EFFECTS OF EXERCISE INTENSITY ON ANTERIOR CEREBRAL PERFUSION IN PREPUBERTAL CHILDREN.

by

Ryan Simair

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The following individuals certify that they have read, and recommend to the College of Graduate Studies for acceptance, a thesis entitled:

EFFECTS OF EXERCISE INTENSITY ON ANTERIOR CEREBRAL PERFUSION IN PREPUBERTAL CHILDREN

Submitted by Ryan Simair in partial fulfillment of the requirements of the degree of Master of Science.

Dr. Ali McManus, Faculty of Health & Social Development

Supervisor

Dr. Glen Foster, Faculty of Health & Social Development

Supervisory Committee Member

Dr. Phil Ainslie, Faculty of Health & Social Development

Supervisory Committee Member

Dr. Paul Shipley, Faculty of Chemistry

University Examiner

Abstract

Introduction: Although high intensity interval exercise (HIIE) has been well characterized in adults as providing superior systemic vascular adaptions compared to moderate intensity exercise (MIE), there is evidence that HIIE poses a challenge to cerebral hemodynamics. Only one study has investigated the child's middle cerebral artery (MCA) response to incremental exercise to maximum, and we do not currently understand the cerebrovascular response to either HIIE or continuous MIE in the child.

Methods: Nine children (aged 7-11 y; 5 girls) completed either HIIE (six 1-minute cycle ergometer sprints at 90% peak power (Wmax) with 1-minute recovery at 20% Wmax) or MIE (15 minutes at 44% Wmax on a cycle ergometer, matched to HIIE for external work). MCA velocity (MCAv), partial pressure of end tidal carbon dioxide ($PETCO_2$) and mean arterial pressure (MAP) were measured at baseline, immediately post-, 30 minutes post- and 60 minutes post-exercise. MCAv was also continuously recorded throughout exercise. A repeated measures ANOVA was used to compare changes from baseline across the time-points and between the exercise conditions.

Results: The MCAv peaked during the first two minutes in both HIIE (minute 1: +12.10±2.70% & minute 2: +12.65±6.20%; p's<0.05) and MIE (minute 1: +7.46±5.37% & minute 2: +9.78±6.40%; p's<0.05). In HIIE, MCAv significantly decreased below baseline for the final 3 sprints (P<0.05), oscillating back to baseline for the remaining rest intervals. In MIE, the MCAv returned to baseline after the 4th minute of exercise, where it remained under exercise cessation. The cerebrovascular resistance index (CVRi) significantly increased (P's<0.05) during the final minute of both MIE (+7.0±6.70%) and HIIE (+21.5±7.60%), with a significant difference between intensities (P<0.05). Immediately post HIIE, the MCAv

uncoupled from $PETCO_2$, whereas immediately post MIE the MCAv and $PETCO_2$ remained at baseline values.

Discussion: The decline in MCAv during the latter half of both HIIE and MIE may reflect adequate cerebral oxygenation because of the elevated MCAv baseline values in children compared to adults. The increase in CVRi in the final minute of HIIE is likely driven via hyperventilatory hypocapnia. Finally, it appears that $PETCO_2$ has a diminished regulatory effect over MCAv in children following HIIE.

Preface

Work described in Chapter 2 and 3 (Methods & Results) was approved by UBC's Clinical Research Ethics Board (H15-02104) and was in accord with the Declaration of Helsinki. Work was conducted in the Pediatric Exercise Research Laboratory by Dr. AM McManus and Ryan Simair. I was responsible for planning and scheduling the experiment as well as data collection. I wrote this thesis with extensive feedback from Dr. AM McManus and Dr. PN Ainslie.

Table of Contents

List of Tables

List of Figures

List of Symbols and Abbreviations

*; significant difference from rest P<0.05; within intensity.

†; significant difference between HIIE and MIE P<0.05.

ACA; Anterior cerebral artery

BA; Basilar artery

CA; Cerebral autoregulation

CBF; Cerebral blood flow

CBFv; Cerebral blood flow velocity

$CMRO_2$; Cerebral metabolic rate for oxygen

CVC; Cerebrovascular conductance

CVRi; Cerebral vascular resistance index

DBP; Diastolic blood pressure

ECA; External carotid artery

HIIE; High intensity interval exercise

HR; Heart rate

HRmax; Heart rate maximum

ICA; Internal carotid artery

La; Lactate

MAP; Mean arterial pressure

MCAv; Middle cerebral artery velocity

MIE; Moderate intensity exercise

MRI; Magnetic resonance imaging

$PaCO_2$; Partial pressure of arterial carbon dioxide

PCA; Posterior carotid artery

$PETCO_2$; Partial pressure of end tidal carbon dioxide

pVO_2 kinetics; Pulmonary oxygen uptake kinetics

SBP; Systolic blood pressure

TCD; Transcranial Doppler ultrasound

VO_2max; Maximal Oxygen consumption

VA; Vertebral artery

Wmax; Maximum external work

Acknowledgements

I would not have made it through my program if it were not for the constant support of Dr. Ali McManus. Dr. McManus challenged me and pushed me to be my best by relating to me on a very real human level. I have had the pleasure of working with Dr. McManus for the passed 3.5 years and although not every day was easy, it certainly was a pleasure. Her passion in her field organically drives her ambition, which is contagious. As my mentor, Dr. McManus helped to engrain in me the scientific process and a plethora of information around our particular field of pediatric cerebrovascular health; And, as my friend she provided constant general life advice and support, watching me grow into the man that I am and playing a significant model role. I am truly grateful for the time spent with Dr. Ali McManus and this incredible chapter of my life.

I am so grateful for my amazing lab mates Victoria Armstrong, Laura Morris, Nathan Sletten, and Christine Tallon who not only supported me through my studies and experiments but also created the laboratory ambiance making each day slightly more manageable with Frisbee, distracting Youtube videos and constant laughs.

Finally, I thank my parents for the constant moral support and love as well as financial contributions. From the home cooked meals on Sunday (and leftovers), repairing the car when needed and massive decompression talks over the many stresses of my day, my parents were the backbone to my education and it would not have been possible without them.

Dedication

This project is dedicated to children of North America to encourage physical activity at a young age and an active lifestyle throughout their lifespan.

Chapter 1 Introduction

Exercise can reduce the risk of cerebrovascular and neurodegenerative diseases and has been associated with extended longevity (Lautenschlager *et al*. 2012), yet only 7% of Canadian children meet current physical activity guidelines (Tremblay et al., 2011B). Instead, most children spend about 60% of their waking hours sedentary, with approximately eight hours a day spent sitting without otherwise moving (Tremblay et al., 2011B). It is concerning that children spend a majority of their day sedentary, given the evidence that sedentary aging is associated with a longitudinal decline in cerebral blood flow (CBF) (Ainslie et al., 2008; Barnes et al., 2013), cerebrovascular reactivity (Bakker et al., 2004), and cerebral autoregulation (CA) (Bailey et al., 2013). Together, these latter changes likely increase the risk of cognitive decline, and stroke (Okazawa et al., 2003).

Physical activity is the number one recommendation for reducing the risk of cardiovascular, cerebrovascular and neurodegenerative diseases across the life-span (Strong et al., 2005). Regular exercise improves cerebral hemodynamics in older adults (Ainslie et al., 2008) and higher levels of aerobic fitness are also associated with improved hippocampal perfusion and cognitive function in children (Chaddock-Heyman et al., 2016; Moore et al., 2013). It is believed that these improvements are linked to the increases in cerebral perfusion during exercise, but there is limited evidence on the impact that an acute bout of exercise has upon the cerebral hemodynamics in children.

While traditional exercise interventions for children have principally involved continuous moderate intensity exercise (MIE) (McMurray et al., 2002; Hansen et al., 1991; Meyer et al.,

2006), the relevance of such programs to the child's habitual sporadic play patterns has been questioned (Bailey et al., 1995). For example, movement patterns in children are intermittent, with multiple low to moderate intensity bursts of movement interspersed with occasional vigorous movement (Bailey et al., 1995). High-intensity interval exercise (HIIE) has emerged as a time efficient and effective alternative to MIE, providing superior metabolic, cardiac and systemic vascular adaptations in adults (Weston *et al*. 2014). Indeed, in the healthy children, HIIE has been shown to improve cardiorespiratory fitness in comparison to lower intensity exercise (Baquet et al., 2010; Baquet et al., 2002; McManus et a., 2005), maximal running velocity (Baquet et al., 2010), peak and submaximal cardiovascular outcomes (McManus et al., 2005), and ventilatory function (Nourry et al., 2005). Regardless of the convenient nature of HIIE and the many reported positive effects, the lack of evidence to date examining how HIIE affects the cerebrovasculature has been outlined (Lucas *et al*. 2015) and there is some evidence, albeit in adults, that HIIE may overly challenge the cerebrovasculature (Curtelin et al. 2017). For example, using a single bout Wingate test Curtelin et al (2017) revealed that adults elicit marked elevations in mean arterial pressure (MAP) and middle cerebral artery velocity (MCAv) during the onset of exercise but also showed significant reductions in MAP immediately post exercise; Perhaps, it is possible that these large instantaneous alterations are overbearing for the cerebrovasculature.

The purpose therefore of this thesis is to compare the cerebrovascular responses during continuous MIE and HIIE, as well as during recovery from both exercise conditions, in prepubertal children. The thesis begins with a review of the literature (Chapter 1), introducing cerebral anatomy and the developmental changes that occur in CBF, focusing upon the cerebrovascular response to exercise. Chapter 2 describes the methods used and

Chapter 3 reveals the main results found. Chapter 4 is a discussion of the results including strengths & limitations and future direction in the field.

1.1 Literature review

1.1.1 Cerebral anatomy

The path that blood travels to supply the anterior brain originates at the heart, emerging from the ascending aorta. The left carotid emerges directly from the aorta, while the right branches from the brachiocephalic trunk. The vertebral arteries (VA) emerge from the right and left subclavian arteries, although the left VA may also branch directly from the aortic arch in about 15% of individuals (Einstein et al. 2016; see figure 1.1).

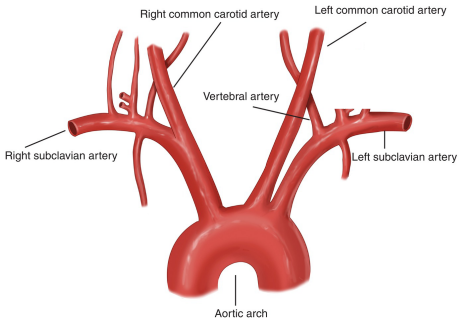

Figure 1.1 Anatomy of aortic orgins of the extracranial vessels. Image adapted from Google.

The carotid artery (left & right) split at the level of the mastoid, into the external carotid artery (ECA) and the internal carotid artery (ICA). The ECA provides the blood supply to the facial region. The ICA does not branch until joining the Circle of Willis and is often thought of as the origin of cerebral perfusion, contributing about 76% of global CBF at rest (Schöning et al, 1994). The ICA undergoes considerable growth during childhood. It is similar in size to the ECA until about 9 years of age (Seong et al., 2005). During maturation, the ICA remodels at the root or carotid sinus, with no corresponding change in the ECA. The resulting arterial remodelling results in the prominent carotid bulb noted in adults, and coincides with maturation of the brain. The carotid sinus

acts as a stretch receptor providing a direct sensor for blood pressure changes, as well as chemoreception (sensing changes in oxygen and carbon dioxide tension). Although the precise reason for this ICA remodelling is not known, this may be a means of providing more mature baro- and chemoreception, and/or may act as a pressure dampener with the carotid sinus slowing flow to protect the maturing brain from surges in pressure (Seong et al., 2005). Either way the carotid sinus most likely supports the maturing needs of the cerebrovascular system.

