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CONTRIBUTION OF EXERCISE-ONSET HYPOTENSION TO CEREBROVASCULAR HEMODYNAMICS DURING AN EXERCISE TRANSITION

A DISSERTATION APPROVED THE DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

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ABSTRACT

Recent evidence suggests cerebral blood flow (CBF) responds to moderate intensity exercise after ~ 40s when using a monoexponential model to characterize CBF kinetics. Considering the brain's reliance on blood flow for O_2 and substrate delivery during increased metabolic demands, this delay is concerning. Especially when other physiological systems that are less dependent on blood flow for immediate energy needs respond to exercise within 10s (e.g. VO_2 kinetics, peripheral blood flow kinetics). Possibly this delay can be explained by a brief, transient exercise-onset-hypotension that occurs during a rest-to-exercise transition.

Purpose: The present study aimed to identify if CBF experiences an initial response not identified with a monoexponential model, and if that response is related to exercise-onset-hypotension at the start of exercise.

Methods: 23 total subjects (10 Females, 23.9 ± 3.3 yrs) completed a rest-to-exercise transition (2 minutes seated baseline followed by 3 minutes of 50W cycling) and an exercise-to-exercise transition (3 minutes of 50W cycling followed by 3 minutes of 75W cycling) on a recumbent cycle ergometer. Middle cerebral artery velocity (MCAv) was filtered and averaged into 3s bins and fit to a monoexponential model [$\Delta MCAv(t) = Amp(1-e^{-(t-TD)/\tau})$]. Time delay (TD), tau (τ) and mean response time (MRT = TD + τ) were obtained from the model. Cerebral perfusion pressure (CPP = mean arterial pressure – Hydrostatic column) and cerebral vascular conductance index (CVCi = MCAv/CPP) were filtered and averaged into 3s bins as well for analysis. Several subjects (N=8) exhibited a rapid response to exercise (TD ≤ 1.5s; "Fast") and were compared against subjects with longer TDs (TD > 3s; "Slow"). Comparisons were made using independent t-tests.

Results: All data are mean±SD. A light-intensity exercise transition (50W) elicited a TD = 19.7 ± 18.7s, τ = 29.7 ± 23.0s, and MRT = 49.1 ± 23.7s. The strongest correlation between variables was MCAv nadir ($MCAv_N$) and TD (-0.560). $MCAv_N$ (-4.1 ± 5.5 Δcm/s) and CPP reached a nadir (CPP_N = -13.5 ± 10.4 ΔmmHg) at similar times (16.5 ± 15.3 vs. 10.3 ± 4.5s, p = 0.07). CVCi reached a maximum ($CVCi_M$) which occurred after $MCAv_N$ (46.9 ± 57.1s). CPP was able to describe the variance in $MCAv_N$ similarly to a more complicated model involving cardiac output (Q), total peripheral resistance (TPR), end-tidal CO_2 ($EtCO_2$), and CVCi (R^2_a = 0.36, AIC = 140.44 vs. R^2_a = 0.25, AIC 140.7, Full model vs. CPP only model). The Slow and Fast groups had differences in TD (30.4 ± 14.6 vs. 1.5 ± 0.0s, p < 0.001), $MCAv_N$ (-7.3 ± 3.4 vs. 2.0 ± 2.6 Δcm/s, p < 0.001), and CPP during $MCAv_N$ (-11.3 ± 11.8 vs. 3.7 ± 3.2 ΔmmHg, p < 0.001).

Discussion: Our data shows $MCAv_N$ occurred at the same time TD, and that TD is directly correlated with $MCAv_N$ (-0.560). From this data, CPP was able to explain a large portion of the variance in $MCAv_N$. These data suggest that using a monoexponential model attributes the drop in MCAv at the start of exercise as a TD. This is further exemplified with the comparisons between Slow and Fast groups. The Slow group had a larger $MCAv_N$ and a predictable longer TD compared to the Fast group. If this type of analysis is to be used on disordered individuals, a better understanding of cerebrovascular mechanisms taking place at the start of exercise is needed to properly identify disordered CBFv responses to exercise onset.

CHAPTER I

INTRODUCTION

The brain is almost exclusively oxidative yet has insufficient stores of metabolic compounds (Brown & Ransom, 2007). Therefore, the brain relies heavily on cerebral blood flow (CBF) in order to meet changes in metabolic activity (Sheth et al., 2004; Willie et al., 2014). Fortunately, the brain has a large multi-branching vascular network allowing for sufficient nutrient supply and metabolic byproduct washing during increased activity (Iadecola, 2004; Kisler et al., 2017). These arteries are controlled by a series of overlapping mechanisms that enable the precise adjustment of CBF. These mechanisms must act rapidly to adjust CBF (Iadecola, 2004), as even small or short-term perturbations in adequate blood supply can lead to dysfunction (de la Torre, 2000). For example, altering arterial CO_2 ($PaCO_2$) concentrations has been shown to cause rapid CBF responses (Caldwell et al., 2021; Peltonen et al., 2015; Poulin et al., 1996), and is often cited as a major contributor to exercise CBF response (Ogoh et al., 2009; Secher et al., 2008). However, $PaCO_2$ does not change in isolation in humans.

Physical activity and exercise elicit a variety of homeostatic disruptions such as increased $PaCO_2$, mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), and metabolic changes within active and inactive tissues. From a cardiovascular perspective, changes in these variables are necessary to adequately supply blood flow to exercising muscles and can have opposing effects on cerebral vessel diameter and flow. This results in an interesting relationship between exercise intensity and CBF. Several studies have shown CBF follows a parabolic relationship with exercise intensity such that, at exercise intensities below 60% of maximal effort, CBF increases. Whereas during exercise above 60% of maximal effort, CBF will plateau or even reduce back towards baseline despite increases in brain neuronal activity (Ashley et al.,

2020; Smith & Ainslie, 2017; Subudhi et al., 2008). These studies are important and provide a great deal of insight. However, they have focused on the steady-state responses at specific exercise intensities throughout a graded exercise test.

Analysis of kinetic variables can provide a greater understanding of the underlying mechanisms and the rates at which physiological variables change. This type of analysis has proven useful in analyzing VO_2 kinetics (Poole & Jones, 2005) and blood flow kinetics (P. B. Barbosa et al., 2011) in various diseased populations. Recent pioneering research by Billinger et al. (2017) performed a similar analysis with cerebral blood flow velocity (CBFv), an analog to CBF. By applying a monoexponential model to CBFv response to exercise, they found differences in kinetic variables between young healthy and old healthy adults (Billinger et al., 2017; Ward et al., 2018), and showed changes to CBFv kinetics in stroke patients (Billinger et al., 2020), leading the authors to conclude CBFv kinetics could be used to identify cerebrovascular dysfunction. Interestingly, young healthy adults were found to have a large time delay (TD) of ~40s prior to an increase in CBFv (Billinger et al., 2017; Ward et al., 2018; Witte et al., 2019). This is surprising given the tight coupling of metabolism and flow required by the brain (Sheth et al., 2004; Willie et al., 2014). For example, active muscle blood flow has a TD that is minimal (< 10s) from the onset of exercise (Craig et al., 2021; MacDonald et al., 1998; Saunders et al., 2005; Tschakovsky et al., 2006). Even CBF seems to have a faster response to isolated changes such as during hypoxia and hypercapnia, TD < 6s (Poulin et al., 1996) or during blood pressure oscillations from thigh cuff release, TD < 10s (Aaslid et al., 1989). A possible explanation for this discrepancy in TD of CBF response to the start of exercise is a transient, yet substantial decrease in MAP (TD ~ 15-25s) during moderate and heavy-intensity leg exercise (Craig et al., 2021). At the start of exercise, there is a rapid vasodilation that is proportional to

exercise intensity in the peripheral circulation, directing a large amount of blood to the working muscles, resulting in a transient drop in arterial pressure (Laughlin, 1987; Tschakovsky et al., 2006; Tschakovsky & Sheriff, 2004) which would impact cerebral perfusion pressure (CPP) and therefore CBF.

The rapid translocation of arterial blood volume to increase muscle blood flow, decreases MAP. These are related and likely contribute to the extended TD seen in CBFv during a rest-to-exercise transition. It has been demonstrated that immediate and sudden drops in pressure result in significant drops in CBFv (Favre & Serrador, 2019; Labrecque et al., 2019). Therefore, the extended TD in CBFv at the start of exercise is likely due to the pressure drop related to skeletal muscle vasodilation. Thus, if monoexponential models are going to be used to assess cerebrovascular responses in healthy and diseased populations as proposed by the work of Billinger et al., the central underpinnings of the components of the model need to be understood to provide proper physiological interpretation. Considering most investigations into CBFv kinetics are conducted at moderate exercise intensities (~65% of max), if a lower intensity exercise is used, this should result in a reduced rapid vasodilation, attenuated drop in MAP and lessened drop in CBFv at the start of exercise, shortening the TD. However, this remains unknown.

Purpose of the Study

Therefore, the present study aimed to identify if CBF experiences an initial response not identified with a monoexponential model, and if that response is related to exercise-onset-hypotension at the start of exercise.

Research Questions:

1. Does the onset of exercise produce an immediate drop in CBFv that alters cerebral hemodynamics as measured by a monoexponential model?
    a. Is this initial drop attributable to an exercise-onset-hypotensive response at the start of exercise?
2. Is the drop in CBFv still present during a step increase from an exercise intensity to a higher exercise intensity (exercise-to-exercise transition)?
    a. Does this mitigate the elongated CBFv kinetics compared to a rest-to-exercise transition?

Hypotheses:

1. Using a monoexponential model to evaluate CBFv response to a rest-to-exercise transition will attribute an initial drop in CBFv as a time delay.
2. A step increase in exercise intensity during an exercise-to-exercise transition will result in faster kinetic parameters.

Significance of Study

Analysis of kinetic data for CBFv can help characterize and determine mechanisms of control within the cerebrovasculature. Understanding these mechanisms can aid in developing treatments for various neurodegenerative diseases such as dementia, mild cognitive impairment, and vascular dementia. These diseases are characterized by reduced CBF response to stimulation and reduced responses to exercise (Benedictus et al., 2017). Kinetic analysis may allow for earlier detection of disordered CBF responses, especially in these chronically developing diseases. Earlier detection ultimately would lead to earlier treatments, which have been shown to improve quality of life (Sabbagh et al., 2020).

Delimitations

1. Subjects were healthy males and females 18-30 years old.
2. Subjects were recreationally active (3-6 hours of physical activity per week).
3. Subjects were free of known cardio-metabolic, musculoskeletal, or pulmonary disorders.
4. Previously acquired data will be sufficient for the current study analysis.

Limitations

1. The results from this study may not be applicable to other populations.
2. The data previously gathered may not meet the requirements for the current study questions.
3. Photoplethysmography provides estimates of brachial artery systolic blood pressure, diastolic blood pressure, cardiac output, total peripheral resistance, and stroke volume.
4. Transcranial Doppler cannot account for changes in middle cerebral artery diameter.

Assumptions

1. Transcranial Doppler is a valid and reliable method for determining cerebral artery blood velocity.
2. Subjects were honest in reporting activity levels and health status.
3. Subjects adhered to the pre-testing guidelines of the study.

Operational Definitions:

- **Cerebral Blood Flow (CBF)**: Volume of blood supplying the brain at a given time (mL/min)**.**
- **Cerebral Blood Flow Velocity (CBFv)**: The velocity of blood cells flowing through a given cerebral artery.

- **Middle Cerebral Artery (MCA)**: The largest of cerebral arteries which largely supplies the cerebrum, motor cortex, and the association cortices.
- **Middle Cerebral Artery Velocity (MCAv):** The velocity of blood cells flowing through the MCA.
- **Cerebrovascular Reactivity (CVR)**: The ability of cerebral vessels to respond to changes in $PaCO_2$.
- **Cerebral Perfusion Pressure (CPP)**: The driving pressure gradient for oxygen delivery to the brain. Calculated by subtracting the hydrostatic column correction from MAP. The hydrostatic column correction is calculated by multiplying the distance from the height correction probe at heart level to the TCD probe by 0.7355 (i.e. CPP = MAP – (distance between probes * 0.7355)).
- **Cerebrovascular Conductance (CVCi)**: An assessment of MCAv relative to perfusion pressure. This provides an estimate for conductance, a measure of vasoconstrictor vs. vasodilator signals. CVCi = MCAv/ (CPP*100 mmHg).
- **Mean Arterial Pressure (MAP)**: The average arterial pressure during a cardiac cycle.
- **Cardiac Output (Q)**: The amount of blood flow out of the heart every minute.
- **Stroke Volume (SV)**: The amount of blood flow out of the heart every beat.
- **Total Peripheral Resistance (TPR)**: An estimate for resistance to flow blood has throughout the body.
- **Oxygen Consumption (VO_2)**: The rate of oxygen consumed per minute of time.
- **End-tidal CO_2 ($EtCO_2$)**: The amount of CO_2 expired at the end of a breath. This reflects the partial pressure of arterial CO_2 ($PaCO_2$) (Barten & Wang, 1994).

