, Liu, & Green, 2005). Despite these desirable physiological outcomes, endurance-trained athletes are more prone to syncope during orthostatic stress (Levine, Lane, Buckey, Friedman, & Blomqvist, 1991). Whether this response is partially due to a reduced capacity of the cerebral vasculature to defend against rapid changes in blood pressure (dynamic cerebral autoregulation, dCA) is equivocal. Following bilateral thigh cuff release-induced hypotension, endurance-trained individuals display a delayed cerebrovascular response with a larger transfer function analysis (TFA)-normalised gain compared to sedentary - indicative of less effective autoregulatory function (Lind-Holst et al., 2011). Ichikawa et al. (2013), using the same thigh cuff release method, demonstrated no difference in the slope of the linear regression line of cerebrovascular conductance index over time in the upright position – known as the rate of regulation. Notably, in the same study Ichikawa et al. reported that the rate of regulation was actually reduced in endurance trained individuals in the supine position. During forced oscillations in arterial blood pressure, induced by repeated squat-stand manoeuvres, it was found young male endurance athletes demonstrated an increased gain compared to sedentary individuals (Labrecque et al., 2017).

However, no change was observed in masters athletes compared with aged-matched sedentary individuals (Aengevaeren, Claassen, Levine, & Zhang, 2012) using the same squat-stand technique.

During dynamic resistance exercise, extreme, sinusoidal and intensity-dependent perturbations in arterial blood pressure can be incurred (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985). This intermittent hypertension has been suggested to produce several maladaptations, including a decrease in central arterial compliance (Kawano et al., 2008). Reductions in arterial compliance are observed immediately, and for at least 30 minutes following resistance exercise (DeVan et al., 2005), that persists at rest following 4 months of training (Miyachi et al., 2004). Reduced central arterial compliance increases pulse wave velocity, an independent risk factor for stroke and coronary artery disease (Mattace-Raso et al., 2006). These arterial blood pressure extremes easily exceed cerebral autoregulatory capacity (Edwards, Martin, & Hughson, 2002), evidenced by concomitant swings in middle cerebral artery blood velocity (MCAv) (Edwards et al., 2002; Perry et al., 2014), and reflect the high pass filter characteristics of the cerebral circulation (Diehl, Linden, Lücke, & Berlit, 1995). Due to the adaptations of central arteries to these marked perturbations in pressure, it is therefore plausible that cerebral arteries may also demonstrate similar chronic adaptation as illustrated by increases in middle cerebral artery (MCA) pulsatility in resistance trained individuals (Nakamura & Muraoka, 2018).

Given the potential for exercise to impact upon central artery function, distal circulations are also likely to be affected, evidenced by the adaptations seen in response to regular endurance exercise (Lucas, Cotter, Brassard, & Bailey, 2015). There is some evidence that endurance-trained individuals may develop lowered dCA compared with sedentary. Nonetheless, we are unaware of any data revealing the effects of regular resistance exercise on dCA. Therefore, this study investigated the effect of habitual resistance and endurance exercise on cerebral autoregulatory function.

Methods

Ethical approval

A total of 36 healthy individuals were recruited for the study, which was approved by the Massey University Human Ethics Committee (SOA 18/29) and the Comité d'éthique de la

recherche de l'Institut universtaire de cardiologie et de pneumologie de Québec-Université Laval (CER: 20869) and conducted in accordance with the Declaration of Helsinki (2013), apart from registration in a database. Written informed consent was obtained from all participants prior to involvement.

Participants

Resistance-trained (*n* = 12 males), endurance-trained (*n* = 12 males), and healthy sedentary individuals (*n* = 12, 3 females) partook in the study (see Table 1 for participant characteristics), after providing their written consent. Participants were not taking any medication (with the exception of oral contraception (all women)), were non-smokers, and had no history or symptoms of cardiovascular, pulmonary, metabolic, or neurological disease. Female participants were included in the sedentary group only (*n* =3) and were tested during the early follicular phase. Resistance-trained participants were identified as individuals who engaged in resistance exercise of any modality (Olympic, bodybuilding, powerlifting) for ≥ 30 minutes, ≥ 3 times per week for ≥ 6 months prior to their inclusion. Endurance-trained individuals were defined as individuals who participate in endurance training (excluding rowing) for ≥ 30 minutes, ≥ 3 times per week for ≥ 6 months. Rowers were excluded from participating as this exercise produces sinusoidal changes in MAP, and subsequently MCAv. This haemodynamic profile is similar to resistance exercise and is produced by repeated Valsalva manoeuvres (Faull, Cotter, & Lucas, 2015). It is therefore plausible that this may evoke similar cerebrovascular adaptions to resistance exercise and confound the results. Participants classified as sedentary did not engage in regular exercise (≤ 1 session per week of any exercise) for ≥ 6 months. Individuals that habitually participated in more than one exercise modality were excluded from the study.