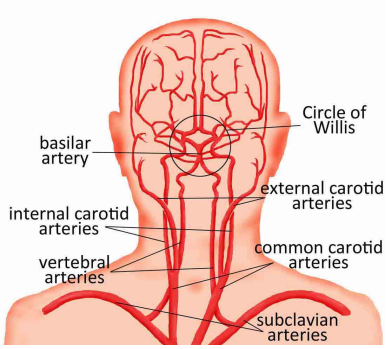

Figure 1.2 Anatomy of the extra- and intracranial vessels feeding to the circle of Willis. Image adapted from Google.

The left and right VA join together at the level of the pons forming the basilar artery (BA), which connects the Circle of Willis. The VA delivers the remaining ~24% of global CBF to the the circle of Willis (Schöning et a., 1994; see figure 1.2).

The Circle of Willis then branches into the basal arteries: the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and the posterior cerebral artery (PCA) (See Figure 1.3). The MCA is the largest intra-cranial artery and supplies a portion of the frontal lobe and the lateral surface of the temporal and parietal lobes, including the primary motor and sensory areas and the areas for speech. The MCA supplies these respective areas with 60-80% of blood flow (Verlhac, 2011).

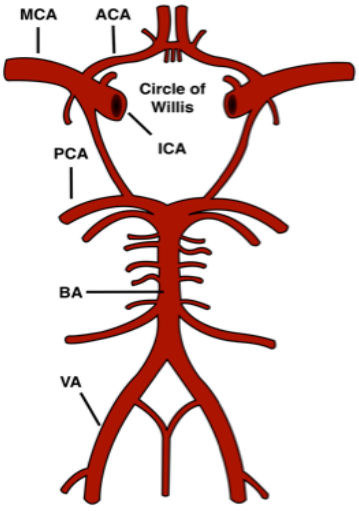

Figure 1.3 Anatomy of the intracranial vessels. Original Image.

1.1.2 CBF in the child

As the child's brain undergoes progressive structural and functional development, alterations to cerebral haemodynamics support these changing needs (Tortori-Donati & Rossi, 2005; Biagi *et al*. 2007; Labarthe *et al*. 2009; Hales *et al*. 2014). Previous work demonstrates that grey matter and white matter CBF is highest during the first two decades of life peaking around 6-10 years of age (Leung *et al*., 2016; see figure 1.4).

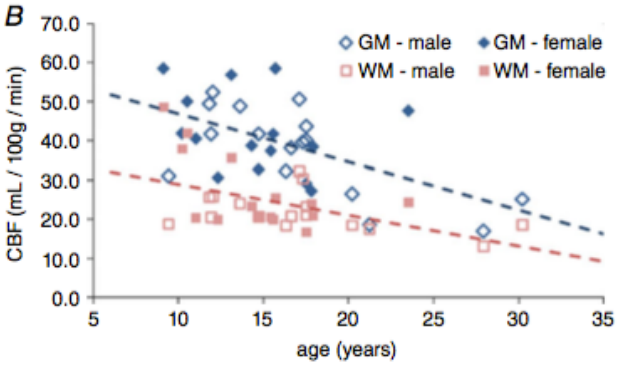

Figure 1.4 CBF decreases with age (GM-grey matter; WM-white matter). Retrieved from Leung et al., 2016 with permission.

Similarly, early cross-sectional work using transcranial Doppler ultrasound (TCD) to measure MCAv analyzed 1,200 examinations from 620 children from birth to 15 years of age, and revealed a rapid increase in MCAv from 2 months of age to 6-8 years, whereby MCAv begins to decline gradually towards adult values by the age of 18 years (Bode & Eden, 1989; see figure 1.5). More recently, Demirkaya et al. (2008) have confirmed the earlier work by Bode and Eden (1989) in a group of 30 males and 33 females aged 6-69 years. They demonstrate a 28.8 $cm.s^{-1}$ decrease in MCAv at rest from 75.7 $cm.s^{-1}$ in 5-10 year olds, declining to a mean value of 46.9 $cm.s^{-1}$ for the over 60's (Demirkaya, Uluc, Bek, & Vural, 2008).

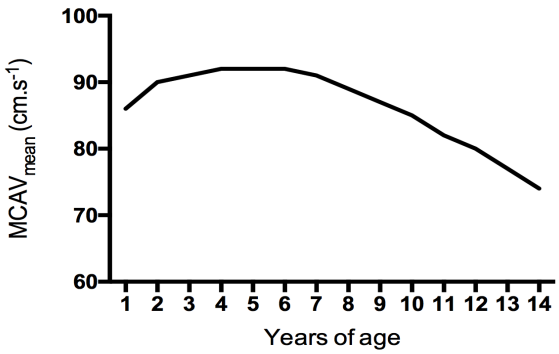

Figure 1.5 Reference values for MCAv from 1 to 14 years of age, adapted from Bode & Eden, 1989.

The elevated resting CBF in childhood is nearly double that of an adult (Chugani, 1998) and reflects the much higher cerebral metabolism of the developing brain (Biagi *et al*. 2007). Indeed, cerebral oxygen consumption is estimated to be about 50% of total body oxygen consumption in the child (Kennedy and Sokoloff, 1957), nearly 1.3 times higher than noted in adults (Chugani 1998).

Sex differences have been examined for resting CBF. Studies using TCD to derive cerebral blood flow velocity (CBFv) demonstrate that adolescent girls have a higher MCAv compared to age matched boys (Vavilala, Kincaid, Muangman, Suz, Rozet & Lam, 2005). Further work has shown that sex differences in CBFv also exist prior to puberty (Tontisirin et al. 2007). Assessing 48 pre-pubertal children aged 4-8 years (24 girls; 24 boys), Tontisirin and collegueages (2007) found that both the anterior and posterior circulations were higher in girls than boys. Values for MCAv were 99±11 $cm.s^{-1}$ and 91±13 $cm.s^{-1}$ in girls and boys respectively. The BA velocity was 70±10 $cm.s^{-1}$ versus 61±9 $cm.s^{-1}$ in girls and boys respectively. There are a number of possible explanations for these documented sex differences including differences in haematocrit and therefore blood viscosity, divergent sex hormones, differing cerebral metabolism, cerebrovascular resistance index (CVRi) and vessel size. However, only CVRi and vessel size show sex divergence prior to puberty, with CVRi (See Equation 1.1) lower in 4 to 8 year-old girls than boys (Tontisirin et al., 2007) and limited evidence of smaller ICA and MCA diameters in females compared with males (Gabrielsen & Greiz, 1970).

Equation 1.1. $CVRi = MAP/MCAv$

Where CVRi = Cerebral Vascular Resistance index; MAP = Mean Arterial Pressure; MCAv = Middle Cerebral Artery velocity.

In contrast, recent work utilizing magnetic resonance imaging (MRI) (Satterthwaite et al., 2014), reported a nonlinear age-by-sex interaction for CBF in multiple brain regions, with CBF values lower in girls compared to boys before 13 years of age. Boys, however, showed a markedly more rapid age-related decline in CBF resulting in higher CBF values in girls than in boys by mid-adolescence. By late adolescence, CBF increases with age in girls, whereas CBF in boys continues to decline (see figure 1.6).

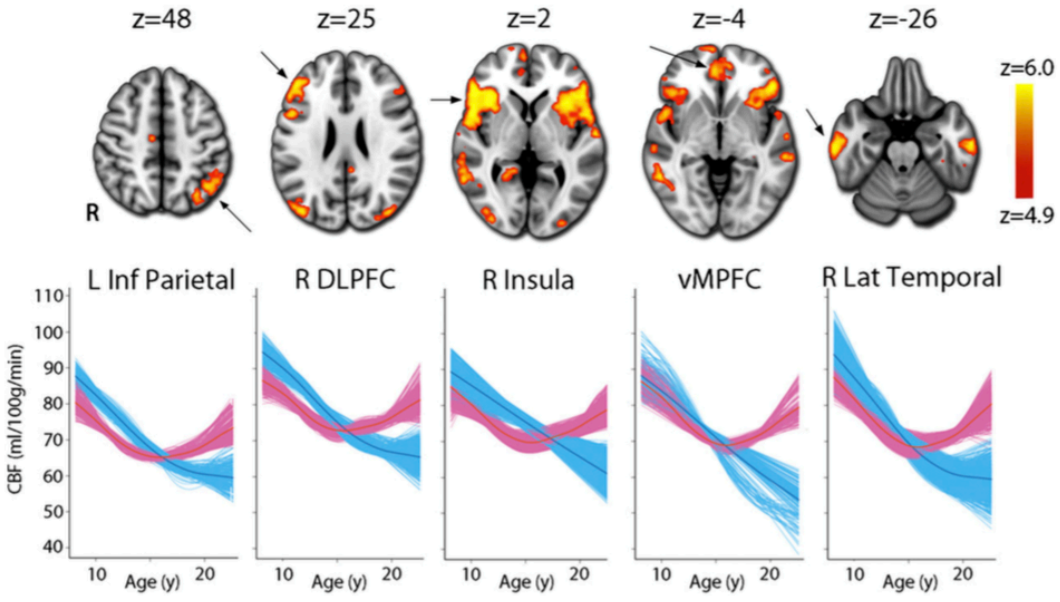

Figure 1.6 Trajectory of CBF development by age and sex. Retrieved from: PNAS in Satterthwaite et al., 2014, no permission required.

When differences in maturational trajectories were accounted for however, the decline in CBF was similar between girls and boys in early puberty (Satterthwaite et al., 2014).

Cerebral perfusion diverges by mid-puberty (See Figure 1.6), with greater declines noted in boys persisting into late puberty and resulting in higher levels of cerebral perfusion in girls than boys by late adolescence (Satterthwaite et al., 2014).

The disparity in findings between the work of Tontisirin et al. (2007) and Satterthwaite et al (2014) may result from the differing techniques as Satterthwaite et al used MRI to index CBF and Tontisirin et al used TCD. There is very limited data regarding sex difference in intra- or extra-cranial vessel diameters in children, but it is possible that if girls have a smaller vessel diameter than boys, female flow velocities may be over-estimated with TCD. Such over estimations may account for the higher CBFv values reported by Tontisirin et al. (2007) with TCD, compared to the lower CBF values acquired with arterial spin labelling MRI from Satterthwaite et al (2014) where vessel diameter is accounted for.