CHAPTER II

LITERATURE REVIEW

Introduction

The brain's vascular network and control have been the subject of countless studies. Recently, the hemodynamics of CBF have gained interest as technologies and analytical methods have advanced. However, it is necessary to analyze the methods used and understand fully what is being assessed and how to interpret the results. As discussed, a monoexponential model has recently been applied to the dynamic response of MCAv from a rest-to-exercise transition. In order to properly assess cerebral hemodynamics during the transition from rest-to-exercise, first an understanding of cerebrovascular and cardiovascular anatomy and how the brain is supplied with blood is needed. Then the response of blood pressure and how the peripheral vasculature's response to exercise affect the blood pressure response will be covered. Lastly, a discussion of how CBF is measured during exercise, and the response of CBF to exercise will be completed.

Cerebrovascular and Cardiovascular Anatomy

The central circulation is tightly connected to CBF. Changes in central cardiovascular variables results in subsequent changes in cerebrovascular variables as well. For instance, a percentage change in Q results in 0.35% change in CBF (Meng et al., 2015). This is in part due to the relatively direct connection between the cerebral circulation and the heart. As blood flows out of the heart into the aorta, it only takes a few forks until the blood reaches the internal carotids and the vertebral arteries, which are responsible for the total blood flow entering the cerebral circulation. Posteriorly, the vertebral arteries conjoin to form the basilar artery and branch to form the posterior cerebral arteries (PCA), which largely supply the cerebellum, the brainstem, and the occipital lobe. Anteriorly, the internal carotid arteries branch into the middle

cerebral arteries (MCA) and the anterior cerebral arteries (ACA). These largely supply the frontal, parietal, and temporal lobes. Together, the PCA, MCA, and ACA anastomose to form the circle of Willis (Cipolla, 2009; Navarro-Orozco & Sánchez-Manso, 2021). This orientation vessels allows for maintenance of flow in the face of a cerebrovascular insult (Cipolla, 2009).

The MCA is one of the most studied cerebral vessels due to its location and ease of access using various methods of analysis. Perhaps more importantly, the MCA is the largest of the cerebral arteries (Navarro-Orozco & Sánchez-Manso, 2021; Uchiyama, 2017), supplies large portions of the cerebrum and the motor cortex (Navarro-Orozco & Sánchez-Manso, 2021), and is the most common site for stroke and aneurism (Navarro-Orozco & Sánchez-Manso, 2021; Nogles & Galuska, 2021). Measuring changes in the MCA provides a correlate for brain activity with high temporal resolution (Lauritzen et al., 2012), especially during exercise (Willie et al., 2011). Neuronal activity of the primary motor cortex and association cortices (e.g. premotor and supplementary motor cortex, prefrontal cortex, insular cortex, and cingulate cortex) is increased during small and large muscle mass exercise (Fontes et al., 2015; Hilty et al., 2011; Liu et al., 2003; Mehta et al., 2009). Increased neuronal activity causes increased metabolism, and therefore increased oxygen requirement and CBF (Sheth et al., 2004). Unlike many other tissues, the brain is highly dependent on blood delivery of glucose (Marty et al., 2007) and oxygen (Cipolla, 2009). Therefore, any increase in metabolism must also be met with an increase in blood flow in order to meet the demand; this is known as functional hyperemia (Cipolla, 2009).

Central and Peripheral Regulators of Blood Pressure Response to Exercise

During exercise, to increase blood flow to meet the demands of increased cerebral and peripheral metabolism, arterial blood pressure must be increased, as blood flow and arterial blood pressure are tightly linked together (Joyner, 1991). Exercise elicits robust changes in

central and peripheral factors aimed to increase perfusion to active tissues. During exercise, skeletal muscles have a rapid and dramatic increase in metabolism and oxygen need. This increase is accompanied with a subsequent increase in perfusion (Heinonen et al., 2010). Alterations to autonomic outflow are pertinent to ensure HR, MAP, Q, SV, and other cardiovascular and hemodynamic variables all change appropriately with exercise. The primary mechanisms for autonomic changes are 1) central command, 2) the exercise pressor reflex and 3) the baroreflex. The central command theory is a feedforward/anticipatory signal associated with the initiation of movement. When exercise begins, the movement must be coordinated between the motor cortex and associated cortices, diencephalon, and several areas within the brainstem. It is likely that there is a concurrent activation of cardiorespiratory control areas, located within the medulla oblongata, during movement as several locomotor control regions have projections through the pons and medulla, which can also elicit alterations in autonomic outflow. For example, the insular cortex has been directly associated with motor control and autonomic control, among many others (Gogolla, 2017; Waldrop et al., 2011). Neuronal activity in the insular cortex is increased during handgrip exercise and decreased at cessation of exercise (Hilty et al., 2011). Therefore, activation of the insular cortex during movement could also lead to concurrent autonomic increases, resulting in HR and MAP changes. This is supported by elevations in HR and MAP during imagined exercise (Williamson et al., 2002). The limited human studies that have aimed to discern central command's role in cardiovascular alterations during exercise seem to be in agreement that 1) the initiation of exercise primarily increases sympathetic outflow centrally (Matsukawa et al., 2013; Raven et al., 2002) while also withdrawing sympathetic vasoconstrictor activity at the muscle vasculature (Matsukawa et al.,

2013), and 2) this occurs independent of physical movement (Gandevia et al., 1993; Hobbs & Gandevia, 1985; Williamson et al., 2002).

Importantly, the contribution of central command to changes in pressure and heart rate during exercise compared to the exercise pressor reflex in humans remains a question. The few studies that have examined this question seem to be in agreement that while central command is important, the role of the exercise pressor reflex in HR and MAP control is greater (Fadel, 2013; Hobbs & Gandevia, 1985; Matsukawa et al., 2013; Victor et al., 1989; Waldrop et al., 2011). The exercise pressor reflex is a feedback mechanism originating from the exercising muscles to aid in increasing perfusion for active tissues (Joyner, 1991). Particularly changes in metabolic byproducts such as lactate and hydrogen ion concentrations, adenosine, ATP and others have been shown to activate the exercise pressor reflex and alter autonomic outflow (Boushel, 2010; Secher & Amann, 2012; Waldrop et al., 2011). Mechanical distortions (mechanoreflex) and metabolic environmental changes (metaboreflex) in the muscle result in group III and IV afferent neuronal firing (Kaufman & Hayes, 2002; Michelini et al., 2015). It is likely these neurons terminate in the nucleus of the solitary tract (NTS) located within the medullary cardiovascular center (Michelini, 2007; Michelini et al., 2015; Widmaier et al., 2016). The NTS modulates parasympathetic and sympathetic outflow by excitation of parasympathetic preganglionic cell bodies within medulla (i.e. dorsal motor nucleus of the vagus nerve and nucleus ambiguous) and by inhibitory neurons that converge on the rostral ventrolateral medulla, the primary premotor nucleus for cardiovascular sympathetic control (Michelini, 2007). Therefore, activation of the exercise pressor reflex increases sympathetic outflow and restrains parasympathetic outflow. This results in increases in MAP, HR, Q and many other cardiovascular variables. It is fairly typical for investigations to either attempt to exacerbate the exercise pressor reflex by applying

suprasystolic pressure preventing the removal of metabolic byproducts, or to eliminate the exercise pressor reflex by administration of a neural block (Secher & Amann, 2012). During ischemic exercise when individuals are instructed to perform a toe extension while a pneumatic cuff was inflated to suprasystolic pressure (250 mmHg), HR and MAP were both elevated compared to the same exercise without the ischemia (Hansen et al., 1994). Additionally, sympathetic nerve activity was dramatically increased in both the exercising and non-exercising limbs during the ischemic trial compared to the nonischemic trial. When given epidurals to block group III/IV afferents, blood pressure increased to a lesser degree compared to the control trials (Secher & Amann, 2012; Smith et al., 2003).

While both the central command and the exercise pressor reflex are important in cardiovascular control during exercise, it would be a mistake to not also include the baroreflex, one of the most important blood pressure controllers during rest and during exercise. The baroreflex is a negative-feedback mechanism responsible for maintenance of blood pressure within a specific range during rest and exercise. Mechanoreceptors in the carotids and aortic arch (referred to together as arterial baroreceptors in this paper) respond to changes in arterial pressures, increasing firing during stretch (i.e., increased arterial pressure) and decreasing firing during relaxation (i.e., reduced arterial pressure) terminating at the NTS. The baroreflex results in complementary inverse autonomic outputs. Increased arterial pressure excites the NTS which in turn increases parasympathetic outflow and inhibits sympathetic outflow. Conversely, reduced arterial pressure withdraws excitation from the NTS, which leads to reduced parasympathetic outflow and increased sympathetic outflow (Mahdi et al., 2013; Michelini, 2007; Widmaier et al., 2016). These opposing autonomic changes have two primary actions regarding the maintenance of arterial pressure. First, changes in sympathetic outflow will primarily alter

vascular resistance through alpha-adrenergic receptors. Second, changes in parasympathetic outflow will primarily alter HR. This may seem counterintuitive during exercise because MAP can increase 10-20 mmHg or more along with elevations in sympathetic outflow and HR, and are maintained throughout exercise (Craig et al., 2021). This could lead one to believe that the baroreflex is inhibited during exercise. However, it is still operational during exercise. By chemically restraining MAP during handgrip exercise, Sherrer et al (1990) showed heart rate increased by 20 bpm and nearly a 300% increase in muscle sympathetic nerve activity (Scherrer et al., 1990). The arterial baroreceptors can also be mechanically manipulated through the use of a cuff affixed to a subject's neck. Pressure or suction is then applied to simulate baroreceptor compression (neck pressure) or stretching (neck suction), regardless of MAP. Application of neck pressure or suction during recumbent pedaling at various intensities results in similar changes to MAP and HR when compared at rest (Michelini, 2007; Ogoh et al., 2003; Raven et al., 2002). It is evident the baroreflex is altering sympathetic and parasympathetic outflow, even at moderate to high intensity exercise, affecting HR and MAP (Norton et al., 1999; Ogoh et al., 2003; Scherrer et al., 1990). Importantly, while the baroreflex is still operational during exercise, it also still functions within the same pressure ranges, only adjusted to a higher pressure. This phenomenon is termed *baroreflex resetting* as the operational range is elevated according to the exercise intensity (Norton et al., 1999; Ogoh et al., 2003; Potts et al., 1993; Raven et al., 2002). The baroreflex must reset in order to allow MAP and HR to remain elevated during exercise. Complete denervation of the baroreflex has been shown to hinder prolonged exercise performance in rats (Pires et al., 2013). This is likely due the baroreflex primarily acting through altering vasomotor tone (Ogoh et al., 2002, 2003). In dogs when the carotid artery is occluded and restricted from expanding (i.e., baroreceptor compression), vascular conductance of the hind

limbs during walking is reduced by ~15% with similar reductions in total vascular conductance (a measure of the body's total vasodilation) (Collins et al., 2001). Similarly, when neck pressure is applied to humans, vascular conductance and blood flow to the exercising limb are reduced (Keller et al., 2003). Conversely, when neck suction is applied during leg extension exercise, MAP is reduced along with an increase in vascular conductance of the non-exercising leg (Keller et al., 2003). Therefore, the baroreflex is required in order to maintain appropriate pressure and blood flow throughout the body as well as to the working muscles.

Central command and the exercise pressor reflex act together to reset the baroreflex during exercise. In animal models, isolation of central command and the exercise pressor reflex individually reset the baroreflex (McIlveen et al., 2001). In humans, the baroreflex follows a reverse sigmoid pattern where at lower carotid pressure, MAP is elevated and at higher carotid pressures MAP is reduced. When subjects were given a neural blockade that inhibited muscle afferent response and attenuated muscle contraction, the reverse sigmoidal curve of the baroreflex was adjusted further upwards and to the right compared to exercise without the blockade (Querry et al., 2001). This means, when muscle afferents were blocked, MAP was elevated at the same given carotid pressure (i.e., the same baroreflex stimulation resulted in increased MAP). The effect of the blockade was twofold. First, it inhibited muscle afferents thereby reducing the potential for the exercise pressor's modulation of the baroreflex. Any changes in the baroreflex operating point would be primarily due to central command. Second, due to the reduced muscle activation, greater central drive was necessary in order to produce the needed force (i.e., greater central command). Therefore, the protocol used likely increased central command and increased its contribution to the baroreflex resetting. The exercise pressor reflex has been shown to have a significant role in the complete resetting of the baroreflex

(Gallagher et al., 2001; Smith et al., 2003). There is still debate regarding the mechanisms central command and the exercise pressor reflex use to reset the baroreflex. Animal and human models have pointed to involvement of various brain regions, including the NTS (Michelini et al., 2015). Lastly, cardiopulmonary baroreceptors located within the atria (referred to as the atrial baroreceptors in this paper) of the heart also can modulate the baroreflex operating point. When blood volume is increased or decreased, the atrial baroreceptors communicate directly with the NTS in a similar mechanism to the carotid baroreceptors already discussed. An increase in blood volume within the atria will stretch the atrial baroreceptors and stimulate the NTS whereas a decrease in blood volume within the atria will withdraw stimulation of the NTS (Michelini, 2007; Michelini et al., 2015). Ultimately, a combination of central command, the exercise pressor reflex, and the baroreceptors all act to drive pressure up and increase vasodilation to direct flow to the active tissue. This occurs in tandem with resetting of the baroreflex in order to maintain the elevated pressure while also maintaining appropriate blood flow distribution throughout the rest of the body during exercise.