Table 1. Participant information

Variables	Resistance	Endurance	Sedentary	*P*-value
Age (years)	25 ± 6	28 ± 9	26 ± 6	0.568
Height (cm)	178 ± 76	180 ± 10	174 ± 12	0.349
Mass (kg)	85 ± 13	74 ± 9	78 ± 16	0.176

Training variables for resistance and endurance cohorts are shown in Table 2. Peak oxygen consumption was measured in the endurance-trained and sedentary group (*n* = 8) only.

Previous training history was used to confirm inclusion into the resistance training group rendering the maximal exercise test superfluous and beyond the scope of this investigation. A maximal exercise test on an electronically braked cycle ergometer (Excalibur sport (endurance- trained group) and Corival (sedentary group), Lode B.V. The Netherlands) utilising a 25-W per minute ramp protocol was completed 4-7 days prior to participation. Respiratory gas exchange was measured using an online gas analysis system (K4b2, Cosmed, Italy (endurance-trained group) and Breezesuite, MedGraphics Corp., MN (sedentary group)). Criteria for achieving maximal aerobic capacity included: no change in oxygen consumption despite increasing workload; achieving within 10% of age-predicted heart rate max, and a respiratory exchange ratio ≥ 1.10. Peak relative oxygen consumption was 65 ± 10 mL · min^{-1}· kg^{-1} and 39 ± 5.0 mL · min^{-1}· kg^{-1} for the endurance-trained and sedentary groups respectively.

Table 2 Self-reported resistance and endurance groups training measurements

Variables	Resistance	Endurance	*P*-value
Training age (years)	6 ± 5	7 ± 9	0.851
Training frequency (per week)	5 ± 1	5 ± 2	0.396
Training session duration (min)	78 ± 20	80 ± 32	0.822

Study design

All participants visited the laboratory twice, once to receive a full familiarisation session of the experimental protocol, and once to undergo the experimental trial. During the familiarisation session all experimental procedures and equipment were explained and participants were familiarised with the squat-stand procedure. This included squatting to the metronome cadence, achieving a knee flexion angle of 45 degrees and avoiding the Valsalva manoeuvre. The experimental trial occurred >1 week following the familiarisation. Participants arrived at the laboratory for the experimental trial having refrained from caffeinated beverages for 12 hours, and vigorous exercise and alcohol consumption for ≥24 hours.

Experimental Design

Experimental design is outlined in Figure 1. Baseline data were recorded in the seated position for 2 min following 15 min of rest. The participant then stood for 1 min and then commenced the first bout of squat-stands. This method has been used previously to provide rhythmic and forced oscillations in mean arterial pressure (MAP) for the assessment of dCA (Claassen, Levine, & Zhang 2009, Labrecque et al. 2017). Oscillations of 0.05 Hz (20 s cycle –10 s squat, 10 s standing) and 0.10 Hz (10 s cycle – 5 s squat, 5 s standing) were timed by metronome. These large oscillations in MAP are extensively buffered by the cerebral vasculature when performed at frequencies within the high-pass filter buffering range (< 0.20 Hz (Zhang, Zuckerman, Giller, & Levine, 1998)). Repeated squat-stands optimizes the signal-to-noise ratio improving the reproducibility and interpretability of observations through a physiologically-relevant MAP stimulus to the cerebral vessels (Smirl, Hoffman, Tzeng, Hansen, & Ainslie, 2015). Participants were reminded throughout to avoid the Valsalva manoeuvre, confirmed by the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) trace. For each frequency, 5 min 30 s of data were collected, with the order randomised and separated by 5 min of seated recovery after ensuring all cardiovascular variables returned to baseline.