1.1.3 CBF during exercise

Much of the information available on the cerebrovascular response to exercise is currently adult-based. The adult CBFv response to incremental aerobic exercise parallels increases in exercise intensity until ~60% of the maximal rate of oxygen consumption (VO_2max), whereby CBFv then either plateaus (Smith et al., 2014) or declines towards baseline values (Ellis et al., 2017; Fisher et al., 2013; Smith et al., 2012). To date, only one study has documented the impact of acute exercise on CBFv in children (Ellis et al., 2017). Ellis and colleagues (2017) assessed the MCAv response to incremental cycle ergometer exercise to max VO_2 in both children and adults. A similar pattern of change in MCAv was noted across the exercise test in the children and adults, but the increase in MCAv was attenuated in

children. For example, the peak increase above baseline noted in MCAv was about 10% in children and occurred by 50% of the ventilatory threshold. The MCAv remained elevated ~10% above baseline up until the respiratory compensation point, where a decline was then noted (See Figure 1.8). These data highlight that exercise intensity from low through to vigorous intensity provide similar gains in CBF in the child. In adults, MCAv was elevated 20% above baseline at the ventilatory threshold, declining thereafter, highlighting that in adults the greatest gains in CBF occur around MIE. Interestingly, there were no sex differences in the response to incremental exercise (Ellis et al., 2017).

In adults, as exercise approaches maximal intensity, hyperventilation causes hypocapnia and MCAv declines back toward or below baseline values (Oogh et al. 2008). In children, Ellis and colleagues (Ellis et al., 2017) demonstrated that partial pressure of end tidal carbon dioxide ($PETCO_2$) and MCAv are not correlated, and the earlier decline in $PETCO_2$ noted in children is not accompanied by a decline in MCAv (Figure 1.7).

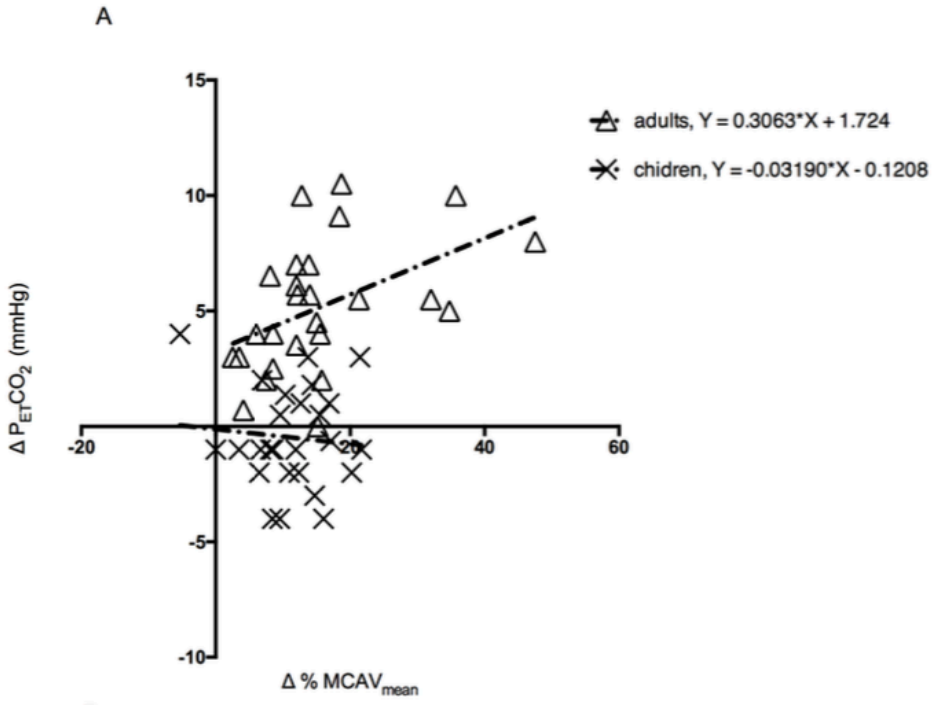

Figure 1.7 Relationship between MCAv and $PETCO_2$ up to the ventilatory threshold. Retrieved from: AJP Heart in Ellis et al., 2017, no permission required.

These data suggest that the regulation of CBF during exercise is developmentally divergent and the impact that exercise of varying intensities may have on the cerebrovasculature is most likely dependent on both age and maturation.

1.1.4 Regulation of CBF at rest and during exercise

Key factors regulating CBF at rest or during exercise include CO_2 (Ainslie and Burgess 2008), metabolism (Iadecola and Nedergaard 2007; Paulson et al. 2011) and CPP (Panerai et al. 1999; Lucas et al. 2010). Of these dominating factors, Giardino et al (2007) suggested that CO_2 might have the greatest influence on CBF, larger than the other intrinsic physiological factors. Indeed, in a more recent review by Smith & Ainslie (2017), they outline the differences of CBF regulation between rest and exercise, identifying the following primary regulatory factors at rest in order of importance: arterial blood gases (particularly the partial pressure of arterial carbon dioxide; $PaCO_2$), cerebral metabolism, arterial blood pressure, neurogenic activity and cardiac output. It appears that $PaCO_2$ is the primary influencing factor during exercise as well (Smith & Ainslie 2017), confirming earlier suggestions by Giardino et al (2007).

In adults, global CBF is positively correlated to $PaCO_2$ in an approximately linear relationship, within the wide physiological range of 20–60 mmHg $PaCO_2$ (Giardino et al, 2007). Within this range, every 1 mmHg change in $PaCO_2$ elicits a corresponding directional change in CBF of approximately 1–2 ml/100g/min, or 2–5% (Poulin et al., 1996; Ide et al., 2003). So, even a small alteration in alveolar ventilation and hence $PaCO_2$ can produce significant changes in global CBF in adults.

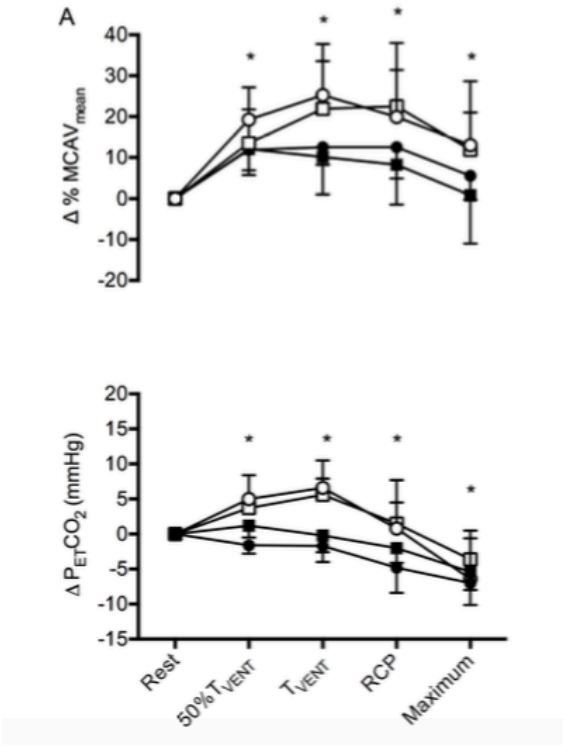

Figure 1.8 The MCAv and $PETCO_2$ responses to maximal exercise in children (black) and adults (white). Retrieved from: AJP Heart in Ellis et al., 2017, no permission required.

The mechanism by which $PaCO_2$ influences CBF is dependent on perturbations in extracellular and perivascular pH, altering the properties of vascular smooth muscle (Gotoh et al., 1961; Kontos, et al., 1977). CO_2 is hydrated in the presence of carbonic anhydrase to form carbonic acid and its dissociation by-products, bicarbonate and a proton. The resultant acidic extracellular environment enhances the vasodilatory effect of adenosine (Fenton et al., 1981) and increases potassium ion conductance across vascular smooth muscle (Karaki & Weiss, 1981), resulting in blood vessel dilation, reduced CVRi and thus increased CBF (Grubb et al., 1974). However, Ellis et al. (2017) recently found that $PETCO_2$ is not coupled to the MCAv response during exercise in children (Figure 1.8). This may be due in part to children having a lower cerebrovascular reactivity to CO_2 (Leung et al., 2016). It is possible that the increased level of resting MCAv in children limits the ability for further increases in blood supply as a potentially protective mechanism against hyperperfusion. Alongside the apparent blunted cerebrovascular reactivity to CO_2 (Leung et al., 2016), children also exhibit a lower ventilatory threshold in response to CO_2 (Gratas-Delamarche et al., 1993).

Cerebral metabolic rate of oxygen ($CMRO_2$) represents the uptake and utilization of oxygen across the arterial and venous circulations in the brain. In 1957, Kennedy and Sokoloff estimated that the child brain uses approximately 50% of total body oxygen consumption at

rest, which Chugani reported (1998) is nearly 1.3 times higher than adults. Ainslie et al later described that the adult brain, despite only weighing 2% of total body mass, still demands an inequitable 20% of basal metabolic oxygen consumption (Ainslie et al., 2016). This increase $CMRO_2$ in the child is therefore supported by an elevated global CBF, nearly doubling that of the adult during rest (Chugani, 1998).

Little is known regarding the response of CBF and $CMRO_2$ during exercise in children, and available studies focus on adult participants. Adult data are equivocal based on exercise intensity performed, with reports of $CMRO_2$ decreasing (Madsen et al., 1993), not changing (Nybo et al., 2003) or increasing (Fisher et al., 2013) with a concomitant drop in CBF during exercise (Figure 1.9).

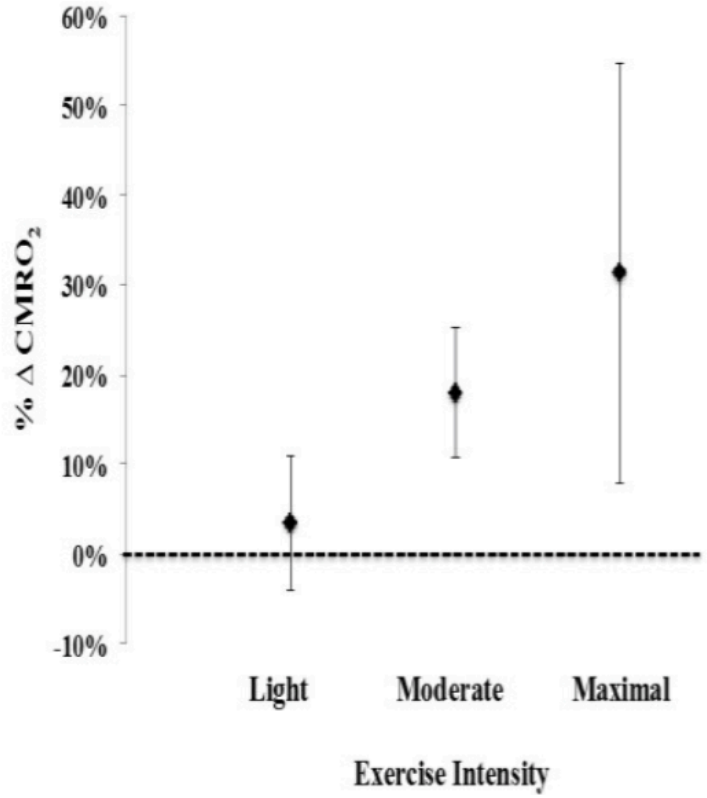

Figure 1.9 The %$CMRO_2$ response to light, moderate and maximal exercise. Retrieved from: Experimental Physiology in doi: 10.1113/EP086249, no permission required.