Peripheral Vascular Response to Exercise

As stated earlier, exercise elicits alterations in sympathetic and parasympathetic outflow centrally, and peripherally at the skeletal muscle. This presents an interesting dilemma for the skeletal muscle's vasculature. The increased sympathetic outflow ultimately will activate α-adrenergic receptors on the vascular smooth muscle and induce vasoconstriction, limiting blood flow (Buckwalter & Clifford, 2001; Hansen et al., 2020). However, during exercise skeletal muscles require more blood flow, therefore the vasculature needs to vasodilate (Saltin et al., 1998). To accomplish this, local vasodilatory signals must be able to generate a large enough stimulus to result in a net vasodilation. A multi-faceted approach is used to enable the local

vasodilatory signals to overcome the sympathetic vasoconstrictor signals. Largely, the net vasodilation is a result of byproducts produced during exercise. Many of these byproducts participate in vasodilation through vascular smooth muscle relaxation, or by reducing the vasoconstriction activity of sympathetic outflow, termed functional sympatholysis. During exercise, increased metabolic activity produces lactate and hydrogen ions (H^+). Although their contributions are small, both have been shown to participate in exercise-induced vasodilation (Chen et al., 1996; Peng et al., 1998). Contraction of the skeletal muscle cells increases potassium (K^+) flow through voltage gated K^+ channels (Widmaier et al., 2016). Increased K^+ concentrations within the interstitial space can aid in dilation either independently, or through co-action with nitric oxide (NO), endothelial hyperpolarizing factor (EDHF), ATP, and/or other mechanisms (Brunt et al., 2013; Clifford & Hellsten, 2004; Wilson et al., 1994). Extracellular adenosine and ATP, potent vasodilators, are produced in several locations such as endothelial cells, red blood cells, neuronal terminals and others (Clifford & Hellsten, 2004). Likely the mechanism for ATP-induced vasodilation is related to nitric oxide (NO), prostaglandins, and K^+ (Brunt et al., 2013; Crecelius et al., 2011). Nitric oxide (NO), also a potent vasodilator, can be released in response to skeletal muscle action (Reid, 1998), oxygen offloading by the red blood cells (Singel & Stamler, 2005), or directly catalyzed by endothelial cells in response to increased shear stress (Corson et al., 1996). These compounds, and others not mentioned, largely act through similar mechanisms utilizing guanylate cyclase and/or adenylate cyclase to reduce intracellular calcium concentrations within the vascular smooth muscle cell, thereby resulting in relaxation (Clifford & Hellsten, 2004). Many of these compounds also contribute to vasodilation by participating in functional sympatholysis.

It is easy to focus heavily on vasodilator signals when discussing blood flow response to exercise. Sympathetic vasoconstriction is equally important and essential for blood flow redistribution to metabolically active tissues other than skeletal muscles during exercise (Buckwalter & Clifford, 2001). Vascular conductance increases dramatically from rest to exercise primarily as a result of skeletal muscle vasodilation. This drives blood flow from nonexercising tissues (e.g., kidneys) towards the active tissues (e.g., skeletal muscle). The skeletal muscle vasculature has an incredibly large capacity for blood. If left unfettered, would result in a dramatic drop in pressure and ultimately a loss of blood flow, as seen in some pathological conditions (Laughlin, 1987). Sympathetic vasoconstriction, albeit attenuated, is still active in skeletal muscle vasculature during exercise during both small muscle (Joyner et al., 1992) and large muscle mass exercise (Hansen et al., 2020). The phenomenon of *how* sympathetic outflow can cause dramatic vasoconstriction in the non-exercising tissue, while allowing vasodilation in the exercising tissue, has been the focus of research for years. A seminal article by Remensynder et al. (1962) demonstrated sympathetic stimulation during exercise had a reduced effect on vascular resistance and blood flow in dogs (Remensnyder et al., 1962). Later, this was demonstrated in humans by measuring sympathetic nerve activity in the calf contralateral to the exercising calf. The result was an increase in blood flow to the exercising calf while the contralateral calf experienced an increase in sympathetic nerve activity (Saito et al., 1992). Desensitization of the α-adrenergic receptors seems to be the primary mechanism of sympatholysis. In rats, femoral vascular conductance is unchanged during contraction of the gastrocnemius when given an α-adrenergic agonist (Thomas et al., 1994). In humans, similar results have been demonstrated. During forearm exercise, infusion of various α-adrenergic agonists failed to significantly alter blood flow (Rosenmeier et al., 2003). Additionally, moderate

intensity forearm exercise blunts α-adrenergic-mediated vasoconstriction, induced through tyramine infusion. At heavy-intensity, tyramine-induced vasoconstriction was almost eliminated (Tschakovsky et al., 2002). This demonstrates that the mechanisms responsible for sympatholysis are intensity dependent. Currently, changes to the chemical environment surrounding the skeletal muscle cells are the primary points of interest. The production of NO has been suggested to moderate sympatholysis. However, there is not a lot of research to support this hypothesis. For example, Chavoshan et al. (2002) demonstrated that administering L-NAME, a NO synthase inhibitor, restored forearm vascular conductance in the presence of lower body negative pressure, a stimulus that increases sympathetic outflow. However, when lower body negative pressure was adjusted to match muscle sympathetic nerve activity, there was no difference (Chavoshan et al., 2002). When Dinenno and Joyner (2003) administered L-NAME during handgrip exercise along with a number of α-adrenergic agonists, vascular conductance was not altered (Dinenno & Joyner, 2003). Although sympatholysis may not be moderated by NO acutely, it might play an important role in training-induced sympatholysis changes (Jendzjowsky & DeLorey, 2013). Other compounds have also shown promising results. When infused, ATP has been shown to blunt the effects of tyramine (Rosenmeier et al., 2008). Additionally, increased extracellular K^+ may play an important role in mediating functional sympatholysis during exercise (Thomas & Segal, 2004). There has yet to be a definitive answer to which is the primary mediator of sympatholysis. It is likely that a combination of all these mechanisms contribute and any one mechanism, on its own, is unable to effectively blunt sympathetic vasoconstriction in the skeletal muscle vasculature.

Measure of Cerebral Blood Flow During Exercise

CBF is the amount of blood traveling through the brain (global), a part of the brain (regional), or through a particular vessel (e.g., an artery like the MCA). There are two main ways to measure CBF. Considered the gold standard, magnetic resonance imaging (MRI) gives a validated and highly accurate estimate of CBF (Calamante et al., 1999). At the core, an MRI scan uses the magnetic gradients from protons within the blood to generate an image. This can then be used to determine artery circumference, blood volume, perfusion, and many other variables (McDonnell et al., 1994). Several drawbacks occur when using MRI to estimate CBF during exercise. Many scans require more than 5 minutes to complete (Calamante et al., 1999), subject movement must be held to a minimum (Chen et al., 2008), the high cost and limited access to an MRI machine that can produce high enough resolution scans, and lastly the need to have MRI-compatible equipment can also be a significant barrier for dynamic exercise (Gusso et al., 2012).

Many of these challenges can be addressed by using TCD to estimate CBF rather than MRI. TCD has been used to measure CBF at least since the 1970s (Aaslid et al., 1982). In short, TCD uses a doppler ultrasound signal at 2 MHz within the temporal window to insonate a cerebral vessel (Aaslid et al., 1982; Bishop et al., 1986). It is important to note the signal received is not blood flow, but rather the velocity of red blood cells flowing through a particular vessel. To determine flow, both velocity and the vessel diameter are needed. If the vessel diameter remains constant throughout a variety of stimuli, blood flow velocity will accurately estimate blood flow. Early investigations regrading changes to cerebrovascular diameter suggested vessel diameter experiences minimal changes in response to hyperventilation and that cerebral blood flow velocity (CBFv) is a valid analog for CBF (Serrador et al., 2000). However, more recent studies have brought this into question. Recently, it’s been found that changes in

$EtCO_2$ of 15 mmHg can result in MCA vessel diameter changes of ~ 5% (Verbree et al., 2014). However, under more physiologically relevant values of 7.5 mmHg, which is typical during exercise (Matsumoto et al., 2000), vessel diameter changes very little (Verbree et al., 2014). Therefore, although there are serious considerations that must be accounted for, there are several advantages of using TCD to estimate CBF compared to using MRI, especially during exercise: 1) TCD can provide velocity measurements at several measurements per second (Aaslid et al., 1982; Bishop et al., 1986). This allows for greater temporal resolution, especially during transitions from baseline. 2) Slight movements of the head are well tolerated. 3) Almost any exercise equipment can be used. All of these allow for the use of TCD during a wide range of exercise types, not just small muscle mass exercise. For these reasons, the use of TCD over MRI to estimate CBF is warranted and in many cases preferred.

Cerebrovascular Response to Exercise

Exercise presents the brain with an unfortunate circumstance where it must simultaneously increase blood flow to meet the increased metabolic demand, while also restricting dramatic increases in blood flow to prevent hyperemia and damage (Paulson et al., 1990). This is demonstrated best through the CBF-Exercise intensity relationship. Initially, CBF increases as exercise intensity increases until about 60% of maximal effort (Ashley et al., 2020; Jorgensen et al., 1992) then plateaus (Larsen et al., 2008; Subudhi et al., 2011) or reduces back towards baseline (Ashley et al., 2020; Subudhi et al., 2008). While these studies have demonstrated important aspects of CBF, these conclusions were based on steady-state responses at specific exercise intensities throughout a graded exercise test.

Most physiological variables respond to the start of exercise relatively quickly. For instance, peripheral circulation responds in under 10s (Craig et al., 2021; Tschakovsky et al.,

2006), and VO_2 and other pulmonary gases respond within 10s (Poole & Jones, 2005; Scheuermann et al., 1999). It would then reasonably be assumed that CBF would follow the same pattern given how reliant the brain is on adequate blood flow to meet increased metabolic demands (Smith & Ainslie, 2017; Willie et al., 2014). While only accounting for 2% of total body weight, the brain receives ~15% of cardiac output and accounts for ~20% of oxygen consumption while at rest (Brown & Ransom, 2007; Magistretti & Pellerin, 1996; Quastel & Wheatley, 1932). Recent pioneering research by Billinger et al. (2017) characterized CBF at the start of exercise to have around 40s of delay in young healthy adults (Billinger et al., 2017; Ward et al., 2018). It is unclear what mechanisms are responsible for this delayed response. However, what we do know is the cerebrovasculature is highly sensitive to changes in $PaCO_2$. Likely, increased $PaCO_2$ results in vasodilation (Kontos et al., 1977; Smith & Ainslie, 2017; Willie et al., 2012) by reducing intracellular calcium and by altering cerebral spinal fluid pH (Yoon et al., 2012). However, $PaCO_2$ increases rapidly (< 10s) as metabolic and nonmetabolic CO_2 is produced (Scheuermann et al., 1999) and CBF responds to isolated changes in $PaCO_2$ rapidly (~ 6s) as well (Poulin et al., 1996). Therefore, $PaCO_2$ is not a likely candidate for the delay observed by Billinger et al. (2017). Simultaneously, central hemodynamic variables such as cardiac output and MAP both increase during exercise in response to autonomic nervous system changes and peripheral mechanisms (Laughlin et al., 2012). Cardiac output and MAP independently alter CBF (Ide et al., 1998; Ogoh et al., 2005; Willie et al., 2014). Although cardiac output seems to respond to the start of exercise nearly instantaneously, < 2s (Lador et al., 2013), MAP does not seem to respond as rapidly.