Measurements

MCAv was measured using a 2 MHz pulsed Doppler Ultrasound system (DWL, Compumedics Ltd., Germany) using search techniques described elsewhere (Aaslid, Markwalder, & Nornes, 1982; Willie et al., 2011). The Doppler probe was secured in position using an adjustable headband (DWL) to maintain a constant insonation angle throughout the trial. Non-invasive beat-to-beat arterial blood pressure was measured by finger photoplethysmography (Finapres Medical Systems, The Netherlands or Nexfin, Edwards Lifesciences, Ontario, Canada) and heart rate was measured via three-lead electrocardiogram (ADInstruments, Australia). Participants breathed through a mouth piece, with expirate analysed for $P_{ET}CO_2$ using a fast-responding gas analyser (ML206, ADInstruments or Breezesuite, MedGraphics, MN). All data were acquired continuously at 1000 Hz (except $P_{ET}CO_2$ from the Breezesuite gas analyser; n = 8 in the sedentary group) via an analogue to digital converter (PowerLab ML870, ADInstruments) interfaced with a computer and then analysed using commercially available software (LabChart v8.1.12 ADInstruments).

Data Analysis

Baseline and $P_{ET}CO_2$ data

Baseline data were averaged over the last minute of the initial seated rest period (see Figure 1). Cerebrovascular conductance index (CVCi) was calculated using the equation $MCAv_{Mean}$/MAP. To evaluate the change in $P_{ET}CO_2$ for each squatting frequency, the first and last five breaths were averaged. The difference between these two values represents the change in $P_{ET}CO_2$ across that frequency as previously reported (Labrecque et al., 2019).

Transfer function analysis

Data were analyzed using the commercially available software Ensemble (Version 1.0.0.14, Elucimed, Wellington, New Zealand) and are in accordance with the recommendations of the Cerebral Autoregulation Research Network (CARNet) (Claassen, Meel-van den Abeelen, Simpson, Panerai, & International Cerebral Autoregulation Research, 2016). Beat-to-beat MAP and MCAv signals were spline interpolated and re-sampled at 4 Hz for spectral analysis and TFA based on the Welch algorithm. Five successive windows that overlapped by 50% were attained from subdividing the final 5-mins of the data recordings. Data within each window were linearly detrended and passed through a Hanning window prior to discrete Fourier transform analysis. For the transfer function analysis, 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 that is linearly related to MCAv), absolute gain (cm/s/mm Hg; amplitude of MCAv change for a given oscillation in MAP), normalized gain (%/mm Hg) and phase (radians and degrees; difference of the timing of the MAP and MCAv waveforms).

The point estimate of the driven frequency of 0.05 Hz and 0.10 Hz was where the transfer function analysis coherence, gain, and phase of the forced MAP oscillations were taken from. These point estimates were chosen as they are in the very low (0.02 - 0.07 Hz) and low (0.07 - 0.20 Hz) frequency ranges where dCA is thought to be most effective (Smirl et al., 2015). Only the TFA phase and gain values where coherence exceeded 0.50 were included in the analysis, to ensure the measures were robust for subsequent analysis (Zhang et al., 1998). Phase wrap-around was not present when coherence exceeds 0.50 in the spontaneous data nor at any of the point-estimate values for squat-stand manoeuvres.

Changes in blood pressure during squat-stand manoeuvres

The magnitude of the blood pressure changes during the squat-stand manoeuvres were assessed by calculation of the mean peak and trough, systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP within each cycle. Additionally, the mean difference between peak and trough pressures (amplitude) was calculated.

Statistical Analysis

Data were analysed using SPSS (version 25, SPSS Inc, Chicago, IL), with statistical significance set at $P < 0.05$. A one-way analysis of variance (ANOVA) was performed to compare baseline measures of the three groups. A two-way (2 frequencies x 3 exercise groups) mixed ANOVA was used to analyse dependent variables of interest. Main effects were isolated using post-hoc pairwise comparisons (Bonferroni corrected, where necessary). All data are displayed as the mean ± SD.

Results

Resting values

Resting cerebrovascular and cardiorespiratory data are displayed in Table 3. Briefly, all baseline data were similar between groups except for heart rate being higher in the resistance group than endurance ($P < 0.001$) and sedentary ($P = 0.021$) groups. However, no difference was observed between endurance and sedentary groups ($P = 0.427$).