Perhaps the difference in reported responses can be attributed to the use of different exercise intensities and duration or the methodology used to assess CBF and $CMRO_2$. Regardless, the literature reveals interactions between global CBF, cerebral oxygen delivery and cerebral O_2 extraction, and highlights that it is the balance between these factors that influences the $CMRO_2$ response to exercise.

In addition to CO_2 and cerebral metabolism, pressure regulation in adults also elicits changes in CBF by altering CVRi (See Equation 1.1). It is thought that $PaCO_2$ and pressure autoregulation compete for the control of vessel diameter (Harper and Glass 1965), but the relationship between CBF and blood pressure alone during incremental exercise is weak. The relationship between only CBF and MAP appears to exist at rest (Willie et al., 2014), and MAP is likely still a factor within the multifaceted balance of CBF along with the other primary regulators described (Smith et al., 2017). For example, Smith et al (2017) summarized that although MAP increases with incremental exercise by 20-30% up to maximal intensities, CBF increases to a lesser extent (+15-25%) and only up to ~60% of maximal intensity, at which point CBF returns to baseline (Ogoh & Ainslie, 2009) uncoupling from MAP elevations. It does, however, seem that the pressure flow relationship remains important during HIIE when blood pressure becomes markedly elevated (Curtelin et al., 2017). The recent work by Curtelin et al (2017) suggests that despite an increase in MAP and MCAv at the onset of an all-out sprint, CBF is quickly adjusted and reduced to limit the potential risk of a hyperperfusion injury (described in detail below).

Far less is known regarding CBF regulation in children compared to adults, but what has been studied mainly describes the pressure-flow relationship in the child. Vavilala et al

(2003B) expanded our knowledge of CBF regulation in children by using metrics such as the lower limit of CA, lower limit reserve and the autoregulatory range to probe their pressure-flow relationship. The lower limit of CA is of importance since MAP decreasing below the lower limit of CA potentially increases the risk of cerebral ischemia (Vavilala et al., 2003B), and the brain seems better suited at buffering hypertension than hypotension (Tzeng et al., 2010).

Determining the lower limit of CA involves inspecting the MCAv/MAP data to determine where CBF no longer remains constant during reductions in MAP (Artru et al., 1989; Drummond, 1997). The lower limit of CA alone however cannot sufficiently estimate the risk of cerebral hypoperfusion without the concepts of lower limit reserve and autoregulatory range. The lower limit reserve is an index representing the safety margin against cerebral hypoperfusion and is derived as the difference between baseline MAP and the lower limit of CA (lower limit reserve = Baseline MAP – lower limit of CA). The relative risk of cerebral hypoperfusion must take into account the relationship of the lower limit of CA to baseline MAP. To express the margin of safety as a function of baseline MAP, the autoregulatory reserve index (autoregulatory range %) is derived from the lower limit reserve and baseline MAP (autoregulatory range % = [lower limit reserve/Baseline MAP] × 100).

Vavilala et al (2003B) set out to determine whether or not differences exist between the adult and child values of the lower limit of CA. They reported the lower limit of CA in sick children for the first time, finding: 1) the range of the lower limit of CA is similar between children under 2 years of age and adults (46–70 mmHg), 2) the lower limit of CA is not related to age, 3) older children have a greater lower limit reserve compared with younger

children, and 4) they found the autoregulatory range to be greater in older children compared with younger children (Vavilala et al., 2003B).

It is important to note that Vavilala et al (2003B) reported that baseline MAP is lower in children compared with adults. Consequently, it is often assumed that the lower limit of CA is also lower in children along with their decreased baseline MAP, allowing them to tolerate hypotension more so than adults. However, early hypotension (Vavilala et al., 2003A) and impaired CA (Kennedy & Sokoloff, 1957) are associated with poor outcome after pediatric traumatic brain injury, yet little is known regarding CA in healthy children (Tontisirin et al., 2007). In adults, a marked decline in MAP was noted immediately following sprint exercise (Curtelin et al., 2017), but it is unknown if a similar decline in MAP occurs following sprint or HIIE in children, which may challenge CA.

1.1.5 High intensity exercise in the child

It appears that HIE is well tolerated in children (Hebestreit, Mimura, & Bar-Or, 1993); however, maturational and developmental disparities exist between children and adults, which may influence the acute response to this type of exercise. Insight into the metabolic response to exercise in the child has been gained from pulmonary oxygen uptake kinetics (pVO_2 kinetics). The child's faster pVO_2 response time or tau (*t*) during MIE (Fawkner et al. 2002) and the attenuated slow-component during high-intensity exercise (Fawkner & Armstrong, 2004) provides evidence of an enhanced oxidative metabolism in the child. It seems that children have a higher arterio-venous oxygen difference (a-v O_2 diff) compared to adults (Prado, Dias, & Trometta, 2006), indicating a better balance of oxygen delivery and oxygen utilization. Indeed, children show faster muscle de-oxyhemoglobin kinetics

compared to adults, reflecting a faster local fractional oxygen extraction (Leclaire et al. 2013). The adjustment of local blood flow to exercise is also faster in the child (Koch & Eriksson, 1973; Leclaire et al. 2013), supporting an enhanced oxygen delivery during moderate and intense exercise (Koch, 1984), thereby increasing blood-myocyte oxygen flux and oxidative phosphorylation (McDonough et al. 2005). Combined, the enhanced oxygen extraction and utilization in children (Leclaire et al. 2013) is likely supported by the larger type I fibre composition (Pringle et al. 2003), enhanced oxidative enzymes (Poole & Jones, 2012), and improved local oxygen delivery (Koch, 1984; Murias et al., 2014).

It is worth clarifying the range of intensities that might encompass 'high intensity'. High intensity could be defined as any exercise within a certain percentage of VO_2max, a percentage of heart rate maximum (HRmax), percentage of the maximum external work (Wmax) achieved in the maximal exercise test, or from the gas exchange (also known as ventilatory) threshold (see Jones and Poole, 2012 for a detailed description of intensity derived from gas exchange threshold). High intensity, however, could equally mean an all-out bout of anaerobic exercise such as the 30s Wingate test. The difference in the protocol is important. If the exercise is high intensity *interval* - such as that used by Bond et al., (2015), an interval protocol of multiple short intervals (eg.. 8 x 1 minute intervals), usually at an intensity derived from a VO_2 max test, such as Wmax or HRmax (e.g., 90% Wmax) is used, and these are interspersed with active recovery periods (e.g, 75s at 20W). This interval style is similar to the start-stop activity free-living activity patterns in children (McManus et al., 2011). In contrast, when a single sprint bout is used (Curtelin et al. 2017), such the Wingate test, the intensity is much higher. This type of high intensity exercise is less likely to be emulated in free-living scenarios, more likely to be found in elite training programs.

There is some evidence that during HIIE children have faster blood H+ removal (Ratel et al. 2002) and faster cellular lactate (La) clearance (Ratel et al. 2003) compared to adults, which allows for blood pH to be maintained at higher levels during exercise. The notion that children can maintain blood pH at higher levels during exercise may relate to the preferential recruitment of type I fibres leading to an attenuated increase in Pi/PCr and decrease in pH (Mizuno et al., 1994), and enhanced oxidation of La to replenish ATP (Ratel et al. 2003). Therefore, children may not produce less La *per se,* but they may be more efficient at either utilizing it as an energy source or removing it through higher rates of ventilation, effectively regulating acid-base balance through $PaCO_2$ regulation (Ratel et al. 2002). The outcome of an enhanced oxidative metabolic engine in the child means they can exercise at intensities close to cardiopulmonary maximum without producing high levels of La resulting in a potentially faster recovery (Tolfrey & Armstrong, 1995).

1.1.6 Exercise recovery

Hill and Lupton (1923) observed that even upon the cessation of exercise, VO_2 remains elevated above resting values. This has been termed the excess post-exercise oxygen consumption (Gaesser & Brooks, 1984), which normally occurs within 1 hour of terminating exercise and works to resynthesize ATP and PCr, aids La removal, and returns ventilatory and circulatory levels to baseline.

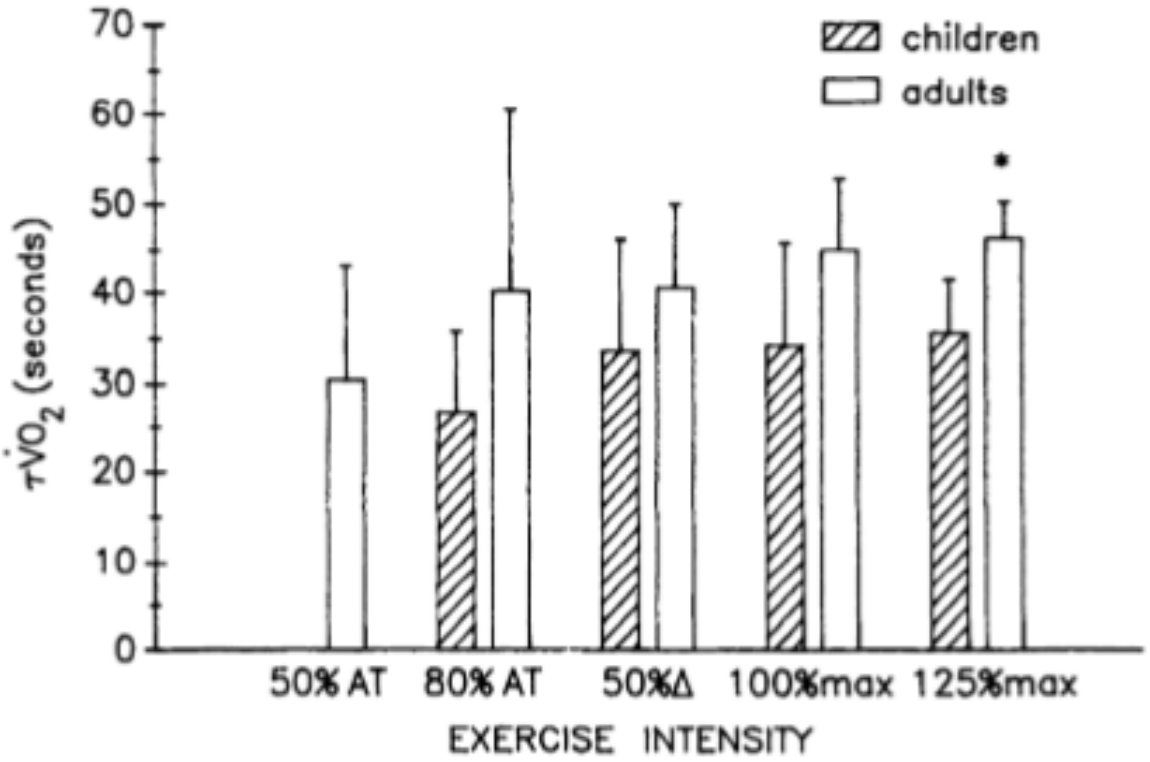

Figure 1.10 The VO_2 recovery in children and adults. The recovery of VO_2, denoted by the speed of *t*, is faster in children at the highest intensity of exercise compared to adults (*$P < 0.001$). Reproduced from Zanconato, Cooper, & Armon, 1991, permission not required.