A recent study by Craig et al. (2021) is one of the first to characterize MAP kinetics. They showed that MAP can have as much as a 23s delay at the start of large muscle mass

exercise (Craig et al., 2021). A noticeable drop in MAP was identified and estimated to be a 3-5 mmHg drop within the first 10s of exercise. Changes in MAP have been well documented to have direct relationship with CBF (Harper, 1966). Therefore, it is reasonable to assume the initial drop in CBF at the start of exercise is related to the drop in MAP. The cerebrovasculature is highly sensitive to changes in MAP and react accordingly in order to maintain CBF. This mechanism is termed cerebral autoregulation. Simply stated, autoregulation is the cerebrovascular adjustment of vessel diameter in response to changes in pressure in order to maintain CBF. This mechanism has long been thought to operate within a fairly large range between 60 and 130 mmHg, (Klabunde, 2012). However, recent evidence indicates a much smaller range of autoregulatory control (Brassard et al., 2021; Claassen et al., 2021; Willie et al., 2014). It also seems that the cerebrovasculature is better suited to accommodate increases than decreases in MAP (Harper, 1966; Payne, 2016; Willie et al., 2014). This means that CBF decreases faster when MAP is reduced compared to increases in CBF when MAP is elevated. Therefore, we can reasonably conclude that the TD described with CBF is likely related to the delay with MAP. This conclusion is supported by evidence of CBF oscillating in tandem with MAP oscillations during postural changes. When subjects were exposed to a sit-to-stand protocol, MAP decreased by ~15 – 20 mmHg along with a similar decrease in MCAv of ~ 15 – 20 cm/s (Favre & Serrador, 2019; Labrecque et al., 2019).

Conclusion

When all these data are taken together, it becomes clear that there are intricate and redundant methods our bodies use to adjust blood flow, especially CBF. At the start of exercise, increases in Q and $PaCO_2$ results in increases in CBF. Simultaneously, rapid vasodilation in the periphery, to drive blood flow towards the exercising limb, causes a brief but substantial

decrease in MAP in an intensity-dependent manner. This means a transition to a higher intensity of exercise will elicit a greater rapid vasodilation response, thereby resulting in a larger drop in MAP, compared to a transition to a lower intensity. From this, we can hypothesize that a greater drop in MAP, due to increased rapid vasodilation, would result in a greater drop in CBF. Due to the limitations of the monoexponential model, this would be identified as an extended TD. However, this is not well understood.

Accurately identifying and describing this initial transition and variance is critical to understanding the control mechanisms of the cerebrovasculature. It has been well reported that individuals with dementia, Alzheimer's, and mild cognitive impairment have reduced CBF (Benedictus et al., 2017; Leijenaar et al., 2017; Ruitenberg et al., 2005). However, these disease states progress over decades and often present in less noticeable manners (Ruitenberg et al., 2005). Using the kinetic response of CBF may allow researchers to better identify mechanisms responsible for the disease progression and aid in more targeted treatments and better health outcomes. Work has already begun to characterize the kinetic CBF response in individuals with various diseases and disorders (Billinger et al., 2020; Kaufman et al., 2019; Ward et al., 2022). However, without properly characterizing healthy CBF dynamics, it is difficult to determine what is a maladaptive vs. a "normal" CBF response to the start of exercise. Therefore, it is necessary to determine the role of exercise-onset-hypotension on CBF dynamics and if this is mitigated during lower intensity exercise, or during a transition from a lower exercise intensity to a higher intensity.

CHAPTER III

METHODOLOGY

Recruitment

All subjects were recruited at the University of Oklahoma Health and Exercise Science Department using approved advertising. Interested subjects were scheduled for a screening visit to determine their eligibility and provide informed consent.

Participants

These data were originally collected as a part of a different study within the Human Circulation Research Lab. The original study (IRB# 10121) required a sample size of 30 participants to achieve a power of at least 0.8 and an $\alpha = 0.05$ using G*Power 3.1.9.4 with an ANOVA design for the primary study. A total of 32 participants were recruited. Each subject was moderately active, as determined by the physical activity questionnaire (iPAQ). All female participants were studied during the early follicular phase of their menstrual cycle (days 1-7 after start of menstruation) to minimize gonadal hormone effects on vascular reactivity (Hashimoto 1995). Of the total subjects, two were removed due to equipment malfunction.

Screening Visit

Participants reported to the Human Circulation Research Laboratory at The University of Oklahoma for the screening visit ≥ 8hr fasted, ≥12hr without caffeine, alcohol, and ≥24hr without NASAIDs (e.g. Tylenol or Aleve) and vigorous exercise. Subjects completed informed consent, health insurance portability and accountability act (HIPAA) form, the 7-day long form iPAQ, demographics form, and medical history questionnaire. After all documents were completed and signed, participants were screened with blood analysis from a venous blood

sample taken by a certified lab member. This sample was used to determine eligibility based on triglycerides, HDL, LDL and glucose according to the inclusion and exclusion criteria. Lastly, it was ensured a quality middle cerebral artery (MCA) signal could be acquired with the TCD. Subject were enrolled based on the following criteria:

Inclusion Criteria

1. Age: 18-30 years old
2. Free of cardiovascular & metabolic diseases
3. Free of any lower body skeletal muscle injuries
4. Systolic Blood Pressure < 130mmHg and Diastolic Blood Pressure < 90mmHg
5. Body mass index: BMI < 30 kg/m^2
6. Females: premenopausal with a regular menstrual cycle

Exclusion Criteria

1. Systolic Blood Pressure ≥ 130mmHg and/or Diastolic Blood Pressure ≥ 90mmHg
2. Diagnosed Cardio-metabolic diseases: Diabetes; Coronary Artery Disease; stroke; heart attack
3. Cardio-metabolic medications (medications prescribed for muscle, metabolic or cardiovascular conditions, e.g., metformin, ACE inhibitors, beta inhibitors, alpha inhibitors, statins, calcium channel inhibitors)
4. Current regular tobacco use (including smokeless) OR former regular tobacco user within the previous year of enrollment
5. Asthma, including exercise induced asthma
6. BMI ≥ 30

7. Abdominal obesity (Waist circumference (WC): Males > 102 cm, Females > 88 inches)
8. Triglycerides ≥ 150 mg/dL
9. HDL cholesterol < 40 mg/dL in males or < 50 mg/dL in females
10. Fasting glucose ≥ 100 mg/dL
11. Pregnancy
12. Transcranial Doppler: Subjects that are unable to get a quality MCAv signal on the TCD were excluded from the study
13. Language: Subjects that did not speak English were excluded from the study.
14. Females: The absence of a regular menstrual cycle. Females taking forms of birth control that alter regular menstrual cycles (i.e., contraceptive injection, hormonal IUD, etc.).

Exercise (EX) Visit

For the exercise visit, participants reported to the Human Circulation Research Laboratory similar to the screening visit ≥ 8hr fasted, ≥12hr without caffeine, alcohol, and ≥24hr without NASAIDs (e.g. Tylenol or Aleve) and vigorous exercise. All females were tested during the early follicular phase (days 1-7) of menstrual cycle, or during the low hormone dose phase of oral contraception, in order to minimize hormonal effects. Participants were fitted with an Equivital vest, seated on the recumbent cycle ergometer, affixed with the TCD headgear and probes, and fitted with the VO_2 mask over it all. A quality TCD signal was found by adjusting the TCD probes until an upward tracing doppler signal was clear. The participant's left arm was then placed in sling with the non-invasive blood pressure monitor attached around the middle finger. Lastly, a pulse oximeter (SpO_2) was placed on the ear. Once all equipment was attached

and recording, a baseline measurement was recorded followed by the EX-protocol (Figure 1).

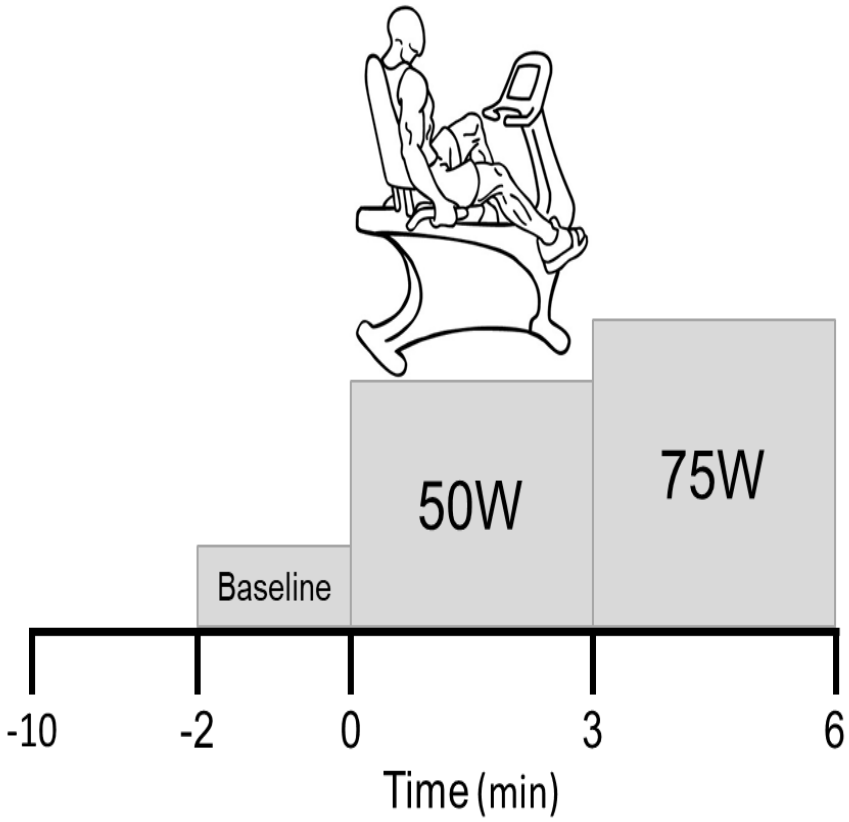

Figure 1. *Exercise (EX) Protocol*. Outline of recumbent cycle ergometer protocol. Participants started with at least 2 minutes of quite rest "Baseline" followed by the first stage at 50W for 3 minutes, followed by the next stage at 75W for 3 minutes. Participants maintained 60-80 RPM for each stage

The EX-protocol was completed on a cycle ergometer (Lode Corival cpet, Groningen, The Netherlands). The test began with a 2-minute baseline with the participant sitting quietly on the cycle ergo cycle ergometer. Subjects were instructed to maintain a pedaling frequency of 60-80 rpm for 50W and then followed by 75W which each lasted 3 minutes each.

Measurements

Anthropometric

Height and weight were measured during the screening visit while the participants wore lightweight clothes and no shoes. Height was measured to the nearest 0.5 cm using a wall mounted stadiometer (Novel Products, Inc., Rockton, IL) with the subject standing straight, arms

at their side with their back against the device. Body weight was recorded within the nearest 0.1 kg using a standard scale (Tanita, Model BWB-800A, Japan). Body mass index (BMI) was calculated as body mass in kilograms divided by the height in meters squared (kg/m^2). WC was measured to the nearest millimeter (mm) using a retractable tape measure after the participant removed bulky clothing. The narrowest part between the lower rib and the iliac crest, or the halfway point between the lower rib and the iliac crest, was used for the measurement.

Cardiovascular

Blood Pressure:

During the screening visit, the lowest of three brachial blood pressure measurements using an automated brachial pressure monitor (HEM-705, Omron, lake Forest, IL, USA) after a 5-minute supine rest separated by at least 1 minute, was used to determine resting blood pressure.

MAP was measured using infrared finger photoplethysmography (ADInstruments, Human Non-invasive Blood Pressure (NIBP), Colorado, USA). This allowed for non-invasive beat-by-beat measurement of arterial BP. Other central cardiovascular parameters such as Q, TPR, and SV were estimated using the NIBP. Although finger photoplethysmography tends to underestimate BP compared to intra-arterial measures, it has been shown to accurately represent changes in BP (Parati, Casadei, Groppelli, Di Rienzo, & Mancia, 1989).

Heart Rate:

HR was measured using a multi-parameter telemetric device (EQO2 (Equivital, EQ02 + SEM, Hidalgo, UK). The Equivital system has been proven to accurately measure ECG and HR on a beat-by-beat basis (Akintola, van de Pol, Bimmel, Maan, & van Heemst, 2016).

Transcranial Doppler Ultrasound

MCAv was measured using a robotic TCD (2 MHz pulsed-wave Robotic TCD probe; Neurovision, Multigon Industries, Elmsford, NY, USA). The MCA can be insonated from the anterior window, just above the zygomatic arch, roughly the temporal fossa towards upper eye level. This provides an almost direct angle to measure the MCA blood velocity (MCAv). Typically, the MCA will be found in depths between 40-65 mm.

Pulmonary Gas Measurements

Both $EtCO_2$ VO_2 were continuously collected throughout baseline and exercise. Exhaled flow data were collected using a respiration mask (7450 Series Silicone V2™ Oro-Nasal Mask, Hans Rudolph Inc., Kansas City, Missouri, USA) connected to a spirometer (ADInstruments, Colorado, USA). Exhaled gas was analyzed using a gas analyzer (CWE Inc., Gemini End-Tidal O_2 and CO_2 Analyzer, Ardmore, PA, USA). $EtCO_2$ has consistently been demonstrated to correlate closely with to the partial pressure of CO_2 in arterial blood (Barten & Wang, 1994).

Blood Analysis

Blood was analyzed using a point of care hand-held blood analysis device CardioChek PA (Polymer Technology Systems, Inc., Indianapolis, United States). Participants were screened for metabolic disease and cardiovascular disease based on the inclusion and exclusion criteria (specifically LDL, HDL, triglycerides, and glucose). The CardioChek analyzer meets the guidelines for total analytical error through the National Institute of Health National Cholesterol Education Program.