Dynamic cerebral autoregulation

Transfer function-derived metrics, BP and MCAv power are shown in Table 4. A significant interaction effect for phase was identified ($P = 0.026$), however, no post- hoc differences were isolated, with only a trend for phase to be lower in resistance-trained individuals than in endurance-trained and sedentary individuals at the 0.05 Hz frequency (see Table 4, *$P = 0.052$ and $P = 0.081$ respectively*). $P_{ET}CO_2$ was unchanged ($P = 0.561$) throughout both squat frequencies for all groups (0.05 Hz: +0.3 ± 1.5, +1.0 ± 2.6 and +1.4 ± 2.7 mm Hg for endurance-trained, resistance-trained and sedentary groups, respectively; 0.10 Hz: -0.3 ± 3.1, +1.1 ± 1.6 and +0.2 ± 1.3 mm Hg).

Table 3 Participants' resting cerebrovascular and cardiovascular measurements

Variables	Resistance	Endurance	Sedentary	*P*-value
$MCAv_{Mean}$ (cm/s)	58 ± 8	59 ± 11	63 ± 12	0.544
SMCAv (cm/s)	96 ± 17	99 ± 19	95 ± 19	0.841
DMCAv (cm/s)	40 ± 7	39 ± 8	46 ± 9	*0.081*
MAP (mm Hg)	93 ± 15	95 ± 7	93 ± 18	0.867
SBP (mm Hg)	135 ± 21	137 ± 13	133 ± 20	0.595
DBP (mm Hg)	72 ± 12	73 ± 6	78 ± 17	0.483
HR (beats/minute)	87 ± 8	67 ± 9*	73 ± 15†	**< 0.001**
$P_{ET}CO_2$ (mm Hg)	38 ± 3	37 ± 3	35 ± 3	0.203
CVCi (cm/s/mm Hg)	0.64 ± 0.12	0.59 ± 0.10	0.70 ± 0.14	0.208

Values are mean ± SD. $MCAv_{Mean}$*, mean middle cerebral artery blood velocity; SMCAv, systolic middle cerebral artery blood velocity; DMCAv, diastolic middle cerebral artery blood velocity; MAP, mean arterial blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, heart rate;* $P_{ET}CO_2$*, partial pressure of end tidal carbon dioxide; CVCi, cerebrovascular conductance index; *, significant difference between resistance and endurance-trained (P < 0.001); †, Significant difference between resistance and sedentary (P = 0.021). P values presented in table 3 are main effects from one-way analysis of variance.*

Blood pressure perturbations

There was no difference between SBP, DBP or MAP peak (pooled means within frequency; 0.1 Hz: 175 ± 25, 0.05 Hz: 174 ± 22; 92 ± 14, 91 ± 12 and 118 ± 17, 119 ± 14 for SBP, DBP and MAP respectively) and trough (122 ± 21, 110 ± 20; 56 ± 14, 53 ± 15 and 78 ± 15, 72 ± 16) between conditions (all > 0.200). However, differences between amplitude of blood pressure changes were identified with data displayed in Table 4

Table 3 Transfer function analysis derived variables

Variables	0.05 Hz			0.1 Hz			*P* Values
	Endurance	Resistance	Sedentary	Endurance	Resistance	Sedentary	Frequency x Exercise
Gain (cm/sec/mm Hg)	0.68 ± 0.18	0.62 ± 0.11	0.58 ± 0.16	1.03 ± 0.21	0.96 ± 0.17	0.81 ± 0.21	0.261
nGain (%/mmHg)	1.16 ± 0.33	1.077 ± 0.21	0.97 ± 0.25	1.61 ± 0.35	1.52 ± 0.27	1.34 ± 0.29	0.804
Phase (radians) (Degrees)	0.90 ± 0.41 (51.7 ± 23.5)	0.63 ± 0.21 (36.1 ± 23.5)	0.85 ± 0.38 (48.7 ± 21.8)	0.57 ± 0.26 (32.7 ± 14.9)	0.48 ± 0.15 (27.5 ± 8.6)	0.48 ± 0.20 (27.5 ± 11.5)	**0.043**
Coherence (arbitrary units)	0.98 ± 0.02	0.99 ± 0.01	0.95 ± 0.00	1.00 ± 0.00	0.99 ± 0.00	0.99 ± 0.01	0.057
MCAv Power $((cm/s)^2$ /kHz)	15.3 ± 10.1	18.4 ± 11.6	6.8 ± 6.7	23.6 ± 9.5	32.4 ± 18.6	13.2 ± 10.8	0.148
BP Power (mm Hg^2/kHz)	33.4 ± 22.5	43.7 ± 23.3	16.3 ± 14.5	23.4 ± 10.7	33.0 ± 12.1	17.7 ± 9.1	0.089
SBP Amplitude (mm Hg)	68 ± 19⁑	79 ± 21†	45 ± 15	47 ± 11	63 ± 18*†	39 ± 8	**0.010**
DBP Amplitude (mm Hg)	40 ± 11	45 ± 10	30 ± 9	35 ± 9	42 ± 10	30 ± 7	0.200
MAP Amplitude (mm Hg)	49 ± 13⁑	56 ± 13†	35 ± 11	39 ± 9	49 ± 12†	33 ± 7	**0.031**