Children recover faster following high intensity exercise than adults and this has been demonstrated using a variety of modalities of high intensity exercise. For example, following a 30s Wingate test, pre-pubertal boys (9-12 y) have faster recovery of ventilation, heart rate (HR), and $\dot{V}O_2$ compared to men (Hebestreit, Mimura, & Bar-Or, 1993). Ratel and colleagues (2006) also show the recovery of oxygen uptake is quicker in children at 125% of VO_2 max (figure 1.10). This was accompanied by a smaller decline in peak power, and running velocity. The faster recovery may reflect a more limited capacity for glycolytic metabolism because of the lower type II muscle fibres in the child (Falk & Dotan, 2006). But, this is also compensated for by the enhanced oxidative metabolism in the child. However, this developmentally divergent metabolic response to high intensity exercise ultimately may impact the adaptive responses and we know little about the impact high-

intensity exercise has in terms of eliciting rapid increases in arterial blood pressure (BP) during the high intensity exercise, or substantial declines after, which both may adversely impact CA.

In adults, exercise above 70% VO_2max results in hyperventilation-induced-hypocapnia and hence cerebrovascular vasoconstriction and subsequent declines in CBF values (Moraine et al., 1993; Subudhi et al., 2008; Smith et al., 2012). This reduction in CBF may be a neuroprotective response to prevent flow disturbances and hyperperfusion injury. Although only found during rest, CBF reductions have been associated with improved CBF regulation during changes in blood pressure (Brassard et al., 2012; Maggio et al., 2013; Aaslid et al., 1989). Ellis et al. (2017) demonstrated in children that during exercise, hyperventilation-induced hypocapnia has minimal impact on MCAv; However, it should be noted that the peak CBFv response to exercise was about 50% of the response in adults. Additionally, Ellis et al (2017) note that although CVRi was lower in children compared to adults, the delta change in MAP with exercise was not related to the delta change in MCAv in children.

1.1.7 High intensity exercise and CBF

There is sparse evidence of CBF during high intensity exercise and to date, none documenting the CBF response to HIIE in children. Previous work has shown that the MCAv response to incremental exercise was attenuated in children compared to adults (Ellis et al., 2017), but values were still elevated 8-10% above baseline at the respiratory compensation point, before returning to baseline as exercise intensity approached maximum.

There is one adult study documenting the CBF and MAP responses to a single 30-s Wingate

test (Curtelin et al. 2017). During the sprint, mean systolic blood pressure (SBP) increased to 200 mmHg, while diastolic blood pressure (DBP) was maintained at pre-sprint values resulting in a 16 mmHg increase in MAP from 115 to 131 mmHg. When examining the time-course, Curtelin and colleagues (2017) showed a downward curvilinear response in CBF, indexed by MCAv. After 7.5s into the Wingate test, adult MCAv peaked to 16% above baseline values, falling thereafter to 10% below baseline by the end of the 30s sprint.

A cerebrovascular conductance (CVC) score of 1.00 indicates impaired cerebrovascular conductance (CBF/MAP). Willie et al (2014) reported a normal CVC range of 0.21 to 0.81 indicating regular CVC. Indeed, Curtelin et al (2017) reported a CVC value of 1.08 during the single all out Wingate sprint, suggesting the cerebral circulation may have been exposed to the potentially harmful effects of high blood pressure combined with increased CBF (hyperperfusion). It is important to consider that immediately following the sprint a fast decline in MAP ensued, and it is possible that the resultant hypotension poses also an additional challenge to cerebral hemodynamics. Within the first 2.5s of recovery Curtelin et al (2017) reported a 26% decline in MAP with a concomitant 18% decline in MCAv from exercise values. Compared to baseline values, MCAv was still reduced by 10% ($P < 0.05$) upon sprint cessation, but despite these marked declines in MAP and MCAv, frontal lobe oxygenation during the first 15 seconds of recovery remained at a similar level to that reached during the last 5 seconds of the sprint, suggesting cerebral oxygenation is preserved despite such hypoperfusive autoregulatory challenges. How HIIE may affect cerebral perfusion in the child is not currently known.

1.1.8 Summary

To summarise, HIIE has emerged as a time efficient and effective alternative to current exercise regimes, providing superior cardiorespiratory adaptations (Baquet *et al*., 2010; Baquet *et al*., 2002; McManus *et al*., 2005) and appears to be better tolerated in children compared to continuous exercise (Timmons & Bar-Or, 2003) Regardless of the reported positive effects and suitability of HIIE, the lack of evidence to date examining how HIIE affects cerebrovascular function raises concerns about its global promotion (Lucas *et al*. 2015).

Evidence in adults suggests that high intensity exercise creates a considerable hemodynamic impact, with marked increases in systolic blood pressure during the sprint and rapid declines in the immediate recovery period challenging cerebrovascular regulation (Curtelin *et al*., 2017). Children support high intensity exercise with a greater oxidative metabolic contribution compared to adults (Chia et al., 1997), making them more fatigue-resistant to repeated bouts of high intensity exercise (Hebbestreit *et al*., 1993). It is unclear if a similar cerebrovascular response to a high intensity exercise bout would be noted in children. Previous work has shown that the MCAv response to incremental exercise was attenuated in the child compared to adults (Ellis et al., 2017), but remained 8-10% elevated above baseline up until the respiratory compensation point, before returning to baseline. In addition, these alterations in MCAv during incremental exercise were not correlated with $PETCO_2$ (and unrelated to changes in MAP (Ellis et al., 2017).

The purpose of this study was to compare the impact HIIE and continuous MIE have on cerebrovascular function in children. To achieve this, a randomized cross-over trial was completed with 7-11 year old boys and girls, completing six high intensity one-minute sprints, as well as continuous MIE matched for external work. The MCAv and $PETCO_2$ were assessed at baseline and during recovery following both exercise conditions (immediately post-, 30 minutes post- and 60 minutes post HIIE and MIE). In addition, MAP was collected at baseline, during the final minute of exercise as well as 30 minutes post- and 60 minutes post HIIE and MIE. The MCAv was also measured continuously throughout HIIE and MIE.

The hypotheses were

(i) Increases in MCAv would be greater in response to MIE compared to HIIE

(ii) MAP will be lower in the final minute of MIE compared to HIIE, resulting in a lower CVRi in MIE compared to HIIE.

(iii) The MCAv would be lower than baseline immediately post HIIE but not MIE, recovering to baseline values by 30 minutes post exercise;

(iv) $PETCO_2$ will be lower immediately post HIIE compared to MIE.

Chapter 2 Methods

Nineteen children aged 7-11 years volunteered to participate in this study. Participants were pre-pubertal (Tanner 1) determined by parental assessment of Tanner staging (Rasmussen et al., 2015). Each participant had a health history clear of cardiorespiratory and cerebrovascular diseases and none had any medical conditions that would influence cerebral perfusion or the ability to exercise. Children were excluded from participating if training >10 hours/week for sport or competition. This study was approved by the Clinical Research Ethics Board of the University of British Columbia (H15-02104). Written consent was obtained from the parents and written assent from the child.

2.1 Experimental design and procedures

A crossover trial with two experimental conditions was employed, including HIIE and MIE both performed on a cycle ergometer.. HIIE consisted of a 3-minute unloaded pedalling warm-up (0 W) followed by six 1 min sprints pedaling at 90% Wmax, separated by active rest intervals of 1 min of pedaling at 20% Wmax. This protocol was selected based on the work by Bond et al in 2015 who used 90% Wmax and 20% Wmax for exercise and rest intervals, respectively, although they incorporated 8 sprint intervals separated by 75s recovery periods. We found that completing 8 sprints was not well tolerated in this age group following pilot testing, so we reduced the protocol to 6 sprints, but limited the recovery period to 60s. The MIE was matched to HIIE for external mechanical work completed, beginning with a 3-minute unloaded warm-up (0 W) and entailed 15 min of cycling at ~44% Wmax. The order of completion was randomized.

Each participant visited the laboratory on 3 occasions separated by a 48 h break. Each visit occurred at the same time of day and participants were asked to arrive 2 hours fasted, well hydrated and having abstained from vigorous exercise and caffeine for 24 hours before participating. A low-fat snack was allowed while participants waited their turn and the same snack was brought for remaining visits. The first visit was used for familiarisation and to complete anthropometric measurements and a maximal exercise test. During the two experimental visits participants completed baseline measurements of HR, MAP, $PETCO_2$ and MCAv. The MCAv was assessed continuously throughout HIIE and MIE and MAP was taken during the final minute of exercise in both conditions. Following exercise, $PETCO_2$ measurement resumed for 5 minute intervals immediately post-, 30-minutes post- and 60 minutes post-exercise, and BP was taken at 30 minutes post- and 60 minutes post-exercise.

2.2 Measurements

2.2.1 History of CBF measurement

In 1945 Seymour Kety and Carl Schmidt were the first to measure CBF in humans using a low concentration of nitrous oxide inhalation (15%) along with internal jugular venous and femoral artery samples. Flow was calculated from a modified Fick equation (Equation 2.1.):

Equation 2.1. $$CBF = 100\ Q_t\ (A\text{-}V)t$$

Where: CBF is cerebral blood flow (in ml/100g brain mass/minute); Q_t is the quantity of oxygen consumed over time (expressed as ml/100g brain mass); *A* and *V* represent the arterial and cerebral venous oxygen content as a percent of volume; *t* is time in minutes.

Previously described techniques of measuring CBF (Kety & Schmidt, 1945; Kety & Schmidt, 1948; Gibbs et al., 1946; Lassen & Munck, 1955; Hoedt-Rasmussen, 1966; Ingvar DH, Lassen, 1961; Ingvar et al., 1965; Olesen et al., 1971) revealed the dynamic changes in CBF since the regional and global CBF measures required 10-20 minutes per measure. In 1982, Aaslid and coworkers (Aaslid et al., 1982) used non-invasive TCD to evade the time scale issue for estimation of CBF with a real-time index.

2.2.2 Principles of TCD

TCD is based on the classic principles of Doppler ultrasound, whereby sound waves are transmitted through the acoustic windows of the cranium to target certain cerebral vessels, namely the MCA for this investigation. The Doppler probe emits a 1.5-2 MHz wave, which provides optimal resolution given the depth of the deeper cerebral arteries (Willie et al., 2011). The transmitted signal from the probe reaches red blood cells within the target vessel and reflects the receiving signal back to the transducer, where the difference is recorded (Doppler Principles; see equation 2.2) (Willie et al., 2011).

Equation 2.2. $\text{Doppler shift} = 2 \times Ft \times V \times \cos\theta / C$

Where: *Ft* is the transmitted frequency (2 MHz); V is the velocity of the reflector (red blood cells); $\cos\theta$ is the correction factor based on the angle of insonation; and C is the speed of sound in the blood (1540m/s).