Physical Activity

Activity level was assessed using the International Physical Activity Questionnaire (iPAQ) long form during the screening visit. Estimates for activity level was completed using the excel template from the iPAQ website (iPAQ Group, 2005).

Data Acquisition and Analysis

All data were recorded continuously and acquired via PowerLab (Powerlab/16SP ML 880; ADInstruments, Colorado, USA). NIBP data (MAP, Q, TPR, and SV), MCAv data and pulmonary data were all connected directly to PowerLab and displayed through LabChart (version 7.3.7, ADInstruments, Colorado, USA) at 200Hz. HR data was connected to LabChart through a Bluetooth dongle. Final analysis of data was completed offline. Most of the data were exported on a beat-by-beat basis by taking the averaged data throughout a cardiac cycle (i.e., QRS complex to QRS complex was identified and values were averaged). For the main outcome variables, MCAv, MAP and CPP, the raw signal data were exported (sampled at 200 Hz) and a lowpass filter (set at 0.2 Hz) was applied. This type of processing has been demonstrated to give the best fit without removing the overall shape of the response (Ferreira et al., 2006). These data were then averaged into 3s time bins (Billinger et al., 2017). Baseline was calculated as an average of the last 30s prior to the start of exercise. The absolute change from baseline (Δ) for each variable was calculated by subtracting the 3s bin timepoint from the last 30s of baseline for the same variable. CPP was calculated by subtracting the hydrostatic column correction (difference between the transcranial probe location and the height correction probe at heart level for finger photoplethysmograph cuff) multiplied by 0.7355 from the measured MAP to obtain mmHg hydrostatic correction. Cerebrovascular conductance index (CVCi) was calculated as:

$$CVC_i = MCA_v / CPP*100mmHg$$

Data were analyzed for the rest-to-exercise transition from baseline (averaged last 30s) through 50W cycling exercise and then the exercise-to-exercise transition from the last 30s of 50W cycling to 75W cycling exercise. Specifically, the transition from baseline to 50W was fit with a monoexponential model using SigmaPlot version 12.5, from Systat Software, Inc., San Jose CA, USA. The model used is as follows:

$$\Delta MCAv(t) = Baseline + Amplitude\ (1 - e^{-(t - TD)/\tau})$$

where "Baseline" is the detected starting point of MCAv (since this is a Δ value, the baseline values were set to 0), "Amplitude" is the change from baseline to the steady-state MCAv, *t* is a given time point, TD is the time delay experienced prior to an increase in MCAv above baseline, and τ is the time constant for the response to reach 63% of steady-state (Phillips et al., 1995). This same model was attempted for the exercise-to-exercise transition from 50W to 75W. The only difference is "Baseline" represents be the last 30s averaged data from 50W and Amplitude is the measured increase in CBF from 50W to 75W cycling. Mean response time (MRT) was calculated by adding TD and τ. This gives a time value for MCAv to reach 63% of the steady-state value (Phillips et al., 1995).

Each monoexponential model for each subject was visually inspected for inclusion. Subjects were removed due to non-monoexponential responses of MCAv and unequal variance in residuals, tested using Sigmaplot's Constant Variance Test which utilizes a Spearman rank correlation between the absolute values of the residuals and the observed value of the dependent variable.

Statistical Analysis:

These kinetic variables were averaged together and reported as mean ± SD. To explain the initial variance in MCAv, the lowest averaged point (nadir) was selected for MCAv ($MCAv_N$) and CPP (CPP_N). $MCAv_N$ was regressed with variables that have been shown to have a strong relationship with CBF (Markwalder et al., 1984; Ogoh et al., 2005; Willie et al., 2011). Each of these variables are the change from baseline to the timepoint $MCAv_N$ occurred. This means if $MCAv_N$ occurred at 10s into the start of exercise, ΔCPP is the change from baseline to 10s (and the same for each Δ variable in this regression).

$$\Delta MCAv_N = \Delta CPP_{@MCAvN} + \Delta CVCi_{@MCAvN} + \Delta Q_{@MCAvN} + \Delta TPR_{@MCAvN} + \Delta EtCO_{2@MCAvN}$$

The same regression was completed for the total change from baseline to the end of 50W cycling exercise to explain the overall MCAv response ($MCAv_{SS}$).

$$\Delta MCAv_{SS} = \Delta CPP + \Delta CVCi + \Delta Q + \Delta TPR + \Delta EtCO_2$$

A dependent samples t-test comparison between the time the nadirs ($MCAv_N$ vs. CPP_N) occurred was completed to determine if the timing of the drop in MCAv coincided with the drop in CPP. The TD and MRT from the monoexponential model were correlated with $MCAv_N$, CPP_N, and the maximum CVCi recorded ($CVCi_M$).

A novel approach to quantifying cerebral autoregulation is being used in this study. As previously stated, autoregulation is a mechanism by which blood flow to the brain is attempted to be maintained in the presence of changes in pressure. Given the way CVCi is calculated (CVCi = MCAv/CPP*100mmHg), as CPP is reduced and MCAv does not change, CVCi will increase.

This would indicate the cerebrovasculature has vasodilated (Claassen et al., 2007). From this calculation, we can infer that for a given CPP and given CVCi, we can calculate an estimated MCAv. Based on this, we can assess the impact of CVCi changing (i.e., changes in cerebral vasodilation) on MCAv during a drop in pressure. According to the Poiseuille equations, if a blood vessel does not change its diameter, pressure and flow are directly related (Chaudhry et al., 2021). To assess autoregulatory function during exercise transition, we compared $MCAv_N$ to the estimated $MCAv_N$ ($MCAv_{EN}$) if CVCi was unchanged from baseline. $MCAv_{EN}$ was calculated using the following equation:

$$MCAv_{EN} = (CVCi_{BL} * CPP_{@MCAvN}) / 100$$

where $CVCi_{BL}$ is the CVCi measured as the last 30s of baseline, $CPP_{@MCAvN}$ is the CPP when $MCAv_N$ occurred. Effectively, $MCAv_{EN}$ is what MCAv would be if the cerebral vessels did not change diameter from baseline. From here, an autoregulatory restrain index (ARRi) can be calculated by

$$ARRi = [1-(MCAv_{EN} / MCAv_N)] * 100$$

this was used to determine the amount $MCAv_N$ was attenuated by autoregulatory mechanisms changing CVCi to buffer/prevent a further decrease in $MCAv_N$.

Lastly, several of the subjects (8 in total) exhibited a rapid increase in MCAv with TDs ≤ 1.5 s. This was the first data point used following the start of exercise in the modeling. These subjects were separated into "Fast" (TD ≤ 1.5s) and "Slow" (TD > 1.5s) groups. The first group (Figure 2) is the largest with more than twice the number of subjects than any other group. This was the basis for the comparative analysis between the "Fast" and "Slow" groups.

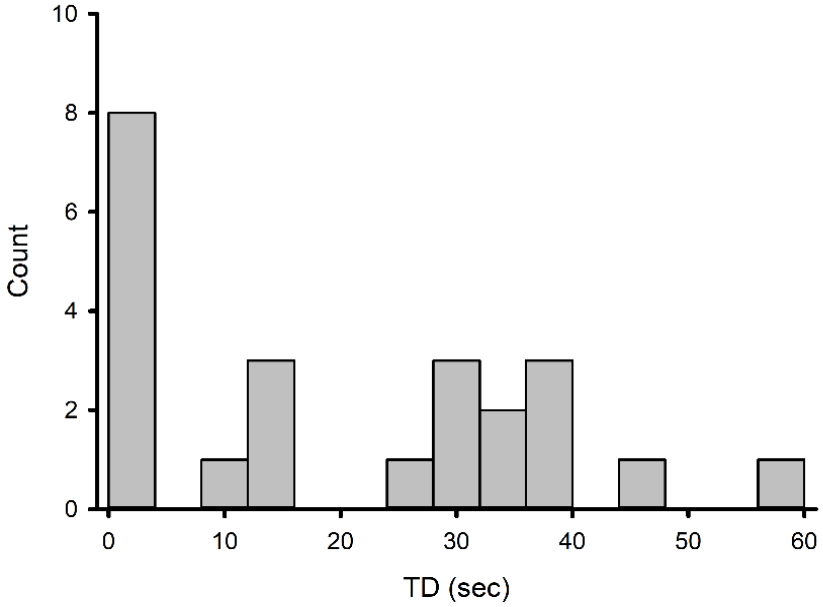

Figure 2. Histogram depicting the time delay (TD) split into 4 second bins. The largest grouping of subjects is seen in the first bin.

Model characteristics were compared using an independent t-test across groups. Statistical analyses were performed using R (R Core Team, 2017) software. All regressions (including the monoexponential model) will be reported with adjusted R^2 (R^2_a) to detail the goodness of fit of the model. The use of R^2_a is done in order to account for the number of parameters and sample size. Therefore, R^2_a is considered an unbiased measure of regression fit and can be used for comparisons across various regressions (Akossou & Palm, 2013). All data are reported as means ± SD with significance set at $P < 0.05$.

CHAPTER IV

RESULTS

Demographics

Of the 32 subjects recruited, 2 subjects were removed due to equipment malfunction. Of the 30 subjects left, 7 subjects were removed from analysis due to failure of Constant Variance violation. Therefore, 23 total subjects were analyzed for this study (see Table 1). These subjects were nearly equally weighted between males and females (M=13, F=10), they were young (23.9 ± 3.3 yrs), not obese (BMI:23.7 ± 2.4 kg/m^2, WC: 82.3 ± 7.4 cm), and were not hypertensive (resting SPB: 117.6 ± 9.5 mmHg, resting DBP: 71.8 ± 8.6 mmHg).

Table 1. Total and Group Demographic Data

Parameter	Total	Slow	Fast
Subjects (N)	23 (F=10)	15 (F=7)	8 (F=3)
Age (yrs)	23.9 (3.3)	24.0 (3.4)	23.9 (3.3)
Height (cm)	175.1 (7.9)	174.6 (9.4)	176.0 (4.1)
Weight (kg)	72.8 (10.4)	72.3 (10.9)	73.8 (10.0)
BMI (kg/m^2)	23.7 (2.4)	23.6 (2.6)	23.8 (2.3)
Triglycerides (mg/dL)	74.4 (22.0)	69.1 (12.1)	84.2 (32.6)
HDL (mg/dL)	56.8 (12.4)	55.0 (10.5)	60.2 (15.5)
LDL (mg/dL)	63.9 (19.0)	60.4 (21.3)	71.1 (11.3)
Glucose (mg/dL)	92.5 (7.6)	92.0 (8.6)	93.3 (5.6)
iPAQ (MET-min/wk)	4563 (3333)	5549 (3442)	2714 (2287)*
VO_{2PEAK} (mL/kg/min)	34.2 (8.7)	35.6 (9.5)	31.6 (6.6)
Baseline:			
HR (bpm)	79.8 (14.5)	78.8 (15.0)	81.6 (14.3)
MAP (mmHg)	92.2 (16.5)	88.7 (11.8)	98.9 (22.4)
MCAv (cm/s)	65.4 (14.0)	67.6 (13.2)	61.2 (15.4)

Values mean (SD) unless stated otherwise. "Total" represents the total sample. "Slow" individuals with TD > 1.5s. "Fast" individuals with TD ≤ 1.5s. Subjects are presented as sample size with females in parenthesis. Baseline data is the averaged last 30s prior to exercise start. * denotes significantly different from Slow, $p < 0.05$

Model Failure Subjects

The 7 subjects that were removed were analyzed to determine possible differences. The removed subjects were mostly female (N=6, 85.7%) compared to the larger group of 23 (females = 10, 43.5%). These subjects had smaller WC (70.3 ± 13.5 vs. 82.3 ± 7.4 cm, $p = 0.001$), and lower systolic blood pressure (103.6 ± 8.7 vs. 117.6 ± 9.5 mmHg, $p < 0.001$). Due to the large percentage of females in this group, these differences are expected (Reckelhoff, 2001). During exercise, there were no differences in responses of MCAv, CPP, Q, or $\%VO_{2PEAK}$.

Rest-to-Exercise Monoexponential Modeling

There were 23 total subjects that exhibited a quality fit ($R^2_a = 0.61 \pm 0.14$) of MCAv with the monoexponential model from rest-to-exercise Figure 3A. The typical response for MCAv, CPP and CVCi to 50W cycling exercise is presented in Figure 3.

Table 2. Model Charac

Model Variables
TD (s)
tau (s)
MRT (s)

Parameters from monoexpon ity (ΔMCAv) from rest to exercise. Time delay (Mean (SD).