*Data are means ± SD. nGain, normalised gain; MCAv power, middle cerebral artery blood velocity power; BP power, blood pressure power; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; *, significant difference between resistance and endurance-trained (P = 0.016); †, Significant difference between resistance and sedentary (P < 0.001); ⁑, Significant difference between endurance-trained and sedentary in the same squat frequency (P < 0.004)*

Discussion

The aim of this study was to examine the effect of habitual endurance and resistance exercise on cerebral autoregulation. Dynamic cerebral autoregulation (dCA) was assessed using TFA-derived metrics during forced oscillations in blood pressure induced by repeated squat-stand manoeuvres. Whilst gain and normalised gain were similar between all groups, an interaction effect was observed for phase. Phase tended to be lower in the resistance group than both endurance and sedentary groups at 0.05 Hz only. These findings indicate – albeit in a cross sectional study - that dCA is largely unaltered by habitual endurance and resistance exercise, especially during fluctuations in blood pressure around 0.10 Hz.

Resting cerebral haemodynamics

Analysis of resting cerebrovascular variables revealed no difference between groups, and is in agreement with some (Bailey et al., 2013; Brugniaux, Marley, Hodson, New, & Bailey, 2014; Labrecque et al., 2017), but not all (Ainslie et al., 2008), previous comparisons between endurance-trained and sedentary individuals. However, no comparative data exist for resistance-trained individuals (to our knowledge). Despite the lack of an observable difference in resting measures, improved CO_2 reactivity has been reported in individuals with greater cardiorespiratory fitness (Bailey et al., 2013; Murrell et al., 2013) and larger increases in MCAv and prefrontal cortical oxygenation during the transition from low to moderate aerobic exercise (Brugniaux et al., 2014). These data indicate an improvement in vascular function in response to stressors associated with endurance exercise – for example, increases in blood flow in response to cortical activation and alterations in arterial CO_2. Peak, and reserve, cardiac output is increased in response to regular endurance training, with cardiac output also acting as a cerebral blood flow modulator independent of blood pressure (Ogoh et al., 2005). Increased cardiorespiratory fitness mitigates the age-related decline in cerebral blood flow (Ainslie et al., 2008), and is associated with a maintenance of cardiac function (Johnson et al., 2016). As such, whilst there was no change in resting values, stressed function may reveal differential adaptations to habitual exercise. Therefore, quantifying and comparing the response to perturbations in other modulating variables of cerebral blood flow may elucidate further adaptations to a given exercise type.

Impact of habitual exercise on dynamic cerebrovascular regulation

Our finding of no difference in dCA between endurance and sedentary is consistent with results from others using repeated sit-stand manoeuvres (Aengevaeren et al., 2012) and bilateral thigh cuff release in the upright position (Ichikawa et al., 2013). However, some authors have reported an increased gain and normalised gain during forced oscillations in MAP produced by repeated squat stand manoeuvres (Labrecque et al., 2017) and bilateral thigh cuff release respectively (Lind-Holst et al., 2011) – indicative of a reduced damping ability of the cerebral circulation. Whilst the reason for these disparate data is not clear, the method of perturbing blood pressure and subsequent analysis may be partially responsible and is discussed below.