The frequency data is then converted to the time domain through a fast Fourier transform for tangible velocity measures. The minimum angle of insonation required for TCD must be

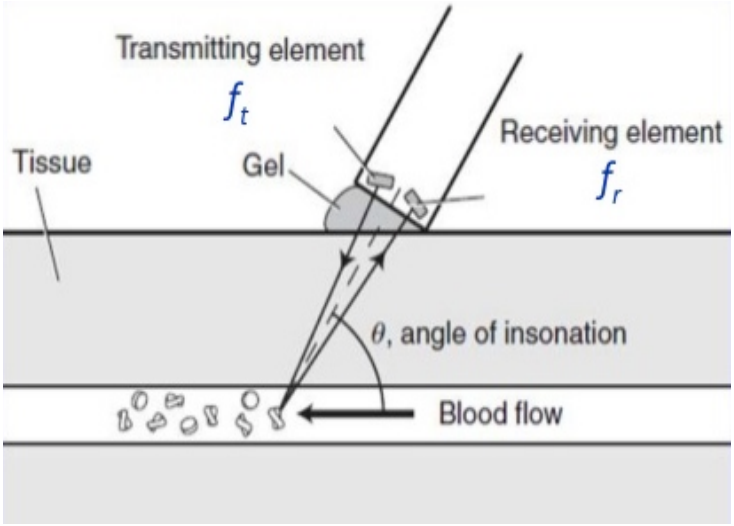

Figure 2.1. Example of the Doppler shift. The frequency difference between the transmitted signal (f_t) and the receiving signal (f_r) is used to determine the direction and velocity of the red blood cells.

below 60 degrees (cosine of 0.50), although it is encouraged to reduce this angle to between 0 and 30 degrees (cosine range 1.00 to 0.87) for optimal quality (See Figure 2.1) (Wintermark et al., 2005). The MCA is particularly in line with the probes typically resulting in an insonation angle below 15 degrees (Wintermark et al., 2005).

2.2.3 Technique of TCD

The process of collecting MCAv measures with TCD begins with a generous application of acoustic gel to the temporal window and probe for optimal signal conduction. An adjustable headband stabilizes probe positioning and maintains the signal quality during data collection. It is imperative that the sonographer has an understanding of the basal structure of the circle of Willis and the common insonation depths associated with each vessel (MCA: 30-65 mm; PCA: 55-75 mm) (Alexandrov et al., 2007). Techniques to confirm the insonated vessel include carotid artery occlusion resulting in a diminished MCAv and unaltered PCAv and an occipital lobe stimulation (eyes open and closed) where the PCAv will increase by up to 20% with eyes open whereas velocity in the MCA will increase much less (<5%).

2.2.4 CBFv acquisition

In this study, MCAv was measured unilaterally (left side) using a 2 MHz TCD ultrasound (Spencer Technologies, Colorado). The MCA was insonated through the trans-temporal window using previously described techniques (Willie et al., 2011). The coefficient of variation for day-to-day reproducibility of MCAv was 6.2% for this study. MCAv was recorded continuously during the VO_2max test, as well as during and after the two experimental exercise conditions.

2.2.5 Anthropometric measurement

Body mass was measured to the nearest 0.1Kg with bioelectrical impedence (Tanita TBF-410GS, Arlington Heights, Illinois). Stature was measured to the nearest 0.1cm with a stadiometer (Seca 213 Portable, Hamburg, Germany). Only healthy weight participants (BMI 16.34±2.09) were included in the data analyses defined as those with a body mass index (BMI) within 1 standard deviation (±) of the World Health Organization (WHO) growth standard median (Onis et al., 2007).

2.2.6 Maximal exercise test

Participants performed a ramp maximal test with supramaximal verification to determine VO_2max and Wmax. The test began with an unloaded 3 minute pedaling warm-up followed by a stature specific workload increase (<110cm 5 $W \cdot min^{-1}$, 110-125cm 10 $W \cdot min^{-1}$, 125-150cm 15 $W \cdot min^{-1}$, >150cm 20 $W \cdot min^{-1}$) until volitional fatigue. Participants were asked to maintain a pedal cadence between 70-80 rpm during exercise and volitional fatigue was

defined as a cadence drop below 60 rpm for five consecutive seconds. Participants completed 5 minutes of unloaded active cool down following exercise then 10 minutes of passive rest prior to a supramaximal verification test. In brief, following a 2-minute warm-up, children completed a 'step' transition to 105% of the maximum power achieved during the ramp test. Participants cycled at this intensity until exhaustion. VO_{2max} was verified if the VO_2 slope of increase between the maximal and supramaximal tests increased by ≤5% (Barker et al., 2011). Respiratory gas exchange was assessed breath-by-breath throughout the duration of the ramp and supramaximal tests using an online gas analyzer (Oxycon Pro, Viasys Jaeger; Hoechberg, Germany) first calibrated with gas of a known concentration and flow volume. Data were interpolated to 1s and averaged every 15s.

2.2.7 HR and arterial blood pressure

A three-lead ECG was used to assess beat-by-beat HR. SBP and DBP were measured 3 consecutive times at rest, averaging the last 2 measurements for the resting value, and then in the final minute of exercise, 30-minutes post and 60-minutes post exercise with a manual sphygmomanometer (Prestige Medical, 79-BLK Standard Aneroid, Northridge CA). Values were recorded to the nearest mmHg. DBP was defined as the point of disappearance of Korotkoff sound (5th phase) and MAP was subsequently calculated.

2.2.8 CVRi acquisition

The CVRi was calculated as MAP divided by MCAv (mmHg/cm.s^{-1}) at rest, the final minute of exercise in both conditions, and during each of the recovery time points.

2.2.9 $PETCO_2$ acquisition

Samples of $PETCO_2$ were collected using a calibrated online gas analyzer (ML206; ADInstruments, Colorado Springs, CO) before and after the two experimental trials (pre, post, 30-minutes post and 60-minutes post exercise), each for 5 minutes in duration. $PETCO_2$ was not assessed during HIIE or MIE because children did not tolerate the mouthpiece/noseclip during HIIE.

2.3 Statistical analyses

Descriptive data are expressed as mean ± SD. Changes in MCAv during exercise is presented as both an absolute (Δ) and relative change (Δ%) from baseline. The response of the main outcome measures (MCAv, $PETCO_2$, MAP & CVRi) during and after MIE and HIIE were examined using repeated measures analyses of variance (ANOVA), with follow-up t-tests where necessary using Bonferroni corrections. The ΔMCAv and $\Delta PETCO_2$ responses were assessed at each recovery point. An alpha level was set a priori at 0.05. Statistical analyses were performed using SPSS (version 24, SPSS Inc., Chicago, IL, USA).

Chapter 3 Results

3.1 Descriptive data

Data are presented on 9 of the 19 participants recruited. One child was not included in the analyses because they were already pubertal (Tanner 3 for both pubic hair and breast development). One child did not want to return after the maximal exercise test, one child ate a bacon sandwich prior to testing, one child performed vigorous exercise within 24 hours and

the MCA could not be insonated or resulted in inconsistent day-to-day measures in the remaining 6. Of the 9 participants included in the analyses, 4 were boys (age 9.0± 2.2y; stature 137.1± 15.2cm; body mass 30.6± 10.3kg) and 5 were girls (age 10.4± 0.9y; stature 148.8± 3.8cm, body mass 37.4± 6.2kg). All children completed a VO_{2max} test with a maximum wattage of 124±27 W (range 67-156W); HRmax of 193 beats.min^{-1} (range 183-195 beats.min^{-1}); maximum MAP of 94.1±11.7 (range 81.3-118.0); the MCAv at maximum VO_2 was 80.4±7.8 cm.s^{-1} (range 66.8-91.6 cm.s^{-1}).

3.2 HR and MCAv responses during HIIE and MIE

Continuous HR was collected with 3-lead ECG throughout the entire protocol. For congruency with other data, HR is displayed in minute-by-minute averages as a descriptive of the cardiovascular effects of the different exercise conditions (See Figure 3.1). When HR was expressed in absolute terms, there was a main effect for time ($F(11, 110) = 42.715$, $P<0.001$, $\eta^2= 987.891$) and intensity ($F(11, 110) = 12.915$, $P<0.001$, $\eta^2= 298.694$; see Figure 3.1).

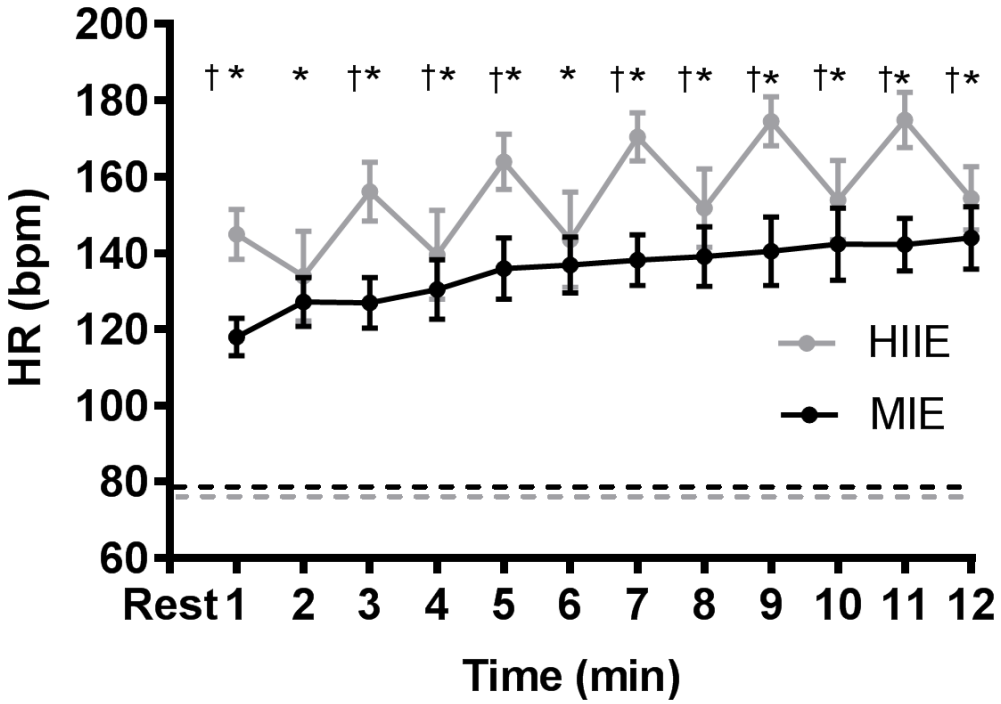

Figure 3.1. Minute-by-minute HR values during HIIE (grey line) and MIE (black line). For the HIIE condition every odd minute (1,3,5 etc.) represents an exercise interval, whereas even minutes (2,4,6 etc.) represent active rest intervals. The dotted lines represent baseline HR values. * significant difference from baseline P<0.05; † significant difference between conditions.

Absolute values for MCAv during HIIE and MIE are provided in Table 3.1 and expressed as minute by minute averages to unveil the difference between rest and exercise intervals during HIIE. The MIE condition was extracted using the same minute to minute technique for the purpose of comparison. When expressed as a percentage change from baseline (%ΔMCAv) there was a main effect for time ($F(12, 192) = 29.096$, $P<0.001$, $\eta^2= 0.645$), in an intensity specific manner ($F(12, 192) = 3.647$, $P<0.001$, $\eta^2= 0.186$; see Figure 3.2). Follow-up analyses revealed that MCAv increased and remained elevated above baseline values (p's<0.05) for the first 3 minutes of HIIE and 4 minutes of MIE, before returning toward baseline (see Table 3.1 & Figure 3.2).

Table 3.1. MCAv during HIIE and MIE.