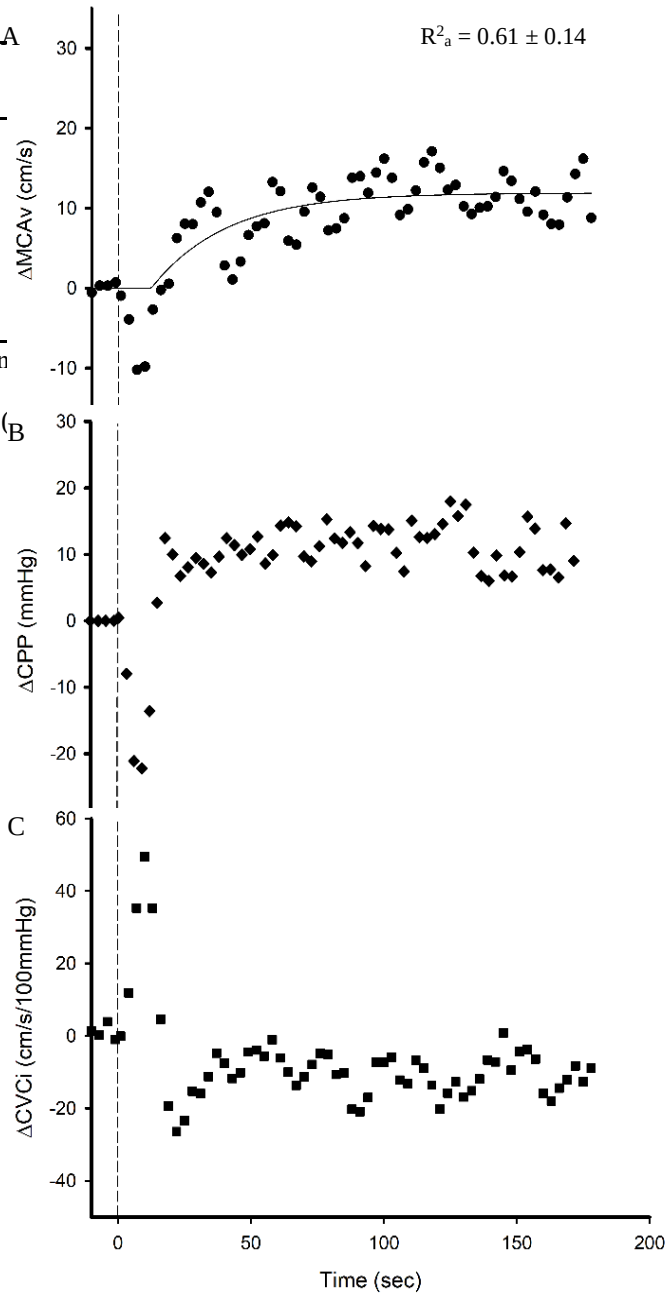

Figure 3. Change from rest (set to 0) to 50W cycling exercise for middle cerebral artery blood velocity (MCAv), A. Solid line represents best fit using a monoexponential model. Exercise start is depicted by the vertical dashed lines. Adjusted R^2 (R^2_a) is the Mean(SD) for all monoexponential models of each subject. Change in cerebral perfusion pressure (CPP) from rest (set to 0) to 50W cycling exercise (B). Change in cerebrovascular conductance index (CVCi) from rest (set to 0) to 50W cycling exercise (C). Exercise start is depicted by the vertical dashed line. All data sets presented are averaged 3s bins and from representative subjects

The results from applying a monoexponential model to MCAv are listed in Table 2.

Table 2. Model Characteristics

Model Variables	Mean (SD)
TD (s)	20.2 (18.1)
tau (s)	29.4 (23.0)
MRT (s)	49.4 (23.6)

Parameters from monoexponential model fit of change of middle cerebral artery blood velocity (ΔMCAv) from rest to exercise. Time delay (TD), tau, mean response time (MRT). Data are represented as Mean (SD).

The steady-state MCAv ($MCAv_{SS}$) response to 50W cycling exercise was analyzed using a multiple linear regression (Table 3). Overall, it was found that CPP, CVCi and $EtCO_2$ were significant predictors of MCAv during 50W of cycling.

Table 3. Results From Multiple Linear Regression of MCAv Steady-State Response

	ΔCPP	**ΔCVCi**	**ΔQ**	**ΔTPR**	**Δ$EtCO_2$**
$MCAv_{SS}$ (R^2_a = 0.83, AIC = 114.00)					
β Coefficient	0.84 (0.08)*	0.46 (0.06)*	0.60 (0.30)	0.04 (0.02)	0.52 (0.22)*

Results from multiple linear regression modeling of middle cerebral artery blood velocity (MCAv). Values are reported as β coefficient (SE). ($MCAv_{SS}$) the MCAv response to 50W cycling, (ΔCPP) responses of cerebral perfusion pressure, (ΔCVCi) *cerebrovascular* conductance index, (ΔQ) cardiac output, (ΔTPR) total peripheral resistance, and (Δ$EtCO_2$) End-tidal CO_2. Adjusted R^2 (R^2_a). * Indicates significance $p < 0.05$.

The $MCAv_N$ (-4.0 ± 5.5 Δcm/s) and CPP_N (-13.5 ± 10.4 ΔmmHg) occurred at similar times (16.5 ± 15.3 vs. 10.3 ± 4.5 s, $p = 0.07$, $d = 0.55$, time of $MCAv_N$ vs. time of CPP_N), seen in Figure 3A. The time $MCAv_N$ occurred was also similar time to the TD (16.5 ± 15.3 vs. 19.7 ± 18.7 s, p=0.967, MCAvN time vs. TD, respectively).

To attempt to explain $MCAv_N$, a regression model was used (see Methods). The results of this model are presented in Table 4. This regression indicates CPP and CVCi were the only

Table 4. Results From Multiple Linear Regression of MCAv Nadir

	$\Delta CPP_{@MCAvN}$	**$\Delta CVCi_{@MCAvN}$**	**$\Delta Q_{@MCAvN}$**	**$\Delta TPR_{@MCAvN}$**	**$\Delta EtCO_{2@MCAvN}$**
$MCAv_N$ (R^2_a = 0.36, AIC = 140.44)					
β Coefficient	0.58 (0.16) *	0.16 (0.06)*	0.20 (0.54)	-0.009 (0.03)	0.41 (0.46)

Results from multiple linear regression modeling of middle cerebral artery blood velocity (MCAv). Values are reported as β coefficient (SE). ($MCAv_N$) The lowest point MCAv achieved during 50W cycling was regressed with the responses of cerebral perfusion pressure at $MCAv_N$ ($\Delta CPP_{@MCAvN}$), cerebrovascular conductance index at $MCAv_N$ ($\Delta CVCi_{@MCAvN}$), cardiac output at $MCAv_N$ ($\Delta Q_{@MCAvN}$), total peripheral resistance at $MCAv_N$ ($\Delta TPR_{@MCAvN}$), and End-tidal CO_2 at $MCAv_N$ ($\Delta EtCO_{2@MCAvN}$). Adjusted R^2 (R^2_a). * Indicates significance $p < 0.05$.

parameters significantly contributing to $MCAv_N$, $p < 0.05$. We then completed another regression with $CPP_{@MCAvN}$ as the only parameter (Figure 4). The overall results of the model fit were similar (R^2_a = 0.36 vs. 0.25; AIC = 140.44 vs. 140.7, $MCAv_N$ regression with full parameters vs. CPP only.

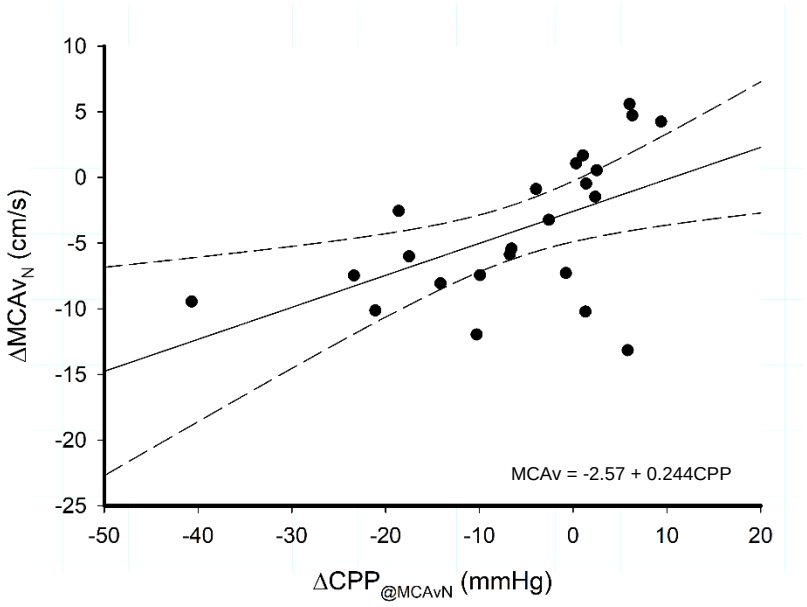

Figure 4. Linear regression between MCAv and CPP at $MCAv_N$. Solid line represents line of best fit, dashed lines represent 95% CI. Adjusted R^2 (R^2_a) = 0.25, p = 0.008, AIC = 140.7

The maximum CVCi ($CVCi_M$) achieved (27.3 ± 24.6 Δcm/s/100 mmHg) was significantly greater than the baseline (119.4 ± 40.2 vs. 92.1 ± 25.7 cm/s/100 mmHg, $CVCi_M$ vs. $CVCi_{BL}$). $CVCi_M$ occurred at 46.9 ± 57.0 s after the start of exercise (Figure 3C). This was after $MCAv_N$ occurred ($p = 0.02$, $d = 0.73$). In order to identify variables that are related to the TD, correlations with the model variables and CPP_N, $MCAv_N$, and $CVCi_M$ were completed (Table 5). The correlations between CPP_N and $CVCi_M$ (-0.740, $p < 0.05$), MRT and tau (0.680, $p < 0.05$), and MRT and TD (0.433, $p < 0.05$) should be assessed with caution. The significance of these correlations was expected due to the mathematical relationships between the variables. CVCi is calculated using CPP and MRT is calculated with both TD and tau. Without the mathematically related variables, the strongest correlation is between $MCAv_N$ and TD (-0.560, $p < 0.05$) and $MCAv_N$ and tau (0.434, $p < 0.05$). Compared to $MCAv_N$, $MCAv_{EN}$ was similar (61.3 ± 13.4 vs. 59.3 ± 17.2 cm/s, $p = 0.37$, $d = 0.13$, $MCAv_N$ vs. $MCAv_{EN}$). The ARRi was calculated as 3.5 ± 16.8 %.

Table 5. Correlation Matrix of Model Parameters and Cerebrovascular Parameters

	TD	tau	MRT	$MCAv_N$	CPP_N	$CVCi_M$
TD (s)	1					
tau (s)	-0.367	1				
MRT (s)	**0.433***	**0.680***	1			
$MCAv_N$ (cm/s)	**-0.560***	**0.434***	-0.021	1		
CPP_N (mmHg)	-0.306	-0.071	-0.31	0.411	1	
$CVCi_M$ (cm/s/100 mmHg)	0.153	-0.148	-0.023	-0.292	**-0.740***	1

Data are correlation coefficients for monoexponential model parameters (time delay, TD, tau, and mean response time, MRT) and cerebrovascular parameters (middle cerebral artery blood velocity nadir, $MCAv_N$; cerebral perfusion pressure nadir, CPP_N; and cerebrovascular conductance index maximum, $CVCi_M$). * denotes significance $p < 0.05$.

Exercise-to-Exercise Transition

The exercise-to-exercise transition elicited a smaller CPP_N (-6.5 ± 7.5 vs. -13.5 ± 10.4 mmHg, p = 0.046) and a smaller $CVCi_M$ (7.2 ± 13.7 vs. 27.3 ± 24.6 cm/s/100mmHg, p = 0.020, exercise-to-exercise vs. rest-to-exercise respectively).

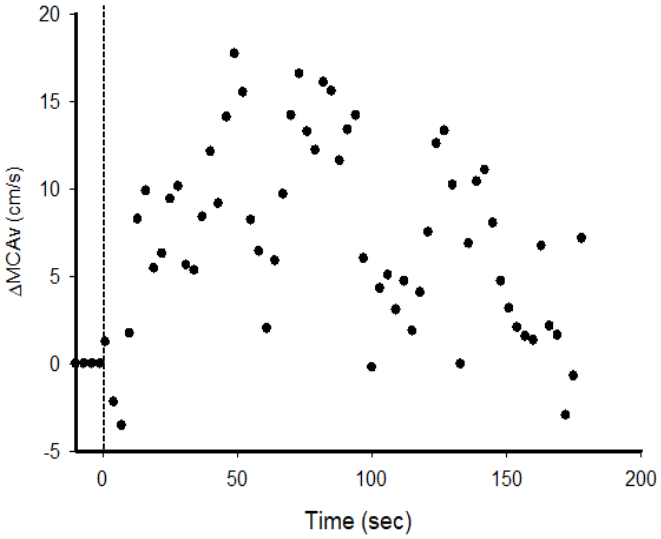

Figure 5. Change in middle cerebral artery blood velocity (MCAv) during a transition from 50W to 75W cycling exercise averaged 3s bins. Transition start is depicted by the vertical dashed line. A monoexponential model could not be fit to this data as there was no pattern to be modeled. Data presented is from a representative subject

We attempted to apply a monoexponential model to ΔMCAv from 50W cycling to 75W cycling exercise. Unfortunately, none of the subjects' responses followed a monoexponential pattern (Figure 5). With an R^2_a = 0.0 and no discernable pattern, we cannot apply a monoexponential model to these data.