Collectively, the current data indicate that regular exercise, irrespective of type, does not alter cerebral autoregulation. However, this may be frequency specific as phase tended to be lower in the resistance group during slower (0.05 Hz) oscillations. Additionally, the resistance trained group experienced the largest SBP and MAP amplitude during both squat frequencies investigated (table 4). Whilst this may result from the larger body mass of this group, it also indicates a greater cerebrovascular challenge for the same intervention. Given that resistance-trained individuals demonstrate both acute (DeVan et al., 2005) and chronic decreases in central arterial compliance (Kawano et al., 2008; Miyachi et al., 2004), presumably as a result of the rapid perturbations in blood pressure, alterations in compliance may extend to the cerebral vasculature and impact dCA. A cross-sectional study by Nakamura and Muraoka (2018) revealed increased MCA pulsatility with concurrent reduced central arterial compliance in resistance trained individuals. This appears to be a chronic adaptation as untrained individuals demonstrated no change in MCA pulsatility following resistance exercise, despite an increase in common carotid artery pulse pressure (Lefferts, Augustine, & Heffernan, 2014). Windkessel models of the cerebral circulation indicate that reductions in cerebral vessel compliance reduce TFA derived gain (Zhang, Behbehani, & Levine, 2009), indicating compliance is a modulator of cerebral autoregulation. Whilst this effect of compliance was found to predominate at the low (0.07-0.20 Hz) and high frequencies (0.20 – 0.35 Hz, Zhang, Behbehani, & Levine, 2009), altered cerebrovascular compliance may underlie the tendency for a reduced phase in the resistance group. However, autoregulation itself is plastic (Panerai, 2014), with rapid (3-4 months) adaptation to changes in perfusion pressure

following hypertensive intervention (Zhang, Witkowski, Fu, Claassen, & Levine, 2007). Prolonged hypertension may also generate compensatory reductions in cerebrovascular compliance, as evidenced by improved autoregulation within the low frequency range (0.03-0.07 Hz), in elderly with uncontrolled hypertension (Serrador et al., 2005). Future research is required to identify the impact of brief and intermittent hypertension on cerebrovascular compliance in order to elucidate the underlying mechanisms responsible for the current results.

In contrast to resistance trained individuals, increases in aortic compliance is observed in endurance trained individuals which acts to buffer the increased stroke volume (Tomoto, Imai, Ogoh, Maeda, & Sugawara, 2018), potentially limiting cerebrovascular pulsatility and reducing end-organ haemodynamic stress (Tomoto et al., 2015). Furthermore, endurance athletes operate on the steep portion of the Starling curve with changes in filing pressure eliciting greater alterations in stroke volume compared with sedentary controls (Levine et al., 1991). Cardiac baroreceptors tend to engage and counterregulate at ~7 s (Aaslid, Lindegaard, Sorteberg, & Nornes, 1989); which is more effective in the regulation of MAP for the slower driven blood pressure oscillations (0.05 Hz). Considering that arterial baroreflex sensitivity seems to be related to dCA (Tzeng, Lucas, Atkinson, Willie, & Ainslie, 2010), the subtle difference in dCA between groups could be due to a differential influence of habitual resistance and endurance exercise training on arterial baroreflex sensitivity. It is possible that the cerebrovascular responses observed in the current investigation stem from a complex interplay of counteracting adaptations within central and peripheral circulations that are exercise modality specific.

Cerebral autoregulatory capacity is more effective in the hypertensive range (Brassard et al., 2017; Panerai et al., 2018); this phenomenon is referred to as hysteresis. During resistance exercise, intermittent and extreme hypertension is experienced, with MAP >300 mm Hg being reported during bilateral leg press exercise (MacDougall et al., 1985). Several authors suggest that this intermittent hypertension is responsible for the observed changes in central arterial compliance, including that in the common carotid arteries (Kawano et al., 2008; Miyachi et al., 2004). These extreme changes in MAP are translated to the cerebrovasculature (Perry et al., 2014) and reflect the high pass filter characteristics of this circulation (Diehl et al., 1995; Zhang et al., 1998). Regular exposure to such extreme intermittent hypertension, and

associated rapid changes in cerebral perfusion, may induce structural modifications in the cerebrovasculature. For example, pre-clinical animal models utilizing 4 weeks of repeated transient hypertension induced cerebrovascular endothelial dysfunction and profibrotic mediated cerebrovascular stiffness (Phillips et al., 2018). We speculate that this modification may underlie the tendency for a reduced phase in the resistance-trained group. Whilst the methods used to perturb blood pressure generate substantial fluctuations (30-50 mmm Hg), functional adaptations may not be revealed until extreme challenges to dCA are produced. For instance, like those seen in intense resistance exercise where blood pressures may increase ~4 fold (MacDougall et al., 1985) and a less compliant vessel may mechanically restrain blood flow.