HIIE (n=9)		MIE (n=9)	
Time (min)	MCAv ($cm.s^{-1}$)	Time (min)	MCAv ($cm.s^{-1}$)
Base	74.20 ± 5.17	Base	72.70 ± 2.01
1	*83.49 ± 6.99	1	*78.18 ± 6.27
2	*83.82 ± 7.34	2	*79.86 ± 6.56
3	*78.38 ± 5.46	3	*77.79 ± 7.23
4	77.11 ± 6.81	4	*76.72 ± 5.96
5	72.96 ± 5.47	5	75.62 ± 5.14
6	73.44 ± 6.90	6	74.81 ± 5.56
7	*70.98 ± 5.33	7	73.61 ± 4.95
8	74.62 ± 7.61	8	74.68 ± 5.14
9	*70.83 ± 5.28	9	73.63 ± 4.08
10	73.54 ± 7.60	10	72.14 ± 4.46
11	*70.38 ± 4.93	11	71.50 ± 5.00
12	72.57 ± 8.20	12	72.08 ± 4.50

MCAv, middle cerebral artery velocity (cm/s); Base, baseline. Table includes twelve minutes of minute-by-minute absolute values. In the HIIE condition every odd minute (1,3,…) represents an exercise interval average and each even minute (2,4,…) represents a rest interval average. MIE is minute-by-minute averages.

*significant difference from baseline $P<0.05$.

The MCAv remained above baseline from the onset of exercise until the 4th minute of MIE (6.9% and 5.4%, respectively; p's <0.05) before declining back to baseline for the remainder of the MIE trial (see figure 3.2). In the HIIE condition, follow-up analyses revealed a 12.1% increase in MCAv during the first sprint interval (P<0.001), remaining elevated above baseline during the first rest interval (12.7%; P<0.05). During the second sprint interval, MCAv remained 5.4% above baseline (P<0.05), but declined thereafter, with significant reductions below baseline by the 4th (-4.6%), 5th (-4.8%) and 6th sprint intervals (-5.3%). During the rest intervals between sprints, MCAv returned to baseline (see figure 3.2).

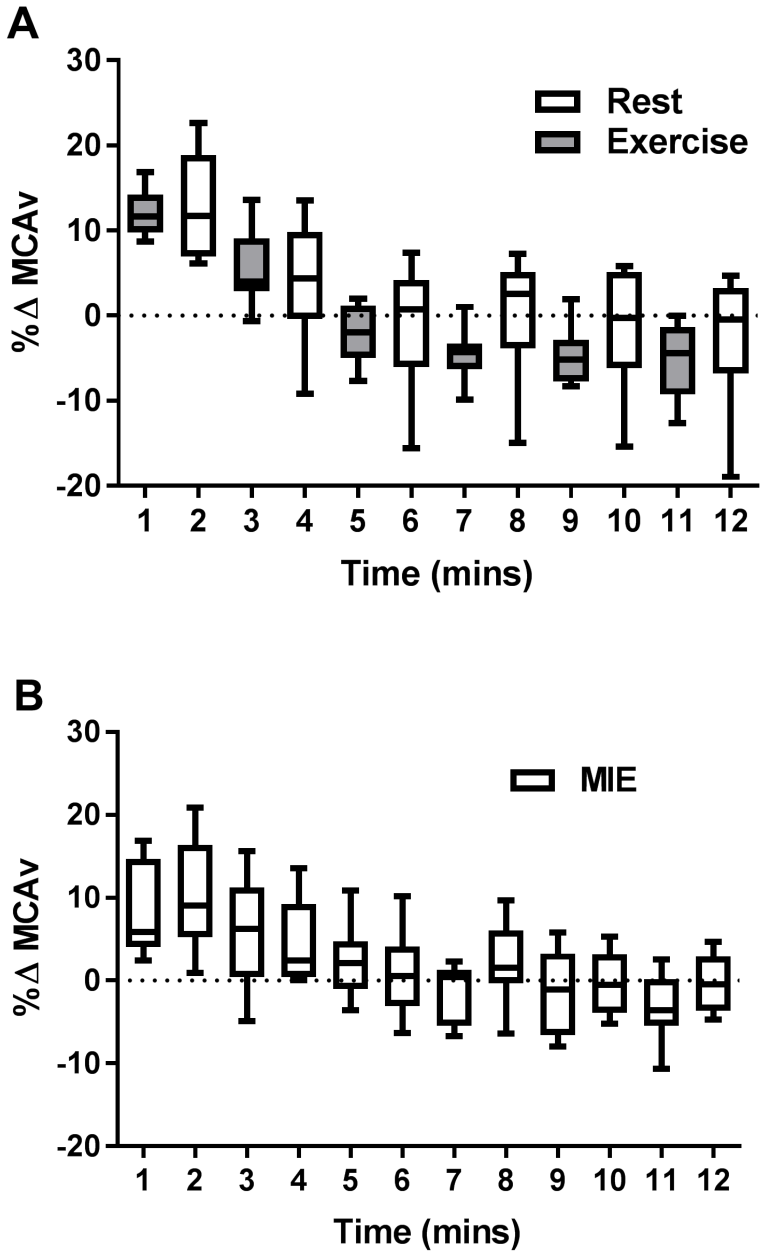

Figure 3.2 The relative change in MCAv (%) during HIIE (panel A) exercise (Ex) and rest (rest) intervals and MIE (panel B). Individual data are provided within the bars (black dots). * significant difference from baseline P<0.05.

It seems that during exercise the MCAv responses are similar between HIIE and MIE at the onset of exercise until the 4th HIIE sprint, thereafter MCAv oscillated significantly below

baseline during HIIE and returned to baseline during rest, whereas MCAv was maintained at baseline values beyond the 4th minute of MIE.

3.3 MCAv and $PETCO_2$ responses following HIIE and MIE

The MCAv is illustrated in figure 3.3 (panel A) at baseline, immediately post exercise, 30 minutes post- and 60 minutes post exercise. There was no main effect for time or an interaction, with MCAv remaining at baseline values after both exercise conditions.

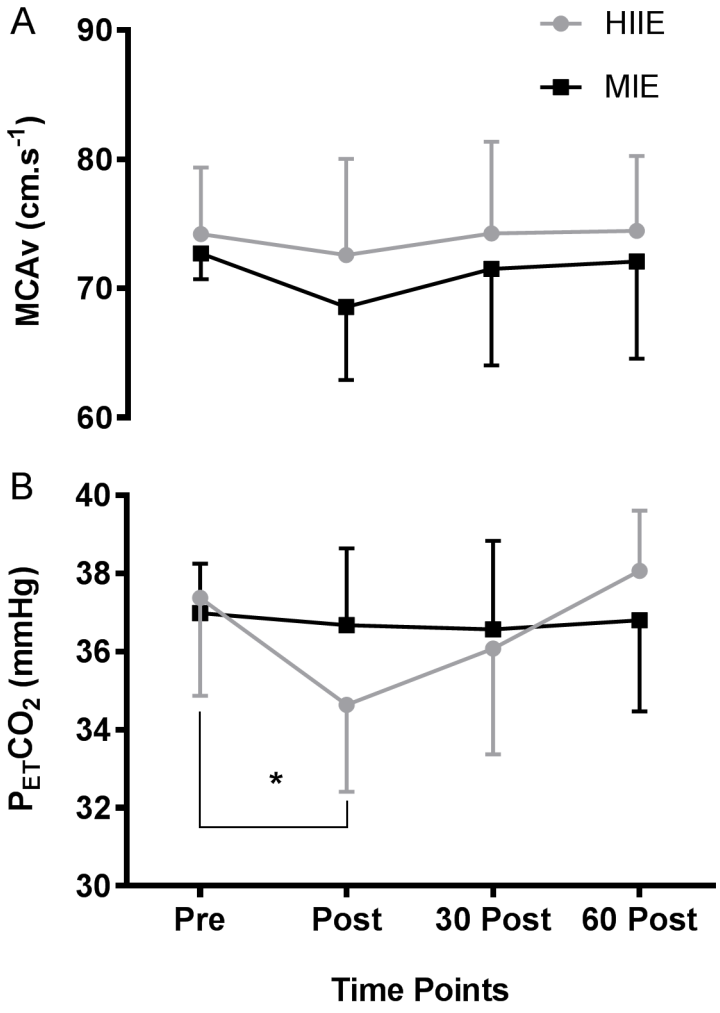

Figure 3.3 The response of MCAv (A) and $PETCO_2$ (B) at baseline (pre), immediately following HIIE and MIE (Post), 30 minutes post exercise (30 Post) and 60 minutes post HIIE and MIE (60 Post). The grey lines represent HIIE and the black lines represent MIE. *significant difference from baseline $P<0.05$.

$PETCO_2$ at baseline, at the end of HIIE and MIE, as well as 30- and 60-minutes post exercise are presented in figure 3.3, panel b. There was a main effect of time ($F(3,48) = 6.339$, $P<0.001$, $\eta^2= 0.284$), and an interaction ($F(3,48) = 4.765$, $P<0.05$, $\eta^2= 0.229$). Simple effects revealed a 7.1% decline in $PETCO_2$ after HIIE, which returned to baseline values within 30 minutes post exercise. The $PETCO_2$ remained unchanged from baseline following MIE and at all recovery time points.

3.4 MAP, MCAv and CVRi during the final minute of HIIE and MIE and during recovery.

MAP was assessed at baseline, at the end of exercise and during recovery. MAP changed with time ($F(3, 48) = 45.184$, $P<0.001$, $\eta^2= 0.738$), but there was no interaction (see Table 3.2). In both exercise conditions, MAP was increased to a similar extent at the end of exercise ($p's<0.001$), before returning to baseline at 30 minutes and 60 minutes post exercise.

Table 3.2. MAP and MCAv and CVRi at baseline, during and following HIIE and MIE.

	Time	MAP (mmHg)	MCAv ($cm.s^{-1}$)	CVRi
HIIE	Base	81.71 ± 3.78	76.78 ± 5.17	1.07 ± 0.09
	Ex	*90.63 ± 3.82	*70.21 ± 4.59	*1.30 ± 0.10
	30 post	82.31 ± 6.70	75.95 ± 5.10	1.07 ± 0.11
	60 post	81.79 ± 5.29	77.06 ± 4.97	1.07 ± 0.10
MIE	Base	81.26 ± 4.18	70.93 ± 6.65	1.15 ± 0.11
	Ex	*87.96 ± 4.35	71.88 ± 7.13	*1.23 ± 0.13
	30 post	81.97 ± 4.15	71.17 ± 7.32	1.17 ± 0.11
	60 post	80.74 ± 4.63	71.89 ± 5.80	1.13 ± 0.09

MAP, mean arterial pressure; MCAv, middle cerebral artery velocity; CVRi, cerebral vascular resistance index; Base, baseline; Ex, final minute of exercise; 30 post, 30 minutes post exercise; 60 post, 60 minutes post exercise.

*significant difference from baseline $P<0.05$.

Figure 3.4 illustrates CVRi expressed as a percentage change. There was a main effect of time ($F(3,48) = 50.852$, $P<0.001$, $\eta^2 = 0.761$) and an interaction ($F(3,48) = 12.606$, $P<0.001$, $\eta^2 = 0.441$).