Fast vs. Slow TD Responses

A rapid MCAv response was recorded in 8 subjects when exercise began (Figure 6).

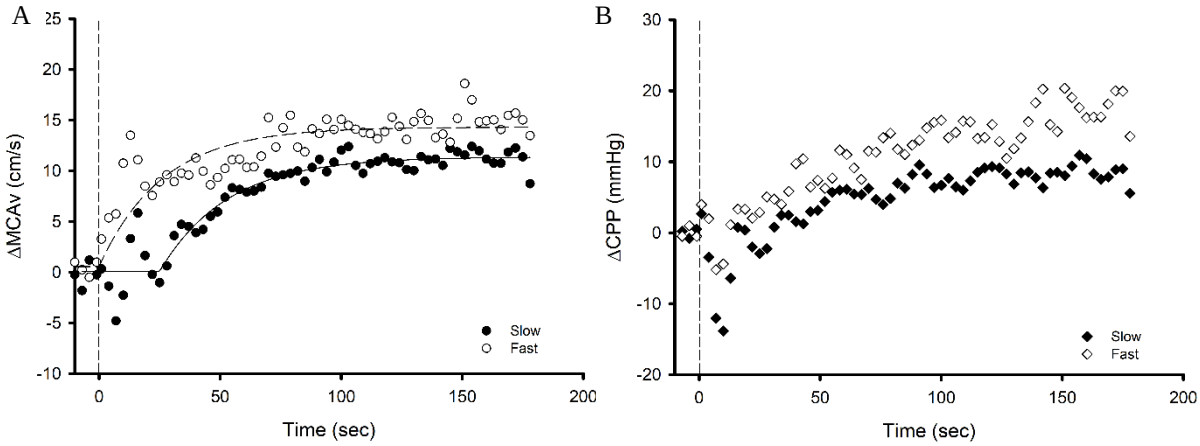

Figure 6. Comparison of change in middle cerebral artery blood velocity (MCAv, A) and cerebral perfusion pressure (CPP, B) from rest-to-exercise of 50W cycling between Fast (open, N=8) and Slow (filled in, N=15) groups. Start of exercise is denoted by vertical dashed lines. Data is averaged responses of subjects in each group. MCAv regression lines (A) are monoexponential model outputs of averaged data. Presented for representation not for analysis.

The demographics of the groups are presented in Table 1. These groups had similar distributions of males and females, had similar fitness levels (35.6 vs. 31.6 mL/kg/min, $p = 0.309$, Slow vs. Fast), and similar resting MCAv (67.6 vs. 61.2 cm/s, $p = 0.311$, Slow vs. Fast; Table 6). The Slow group seemed to be more physically active compared to the Fast (5549 vs. 2714 MET-min/wk, $p = 0.049$).

Table 6. **Model Characteristics Between Fast and Slow Groups**

Parameter	Slow (N=15)	Fast (N=8)	*p*	*d*
TD (s)	30.1 (14.6)	1.5 (0.0)*	<0.001	2.41
tau (s)	22.9 (21.5)	41.6 (21.9)	0.061	0.86
MRT (s)	53.1 (24.4)	42.5 (21.9)	0.280	0.49

Data are of Slow (individual with a TD > 1.5s) and Fast (individuals with a TD ≤ 1.5s). Parameters from monoexponential model fit of change of middle cerebral artery blood velocity (ΔMCAv) from rest to exercise. Time delay (TD), mean response time (MRT) and tau are variables gathered from monoexponential model fitting. Data are represented as Mean (SD). * denotes significant difference from Slow, $p < 0.05$.

Model characteristics comparing the Fast and Slow group are presented in Table 6. As expected, TD was different (30.1 ± 14.6 vs. 1.5 ± 0.0 s, $p < 0.001$, $d = 2.41$, Slow vs. Fast respectively)

between the groups. Tau tended to be different (41.6 ± 21.9 vs. 22.9 ± 21.5 s, $p = 0.061$, $d = 0.86$, Fast vs. Slow) whereas MRT was similar (42.5 ± 21.9 vs. 53.1 ± 24.4 s, $p = 0.279$, $d = 0.49$, Fast vs. Slow). Further illustrating the relationship between TD and $MCAv_N$, there were differences in $MCAv_N$ (-7.3 ± 3.4 vs. 2.0 ± 2.6 Δcm/s, $p < 0.001$, $d = 2.91$, Slow vs. Fast, Table 7). The Fast group also had a greater CPP response to exercise compared to the Slow group (17.3 ± 8.5 vs. 8.6 ± 8.6 ΔmmHg, $p = 0.030$, $d = 1.02$). The vascular responses, ARRi and CVCi, were opposite during $MCAv_N$ between the two groups, Table 7.

Table 7. **Comparison Between Fast and Slow Groups**

Parameter	Slow (N=15)	Fast (N=8)	*p*	*d*
ΔMCAv (cm/s)	11.6 (6.4)	15.5 (4.8)	0.143	0.67
ΔCPP (mmHg)	8.6 (8.6)	17.3 (8.4)*	0.030	1.02
ΔCVCi (cm/s/100 mmHg)	3.2 (15.7)	0.1 (6.6)	0.600	0.23
$\Delta MCAv_N$ (cm/s)	-7.3 (3.4)	2.0 (2.6)*	<0.001	2.91
ΔCPP_N (mmHg)	-16.1 (9.3)	-8.7 (11.2)	0.106	0.74
$\Delta CPP_{@MCAvN}$ (mmHg)	-11.3 (11.8)	3.7 (3.2)*	<0.001	1.53
$\Delta CVCi_{@MCAvN}$ (cm/s/100 mmHg)	11.0 (26.2)	-1.4 (1.8)	0.099	0.60
AARi (%)	6.4 (20.4)	-2.0 (1.9)	0.266	0.50

Data are of Slow (individual with a TD > 1.5s) and Fast (individuals with a TD ≤ 1.5s). Change values (ΔMCAv, ΔCPP, Δ CVCi) are the differences from baseline and the last 30s averaged of 50W cycling for each variable. $\Delta MCAv_N$ and ΔCPP_N are the change from baseline to the nadir. $\Delta CPP_{@MCvN}$ and $\Delta CVCi_{@MCAvN}$ are the change from baseline to the value recorded when $MCAv_N$ occurred. Autoregulatory Restrain index (ARRi) a calculated measure for autoregulation during the EoH.. Data are represented as Mean (SD). * denotes significant difference from slow, $p < 0.05$.

CHAPTER V

DISCUSSION

In accordance with the first hypothesis of this study, the rest-to-exercise transition elicited a brief drop in CBFv which altered CBFv dynamics as measured by a monoexponential model. Our data showed $MCAv_N$ occurred at a similar time as TD (16.5 vs. 20.2 s, $p = 0.389$), and the strongest correlation (of variables not mathematically related) were between $MCAv_N$ and TD (-0.560). Additionally, we showed CPP_N occurred at a similar time to $MCAv_N$ (16.5 ± 15.3 s vs. 10.3 ± 4.5 s, $p = 0.07$). This was immediately followed by $CVCi_M$ (46.9 ± 57.1 s), indicating a large cerebral vasodilation in response to the drop in CPP and MCAv. The second hypothesis, "A step increase in exercise intensity during a transition from a lower intensity exercise to a higher intensity exercise will result in faster kinetic parameters," could not fully be assessed due to the exercise-to-exercise transition of MCAv data exhibiting no discernable pattern and failing to be fit with a monoexponential model. However, the hypotensive response from an exercise-to-exercise was lower compared to the rest-to-exercise transition ($p = 0.046$).

MCAv Monoexponential Responses

Previous research has demonstrated that CBFv follows a monoexponential model in response to various stimuli (Billinger et al., 2017; Kaufman et al., 2019; Ogoh et al., 2009, 2022; Poulin et al., 1996; Sato et al., 2009; Ward et al., 2018). Application of a monoexponential model to this type of data has resulted in varying interpretations. When applied to an isolated stimulus such as hypercapnia or hypoxia, CBFv shows minimal delay of ~ 5s (Ogoh et al., 2009; Poulin et al., 1996). However, when applied during dynamic exercise, such as cycling, the delay is dramatically increased to ~ 40-50s before CBFv begins to increase (Billinger et al., 2017;

Ward et al., 2018). Therefore, it is clear that exercise presents a set of factors which contribute to this large delay.

Independently, neuronal tissue has the ability to rapidly increase CBF in response to environmental changes (Poulin et al., 1996; Sato et al., 2009) and metabolic changes (González-Alonso et al., 2004; Masamoto & Tanishita, 2009). Even though exercise increases neuronal activity and oxygen consumption (Fontes et al., 2015; Hilty et al., 2011; Kim et al., 2015; Liu et al., 2003; Mehta et al., 2009), and ultimately increases CBF (Sheth et al., 2004), there is still a measured and unexplained delay in CBFv response at exercise onset. Compared to previous data, the present study indicates that this delay is related to exercise intensity. The current study showed an overall faster MCAv response (TD = 20.2 ± 18.1 s) using light-intensity exercise compared to previous studies that administered moderate-intensity exercise which showed TD of 40-50s (Billinger et al., 2017; Ward et al., 2018). Due to the transparency of Billinger et al.'s group to post each subjects' data, we can directly compare their data to ours. Specifically, our TD (20.2 ± 18.1 vs. 52.9 ± 16.0 s, $p < 0.001$) and MRT (49.4 ± 23.6 vs. 82.7 ± 15.7 s, $p < 0.001$) were faster while the baseline (65.4 ± 14.0 vs. 66.9 ± 9.1cm/s, $p = 0.786$) and tau (29.4 ± 23.0 vs. 29.8 ± 13.0s, $p = 0.968$) were similar (Billinger et al., 2017). The current study used a light-intensity exercise (50W, 34.2 ± 8.7 % of VO_{2PEAK}) whereas Billinger et al. (2017) used a moderate-intensity exercise (85-125W, 45-55% of HR reserve). These results suggest that TD is related to exercise intensity. During the initial transition from rest-to-exercise, MCAv follows a distinct, predictable pattern that is present in the current study (Figure 3A), and in others using dynamic exercise (Billinger et al., 2017; Ogoh et al., 2022; Ward et al., 2018). The current use of a monoexponential model largely ignores this variance, omitting it as a TD. However, our data suggests that this is misguided as during this initial transition, significant alterations to central

and peripheral variables produce a large multifaceted disturbance which the cerebrovasculature must respond to in order mitigate any deleterious effects of these disturbances.