In comparison to healthy sedentary, endurance-trained individuals demonstrate larger decreases in MAP, MCAv and cerebral oxygenation during upright thigh cuff release (Ichikawa et al., 2013) and are more prone to syncope (Levine et al., 1991) – indicating reduced dCA in endurance athletes during hypotensive challenges. However, Ichikawa et al. (2013) found no change in rate of regulation in the upright position - functionally significant given the threat orthostasis presents to the cerebral circulation. While comparing studies that used differential analyses is difficult (Tzeng et al. 2012), we have shown increased TFA-derived gain during 0.10 Hz MAP oscillations in endurance athletes, utilising the same technique employed in the current study (Labrecque et al., 2017). Notably, Labrecque et al. (2017) found no differences in TFA derived metrics during spontaneous fluctuations or the rate of regulation in response to a sit-to-stand manoeuvre. The reason for these differences between the current findings and those of Labrecque et al. (2017) is unclear and may be due in part to the small sample size in both studies. The endurance cohorts were both well trained, with the endurance group in the current study having a greater cardiorespiratory fitness than that of Labrecque et al. (2017), average peak relative oxygen consumption of ~10 $mL \cdot min^{-1} \cdot kg^{-1}$ higher). An elevated cardiorespiratory fitness, and therefore training status, would be expected to amplify any potential exercise impact on dCA. Further investigation is required to clarify these disparities.

Limitations

We used transcranial Doppler ultrasound to measure cerebral blood velocity of the MCA, under the assumption that the diameter of the vessel remains unchanged. Giller, Bowman,

Dyer, Mootz, and Krippner (1993) reported that during small changes in MAP (30 ± 16 mm Hg) the diameter changes <4%. Using high resolution magnetic resonance imaging, MCA diameter is altered in response to hypercapnia (Verbree et al., 2014) and during handgrip exercise (Verbree et al., 2017). Therefore, these results require confirmation with other methods of cerebral blood flow quantification. Whilst repeated squat-stands provide robust perturbations in blood pressure, the dynamic nature of the manoeuvres will concurrently activate motor cortices, which alone increase MCAv (Jorgensen, Perko, & Secher, 1992). As such, during the stand phase of the manoeuvre, in which cerebral perfusion pressure would be decreasing, MCAv responses to cortical activation may be misinterpreted as an autoregulatory response. Similarly, during the squat phase the rapid increase in blood pressure may accentuate cortical activation. Furthermore, we utilised only one method for dCA characterisation, i.e., TFA. Considering that several dCA metrics are generally unrelated to each other (Tzeng et al., 2012), further investigation using multiple methods for assessing autoregulatory function is needed to support the current data.

Importantly, a larger sample size would be required to elucidate the effect of resistance exercise on cerebrovascular function as only trends were identified in the current study. This study recruited only young and healthy participants and the findings cannot be generalised to clinical populations. The female cohort was also limited to 3 individuals in the sedentary group. Some authors report improved dCA in women compared to males (Favre & Serrador, 2019), whilst others report a reduction in dCA capacity in endurance trained females compared to age-matched, endurance-trained males (Labrecque et al., 2019). Abidi et al. (2017) also suggested a modulatory role of ovarian hormones and oral contraceptives on cerebrovascular function to challenges such as standing and the Valsalva manoeuvre. To mitigate this confounding influence, all females were tested in the early follicular phase. Further investigation is required to fully elucidate the interaction between sex and habitual exercise and how this may have impacted the results presented here.

Conclusion

This study did not identify clear differences in dCA between athletic groups. Further investigation is required to identify whether directionally-specific adaptations are apparent with regard to a hyper- or hypotensive challenge. Nevertheless, the trend for lower dCA phase

indicates a possibility that the previously reported decreased central arterial compliance observed in central arteries of habitual resistance exercisers may also be apparent in the cerebral vasculature. Whether this impacts other vital cerebrovascular functions (e.g. reactivity to CO_2) remains to be seen and warrants investigation.

Author Contributions

Data was collected at the School of Sport, Exercise and Nutrition, Massey University, Wellington, New Zealand and Research center of the Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada. B.G.P, J.D.C and S.J.E.L were responsible for the study concept and design. B.G.P, S.K, L.L, M.P., O.L.B. and P.B collected the data. All authors contributed to the analysis of data, drafting this manuscript and all authors approve the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Figure captions

Figure 1 Protocol overview

Figure 2. Individual Gain and Phase for all participants for both squat-stand frequencies. Each data point illustrates one participant with the lines representing the change in mean for each group.

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