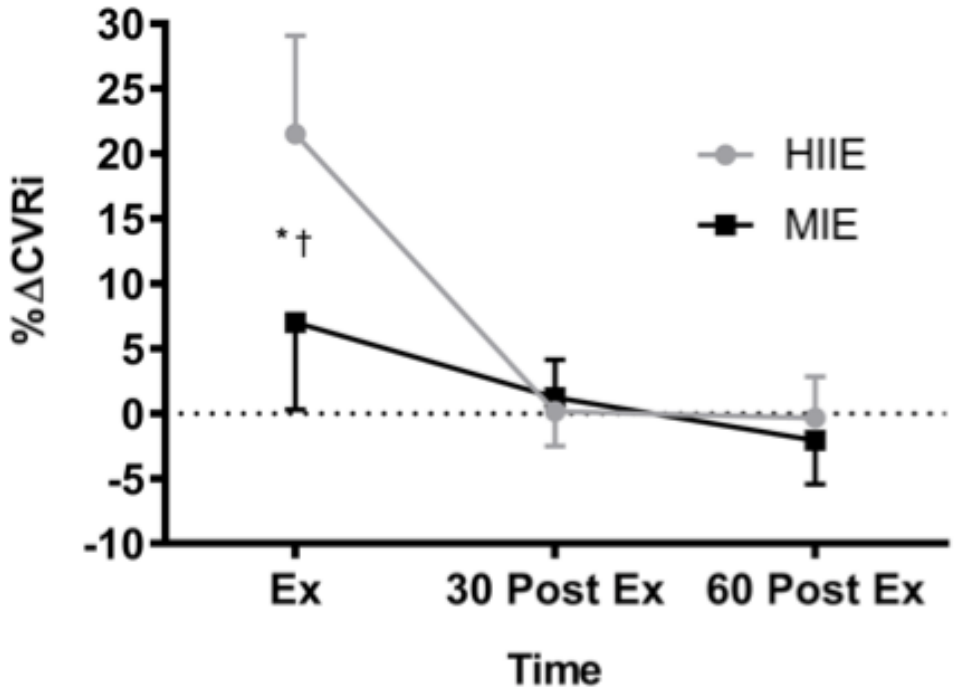

Figure 3.4 The response of the relative change in CVRi to exercise and during recovery. Ex, final minute of exercise; 30 Post Ex, 30 minutes post exercise; 60 Post Ex, 60 minutes post exercise. * significant difference ($P<0.05$) from baseline; † significant difference ($P<0.05$) between HIIE and MIE.

The %ΔCVRi significantly increased from baseline during the final minute in both exercise conditions (p's<0.05), although the magnitude of this increase was greater during HIIE, with CVRi elevated 21.5% above baseline during the final minute of HIIE, and only 7.0% during MIE. CVRi returned to baseline values 30 minutes post exercise in both conditions (see figure 3.4).

Chapter 4 Discussion

4.1 Experimental findings

The main findings of the current study were as follows: HIIE and MIE elicited a similar MCAv response during the first 3 minutes of exercise, with MCAv elevated for the first 3 minutes of HIIE and for the first 4 minutes of MIE. Although MCAv was maintained at baseline values throughout the remaining duration of MIE, this differed from the HIIE condition whereby MCAv decreased significantly below baseline for the final 3 sprints and oscillated back to baseline in the remaining rest intervals. The oscillatory nature of MCAv during HIIE may be due in part to the rapid redistribution of blood to the working muscles during exercise resulting in decreased MCAv at that time. The CVRi was higher in HIIE compared to MIE during the final minute of both exercise intensities ($P<0.05$). Although this difference was perhaps mediated via the selective hypocapnia resulting from hyperventilation during HIIE, we did not collect $PETCO_2$ during exercise. The changes in CVRi were normalized at 30 minutes post- and 60 minutes post exercise in both conditions. Immediately post HIIE, MCAv returned to baseline uncoupling from the $PETCO_2$ response, which fell significantly below baseline ($P<0.05$). Following MIE, however, MCAv and $PETCO_2$ exhibited a similar response remaining at baseline immediately post MIE (See Figure 3.3). The following discussion outlines these findings and highlights strengths and limitations associated with our experimental design.

4.1.1 Cerebrovascular responses during HIIE and MIE

Contrary to our first hypothesis, we did not find a significantly greater increase in MCAv during MIE compared to HIIE. In previous work investigating the child's cerebrovascular response during maximal exercise, Ellis et al (2017) found no significant change in the child's %MCAv from baseline, despite modest increases of ~10% up until the respiratory compensation point, before MCAv began to decline back toward baseline. Similar to the work by Ellis et al (2017) we found that during HIIE, the MCAv increased above baseline in the initial 3 minutes of HIIE before declining to and below baseline for the remainder of the protocol. Regarding the effects of MIE on MCAv, Ogoh & Ainslie (2009) summarized in adults that MCAv remains elevated above baseline throughout the duration of a continuous bout of MIE, although no child data other than those presented here is currently available. We found that the child's MCAv remained elevated only for the first four minutes of continuous MIE before returning to baseline values for the remainder of the test. Perhaps, this is in part due to the already elevated resting MCAv levels in children compared to adults, which is sufficient for the child's cerebral oxygen demands.

Finally, during the last minute of exercise in HIIE and MIE, the CVRi was calculated to investigate a metric considering both MAP and MCAv (see Equation 1.1). We found that CVRi significantly increased in the final minute of exercise in both HIIE and MIE ($P's<0.05$), but this was exacerbated in HIIE ($P<0.05$). The elevated CVRi response noted in HIIE compared to MIE may be partly due to the hyperventilation-induced hypocapnia resulting from a harder work rate associated with HIIE compared to MIE. The $PETCO_2$ was only collected during recovery (discussed below), however, so no further conclusions can be

made since we did not monitor $PETCO_2$ during the final minute of exercise. Although MAP significantly increased from baseline during the final minute of exercise in both conditions, MAP did not significantly differ between intensities. Interestingly, MCAv during the final minute of exercise was at baseline in MIE and below baseline in HIIE, suggesting that perhaps HIIE does not pose any risk of hyperperfusion to the child compared to MIE.

4.1.2 Cerebrovascular responses following HIIE and MIE

As a surrogate measure of $PaCO_2$, intermittent samples of $PETCO_2$ were collected at baseline as well as throughout acute recovery following both HIIE and MIE, and findings support the final hypothesis. Immediately post HIIE, the $PETCO_2$ values fell significantly below baseline, which may correspond with the harder work rate and likely increased ventilation during HIIE compared to MIE. The decline in $PETCO_2$ immediately post HIIE was not coupled with a decrease in MCAv. The CVRi significantly increased during the last minute of exercise in HIIE, and perhaps this was mediated via a hypocapnic response associated with HIIE eliciting the decline in MCAv in the final minute of HIIE. Thereafter, the CVRi returned to baseline in HIIE following 30 minutes of recovery, as did $PETCO_2$. The MCAv and $PETCO_2$ values immediately following MIE remained at baseline values and did not change throughout the hour of recovery.

4.1.3 Experimental considerations

A similar approach to Bond et al (2015) was used to determine the work rates of HIIE. Exercise intervals in HIIE were performed at 90% Wmax, lasting 1 minute in duration as Bond et al (2015) did. The protocol differed from that used by Bond et al (2015) in rest

intervals, which were calculated as 20% Wmax rather than a set 20W resistance, and the recovery time was reduced from 75 seconds to 60 seconds. Work completed during rest intervals was altered so it was relative to the individual child and a reduced resting period time compared to Bond et al (2015) was incorporated compensate for decreasing the 8 exercise intervals used down to 6 intervals in our experiment. We reduced the number of intervals due to lack of completion by the first 3 participants despite lots of encouragement. Our participants achieved an average HR of 80% HR max across the entire HIIE protocol, although this is an average and was not achieved in every participant. Across all exercise intervals the average HR increased to 85% HR max indicating hard working efforts. There is, however, an issue in the derivation of such values from an initial maximum test that may not sufficiently stress the child's anaerobic system. Previous findings demonstrate that children completing a standard VO_2max test do not experience significant increases in blood La (Armstrong et al., 1996). Armstrong and colleagues (1996) found that blood La can be further increased in children when completing a supramaximal exercise test. We specifically chose a high-intensity, interval modality as this is closer to the free-living physical activity patterns in children (Berman et al., 1998), compared to a one-off Wingate all-out bout of exercise (Curtelin et al., 2017). It is likely our findings are indicative of free-living 'high-intensity' exercise, but do not reflect response to all-out exercise such as the Wingate test.

4.1.4 Strengths and limitations

Limitations to this experiment include a reduced sample size, not separating for sex differences, not providing continuous measures of MAP or $PETCO_2$, not collecting La and using velocity measures as opposed to true CBF. Initially 19 participants were recruited to

participate in this study and sex differences would have been explored. The main reason for exclusion was an inability to repeat the day-to-day MCAv baseline values across all three visits.

The use of TCD has been under scrutiny since recent MRI work revealed MCAv diameter increases in response to increases in $PETCO_2$ greater than ~8 mmHg (Coverdale et al., 2014; Verbree et al., 2014). A large reduction in $PETCO_2$ may result in constriction of the MCA diameter by ~4% (Coverdale et al., 2014). However, the changes in $PETCO_2$ during HIIE and MIE in the current experiment were relatively minor and are unlikely to have elicited either constriction or dilation in the MCA.

The protocol used in this experiment, although eliciting a higher cardiovascular response, was not as metabolically taxing as expected. Perhaps future work investigating the effects of HIIE on the child's cerebrovasculature should consider the recent protocol used by Curtelin et al (2017), who tested the cerebrovascular response in adults to an all-out Wingate (30s) test. The time-course of CBFv, $PETCO_2$ and MAP could be explored, and it might also be prudent to collect blood La, although acquiring beat to beat blood pressure and La during HIIE would likely prove to be too invasive in child.

4.2 Conclusion

To conclude, although the current findings reveal noteworthy differences in the cerebrovascular responses to HIIE and MIE (See Figure 3.2), it appears that HIIE poses no additive risk of hyperperfusion injury compared to MIE in the child. The regulatory effects of $PaCO_2$ ($PETCO_2$) may be diminished in children immediately following HIIE, although this differs from MIE as $PETCO_2$ and MCAv remained coupled at baseline. The uncoupling

between MCAv and $PETCO_2$ noted immediately following HIIE corroborates recent work by Ellis et al. (2017), supporting the contention that the regulatory mechanisms of the CBFv response to high intensity exercise may be developmentally divergent.

The MCAv decline back to baseline in the latter half of MIE is perhaps an outcome of the child's elevated baseline MCAv compared to adults. This elevated MCAv sufficiently supplies the child's cerebral oxygen demands during exercise. In HIIE, however, significant MCAv reductions below baseline occurred in the final 3 sprints, which could pose a hypoperfusive threat to the cerebrovasculature. It is likely that the increased MAP during HIIE likely countered the effects of the decreased MCAv. This increase in MAP during HIIE did not differ from that of MIE, so MAP is elevated during exercise to counter potential decreases in CBFv, or whether these are not related remains to be determined.

To conclude, Canadian children are not currently meeting physical activity guideline recommendations (Tremblay et al., 2011B). The similar cerebrovascular responses at the onset of HIIE and MIE means HIIE is an equally attractive exercise modality for the child and one that is time efficient and congruent with their naturally sporadic movement characteristics (Bailey et al., 1995).

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