Initial MCAv Variance at Exercise Onset

At the start of exercise, there is a consistent and noticeable drop in MCAv towards a nadir, which then rebounds and increases above baseline to a steady state (Figure 3A). In this study, the strongest correlation with TD was $MCAv_N$ (Table 5) apart from the mathematically related variables (MRT vs. tau, MRT vs. TD, and CPP_N vs. $CVCi_M$, See Results). This can be interpreted as a greater $MCAv_N$ (meaning a greater drop in MCAv from baseline, i.e., a more negative number) is correlated with a larger TD. Therefore, in order to explain this extended TD, we also need to explain the $MCAv_N$. To accomplish this, we applied a multiple linear regression to $MCAv_N$ parameters that are known to have effects on MCAv (Markwalder et al., 1984; Ogoh et al., 2005; Willie et al., 2011) in an attempt to determine which, if any, are contributing to $MCAv_N$. The regression: $\Delta MCAv_N = \Delta CVCi_{@MCAvN} + \Delta CPP_{@MCAvN} + \Delta Q_{@MCAvN} + \Delta TPR_{@MCAvN} + \Delta EtCO_{2@MCAvN}$ (see Methods) gave us an understanding of the contributions of each of these parameters at the time $MCAv_N$ occurred. The only variables that significantly contributed to $\Delta MCAv_N$ were the change in ΔCVCi and ΔCPP and the total model was able to account for 36% of $MCAv_N$ variance (Table 3). The calculated variable CVCi is mathematically related to MCAv and CPP (i.e., CVCi = MCAv/CPP). Therefore, CVCi being significantly related to $MCAv_N$ is not surprising. It was surprising when a linear regression of $\Delta MCAv_N$ with ΔCPP as the only parameter was completed, the model fits were similar (AIC 140.44 vs. 140.7, Full $MCAv_N$ model vs. $MCAv_N$ model with CPP only) and they explained similar amounts of variance (36% vs. 25%, Full $MCAv_N$ model vs. $MCAv_N$ model with CPP only). This indicates that CPP alone is able to account for a large portion of the variance of $MCAv_N$ explained by the

full $MCAv_N$ model. With a β coefficient of 0.244, we can interpret this as a greater drop in CPP is associated with a greater drop in MCAv. The role of pressure changes and MCAv has been well studied and explained. Cerebral autoregulation attempts to sustain a constant CBF in the face of changes in pressure. Within a normal physiological pressure range, cerebral autoregulation maintains CBF surprisingly well (Brassard et al., 2021; Claassen et al., 2021; Tan, 2012). This maintenance is achieved, in part, through a series of mechanisms that respond to changes in pressure and flow by altering vessel diameter (Aaslid et al., 1989; Koller & Toth, 2012; Paulson et al., 1990; Payne, 2016). However, outside of normal pressures the cerebrovasculature is worse at maintaining CBF during hypotensive pressures compared to hypertensive pressures (Brassard et al., 2021; Claassen et al., 2021; Tan, 2012; Willie et al., 2014). CBFv drops when pressure is reduced through postural oscillations (Claassen et al., 2007; Favre & Serrador, 2019; Labrecque et al., 2019), thigh cuff release (Aaslid et al., 1989), and when lower body negative pressure is applied (Kay & Rickards, 2016). Although TCD is unable to directly measure vessel diameter, we can estimate cerebral vasodilation through CVCi calculation (Burley et al., 2021; Claassen et al., 2007). During the transition from rest-to-exercise, CPP and MCAv move towards nadirs at the same time. These changes activate various vascular mechanisms that ultimately result in cerebral resistance vasculature dilation in order to maintain flow (Koller & Toth, 2012). This can be seen in the present data as CVCi increases just after CPP and MCAv reach their nadirs (Figure 3). Although MCAv did drop as a result of the drop in CPP, this drop was mitigated due to the CVCi changes of the MCA. Had the cerebrovasculature been impaired and unable to vasodilate to maintain CBF, the drop in CPP would have caused a greater reduction in MCAv (Chaudhry et al., 2021). In the present study, $MCAv_{EN}$ is an estimated value MCAv would have achieved during $CPP_{@MCAvN}$ had there been

no cerebral autoregulatory response. ARRi is a calculated index that indicates CVCi changing during the initial rest-to-exercise transition was able to attenuate the drop in MCAv and prevent a greater degree of hypoperfusion. In this study, ARRi was found to be 3.5 %. This can be interpreted as autoregulation was able to attenuate the drop in MCAv at the start of exercise by 3.5%.

Cerebral autoregulation has been shown to buffer MCAv dropping during hypotensive pressure oscillations by 18% (Tan, 2012). During lower body negative pressure oscillations, Tan (2012) found the slope of percent change CBF over percent change MAP to be 0.81. Therefore, for each percentage change in MAP, CBF is altered by 0.81 % (Tan, 2012). In the absence of autoregulation, CBF would be directly proportional to pressure changes and this slope would be 1.0. If we interpret their data another way, by taking the complement (i.e., 1- 0.81), we get 0.18. As in the present study, this can be assessed as autoregulation was able to resist the effect of the pressure drop by 0.18, or 18% at hypotensive pressures. This is higher than the present study which shows cerebral autoregulation was able to mitigate the drop in MCAv at the start of exercise by 3.5%. It is important to note that Tan (2012) applied these oscillations in isolation. This is quite different to the responses during exercise which are accompanied with increases in MAP, Q, SV, HR and other cardiorespiratory variables, all of which play important roles in CBF maintenance (Markwalder et al., 1984; Ogoh et al., 2005; Willie et al., 2011). Likely the differences in determination (regression vs. calculation) and methodology (pressure oscillations vs. exercise onset) are the primary reasons for the differences observed in results. For a more direct comparison, we need to examine pressure changes at the start of exercise.

In the present study, at the start of exercise pressure and MCAv drop to a nadir. This relationship is similar to a recent paper by Ogoh et al. (2022) who examined the contributions of

MAP to CBFv at the start of exercise. They found at the onset of 20W cycling exercise, MAP and CBFv decreased to a nadir in a similar manner compared to the present study. When a correlation was applied to the percent drop in MAP to the percent drop in MCAv from the start of exercise to their nadirs, they found a significant relationship between the two with an R^2 = 0.28 (Ogoh et al., 2022). This is similar to the R^2_a we report (R^2_a= 0.25) for the regression of $\Delta MCAv_N$ with $\Delta CPP_{@MCAvN}$. The phenomenon of pressure dropping at the start of exercise is not a new concept, but it is not a well understood concept either. Traditionally, the understanding of pressure's relationship with exercise was an increase to a steady state required by the exercise intensity. However, a seminal paper by Wieling et al. (1996) demonstrated that MAP initially increases and is followed immediately by a significant drop in pressure 12s after onset of 50W upright cycling (-21 ± 4 mmHg) and onset of 50W of supine cycling (-12 ± 2 mmHg) (Wieling et al., 1996). This is consistent with our data which CPP_N was measured at -13.5 ± 10.4 mmHg occurring at 10.3 ± 4.5s after the start of 50W recumbent cycling. Largely, this drop in pressure can be attributed to the fall of TPR (Bringard et al., 2017; Wieling et al., 1996) driven by a combination of rapid skeletal muscle vasodilation as a result of mechanical and environment changes (Kaufman & Hayes, 2002; Kirby et al., 2007; Laughlin et al., 2012; Michelini et al., 2015; Tschakovsky et al., 2006; Tschakovsky & Sheriff, 2004) and atrial baroreceptor activation at the start of exercise as a result of the skeletal muscle pump (Barbosa et al., 2015, 2016; Michelini, 2007; Tschakovsky & Sheriff, 2004).

Collectively, these data indicate that there are a multitude of physiological mechanisms taking place during the initial transition from rest to exercise. Most conclusions point to a combination of the atrial baroreceptors and rapid skeletal muscle vasodilation as the primary mediators for exercise-onset-hypotension during dynamic exercise. However, without further

direct assessment, the exact mechanisms and their contributions to exercise-onset-hypotension and the initial MCAv variance at the start of exercise remains unclear.

Exercise-to-Exercise Transition

In the present study, MCAv did not follow a monoexponential increase during a step increase in exercise intensity during an exercise-to-exercise transition. This is surprising because other physiological variables, (e.g., skeletal muscle blood flow, VO_2) do follow a monoexponential model from an exercise-to-exercise transition (DiMenna et al., 2010; Saunders et al., 2005). In total, there was no discernable pattern in the MCAv (Figure 5) transition from 50W to 75W of cycling exercise. Although we cannot assess MCAv with a monoexponential model, we can still look at the response in comparison with the rest-to-exercise transition. Surprisingly, CPP still exhibited a drop from at the start of the transition from 50W to 75W exercise. However, this drop was attenuated compared to the rest-to-exercise transition (CPP_N = -13.49 ± 10.40 vs. -6.48 ± 7.45 mmHg, p=0.013, rest-to-exercise vs. exercise-to-exercise). This would support the claim that pressure drop at the start of exercise is induced by a combination of rapid vasodilation and atrial baroreceptor activity as rapid vasodilation would largely have already occurred and the baroreflex would already be reset.

Fast vs. Slow Responders

An exploratory analysis was completed based on an interesting separation that occurred when applying the monoexponential model to the subject's data (Figure 2). Several subjects exhibited a rapid increase in MCAv (Figure 6A) at the start of exercise (Fast, N = 8). Once separated and compared to the larger group (Slow, N = 15), we noticed a few trends that we would assume with the data already discussed. First, there were no differences in demographics or fitness levels (35.6 ± 9.5 vs. 31.6 ± 6.6 mL/kg/min, Slow vs. Fast) between the groups.

However, physical activity as measured by iPAQ was different (5549 vs. 2714 MET-min/week, Slow vs. Fast). The TD between the two groups were different (30.15 ± 14.55 vs. 1.50 ± 0.00, $p < 0.001$, $d = 2.41$, Slow vs. Fast respectively). We have already established that $MCAv_N$ is correlated with the TD (Table 5), it is no surprise then that the $MCAv_N$ for the Fast group was nonexistent and was different compared to the Slow group (-7.3 ± 3.4 vs. 2.0 ± 2.6 Δcm/s, $p < 0.001$, $d = 2.91$, Slow vs. Fast respectively). Although CPP_N did not reach significance (p=0.106) there was a large effect size (d=0.74), and $CPP_{@MCAvN}$ was significantly greater (larger drop) in the Slow group (-11.3 ± 11.8 vs. 3.7 ± 3.2 ΔmmHg, $p < 0.001$, Slow vs. Fast). Looking at Figure 6B, the overall shape of CPP responses was similar between groups, but some noticeable differences can be seen. The response of CPP from baseline to the end of stage 1 showed the Fast group increased CPP to a greater extent compared to the Slow group (17.3 ± 8.4 vs. 8.6 ± 8.6 ΔmmHg, $p = 0.030$, $d = 1.02$). During $MCAv_N$, the Fast group had no drop in CPP (3.7 mmHg) whereas the Slow group did (-11.3 mmHg). Autoregulation largely responds to changes in pressure and flow (Koller & Toth, 2012; Paulson et al., 1990; Payne, 2016). When $MCAv_N$ occurs, these two groups are experiencing different stimuli (Figure 6). The Fast group are experiencing an increase in MCAv (2.0 Δcm/s) and CPP (3.7 ΔmmHg $CPP_{@MCAvN}$) at this time whereas the Slow group are experiencing a decrease in MCAv (-7.3 Δcm/s) and a drop in CPP (-11.3 ΔmmHg $CPP_{@MCAvN}$). This difference is revealed in the ARRi which showed the Fast group with a -2.0% vs the Slow group which had a 6.4%. This would suggest the Fast group vasoconstricted in order to reduce MCAv to prevent hyperperfusion where the Slow group vasodilated in order to increase MCAv to prevent hypoperfusion (Paulson et al., 1990; Payne, 2016; Smith & Ainslie, 2017; Tan, 2012) . Overall, this dataset was exploratory and used to

enhance the overall conclusions drawn from the greater dataset and the accompanying research articles. To make any further conclusions would be misguided and should be done with caution.

Future Directions

The results of this study indicates a monoexponential model applied to rest-to-exercise CBFv data disregards the initial variation missing the largest vasomotion the cerebral arterial undergo. This vasomotion is likely a result of the drop in CPP at the start of exercise, activating cerebral autoregulatory mechanisms to maintain CBF. As our data show, CPP and MCAv are dropping (Figure 3A and 3B) and CVCi is reaching a peak (Figure 3C), attenuating CPP's effect on MCAv. Attributing this transition to a TD ignores this important vasomotor action and would likely mask potential differences. Closer examination of all variables calculated by applying a monoexponential model may yield a better understanding of the dynamic response happening at the start of exercise.

If this type of analysis is to be utilized in diseased populations, which it already has been in stroke patients (Billinger et al., 2020; Kaufman et al., 2019) and kidney transplant recipients (Ward et al., 2022), we need to fully understand what information this analysis is providing: otherwise, it will be difficult to interpret. For instance, immediately following a stroke, the non-affected MCAv seems to have a faster TD (Kaufman et al., 2019). Additionally, TD is shorter (meaning faster overall MCAv kinetics) at the start of exercise following a kidney transplant compared to healthy controls (Ward et al., 2022). While it may appear that a more rapid MCAv onset is better for the blood flow-dependent brain, with these data it is difficult to determine this. Ultimately, more research is needed to elucidate the mechanisms mediating the kinetic variables gathered through the use of a monoexponential model before making comparisons to diseased populations. Through this understanding, we will be able to utilize the full benefits of the TCD

and enhance our understanding of disease progression, which may lead to improved disease identification, earlier interventions and eventually improved health outcomes.

Conclusion

The results of the present study suggests light-intensity exercise elicited an exercise-onset-hypotensive response, measured by $CPP_{N,}$ that drove MCAv towards a nadir. The larger the $MCAv_N$, the greater the TD reported through the use of a monoexponential model. Therefore, any factor that enhances the exercise-onset-hypotensive response will lead to a greater drop in MCAv, ultimately resulting in the model extending the time before an increase in MCAv above baseline is detected by the monoexponential model. Our data support only assessing this as TD is misguided and ignores the greatest autoregulatory response during a rest-to-exercise transition the cerebrovasculature faces. Inclusion and assessment of tau and MRT may prove to be as important of components and help elucidate some of this important autoregulation occurring at the start of exercise. In the present study, when MCAv reached its nadir, CPP also hit its nadir. This was then immediately followed with CVCi reaching its peak. This indicates that the cerebrovasculature dilated in order to mitigate the drop in CBFv when CPP reached its nadir. The importance of this initial variance is not well understood as this type of analysis is still new. However, more research is needed to determine what mechanisms are driving these variables.

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