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# SEX DIFFERENCES IN CEREBROVASCULAR RESPONSE TO SUBMAXIMAL AND MAXIMAL EXERCISE

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SEX DIFFERENCES IN CEREBROVASCULAR RESPONSE TO SUBMAXIMAL AND MAXIMAL EXERCISE

A THESIS APPROVED FOR

THE DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

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## ABSTRACT

Dysfunctional cerebrovascular control is closely linked to the increased incidence of cerebrovascular and neurodegenerative diseases (e.g. dementia and Alzheimer's). Epidemiological evidence identifies sex-specific differences in the course of prevention (risk factor) and treatment (prognosis) of cerebrovascular and brain diseases. Therefore, examining sex differences in cerebral blood flow (CBF) regulation is essential. Despite previous studies identifying muscle blood flow sex discrepancies to both handgrip and knee extensor exercise, CBF responses during exercise in women are underrepresented in the literature. Therefore, it remains unclear if sex differences in cerebrovascular control to exercise exists. **Purpose:** Address whether cerebrovascular responses were different between men (MN) and women (WM) during a graded exercise test (GXT) and provide better insight into the relationship between sex and cerebrovascular reactivity at differing exercise intensities. **Methods**: 26 young healthy adults (13 WN, 24.2±3.6 yrs) completed a graded-exercise-test (GXT, stage length 3-min, 50W, 75W, 100W; after which MN increases by 40W, WN increased by 30W maintaining 60-80 RPM) on a recumbent cycle ergometer to volitional exhaustion. The highest completed stage was determined as Maximal Wattage (Wmax). Middle cerebral artery velocity ($MCA_v$; transcranial Doppler ultrasound) and mean arterial pressure (MAP; finger photoplethysmography, CPP was calculated MAP – [0.7355* vertical distance of TCD probe from heart-level]), were measured on a beat-by-beat basis to calculate $CVC_i$ = $MCA_v$/CPP*100mmHg. End-Tidal $CO_2$ ($ETCO_2$) was also collected (Gemini Gas Analyzer). **Results:** Mean ± SD, MN and WN exhibited similar MCAv responses to changes in exercise intensity with peak MCAv obtained ~ 60% Wmax (ΔMCAv, WN = 18.4 ± 5.0, MN = 15.8 ± 3.1 cm/s, $p = 0.07$) and declined as intensity increased. There was a trend for WN to have a greater ΔMCAv with increasing relative exercise intensity ($p = 0.06$) with the greatest difference between WN and MN observed at 100%Wmax (ΔMCAv, WN= 11.0±2.2, MN= 5.9±3.2 cm/s, $p<0.01$). Interestingly, MN had a greater exercise cerebral prefusion pressor response with increasing exercise intensity ($p < 0.01$) with the largest difference being observed at 100% Wmax (ΔCPP, WN 35.8±5.3, MN 44.7±9.6 mmHg, $p < 0.01$). Additionally, WN experienced greater CVCi ($p<0.01$) at higher exercise intensities compared to MN, with the greatest difference observes at 100% Wmax (ΔCVCi, WN= -22.5±10.9; MN= -31.5±7.2 cm/s/100mmHg, $p<0.01$). There was no difference in ETCO2 across the entire GXT ($p=0.40$). **Conclusion:** Young females were able maintain MCAv in response to GXT through increased CVCi, while young males were able to sustain similar MCAv values through significant increases in CPP. Additionally, the similar $ETCO_2$ values between groups suggests either the sex-linked mechanistic differences in cerebrovascular response GXT independent of $ETCO_2$.

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# Chapter I

## Introduction

The human brain is the most oxidative organ, as it consumes ~ 20% of total body oxygen utilization yet, is only ~ 2 % of the body's total mass (Clarke DD, 1999). Maintenance of cerebral blood flow (CBF) is crucial to brain neuronal function as it is responsible for delivery of nutrients (e.g. glucose) and oxygen ($O_2$) as well as, removing metabolites such as carbon dioxide ($CO_2$). Brain neurons are particularly sensitive to perturbations in CBF due to a lack of energy storage, making them dependent on the circulation to deliver glucose and $O_2$ (Allaman & Magistretti, 2013). In order to meet the high metabolic demands, the brain contains a vast microvascular network to lower resistance to ensure a robust flow along with greater efficiency for nutrient delivery.

Therefore, the cerebrovasculature control is fundamental to human health. In fact, cerebrovascular disease (CBVD) is one of the leading causes of death for both males and females (Seidel, Giovannetti, & Libon, 2012). Further, evidence suggest that poor cerebrovascular function leads to reductions in CBF over time and may contribute to Alzheimer's and other neurodegenerative diseases (Leijenaar et al., 2017). In contrast, aerobic fitness has been found to improve resting CBF in males, regardless of age (Ainslie et al., 2008). And aerobic fitness has been found to be negatively correlated with dementia (Ahlskog, Geda, Graff-Radford, & Petersen, 2011; P. J. Smith et al., 2010).

Habitual exercise has been shown to decrease this vascular risk by improving or maintaining microvascular function which enables the stabilization of CBF while also decreasing vascular stiffness (DeSouza et al., 2000) and elevating cerebrovascular reactivity (Murrell et al.,

2013). Cerebrovascular reactivity (CR) refers to the ability of the cerebral vessels to respond to changes in $PaCO_2$ (Madden, 1993), and is often used to asses cerebral microvascular function (Xie et al., 2006). The ability of habitual exercise to elevate CR may be an essential non-pharmacological tool to combat CBVD and neurological disease. This theory has led a body of research using exercise to combat the effects of cardio- and cerebrovascular disease. From a cardiovascular disease perspective, substantial evidence exists that systemic vascular control during exercise differs between males and females. However, there has been little research to determine if there are sex-linked differences in CBF response to exercise, despite the difference in incident rates of CBVD (Haast, Gustafson, & Kiliaan, 2012; Haberman, Capildeo, & Rose, 1981).

A large body of literature has been developing over the years indicating that even in young healthy humans, vascular outcomes and mechanisms that regulate blood pressure and flow can be very different between males and females (Jill N. Barnes, 2017; J. N. Barnes, Taylor, Kluck, Johnson, & Joyner, 2013; V. M. Miller et al., 2013). For instance, several studies have indicated that females have greater vasodilation to skeletal muscle during exercise than males (Kellawan et al., 2015; Parker et al., 2007). With regard to the cerebrovasculature, females have been found to have a greater resting middle cerebral artery blood velocity when compared to males (Peltonen et al., 2015; Tegeler et al., 2013). In contrast, cerebrovascular responses to environmental challenges, such as hypoxia and hypercapnia have been equivocal. Where similar cerebrovascular responses have been observed in hypoxia (Peltonen et al., 2015) and differential findings in response to hypercapnia with some finding no differences between the sexes (Peltonen et al., 2015) and others finding greater dilation in females (Olah et al., 2000). To add to the confusion, recent work has found females to have greater cerebral autoregulatory responses

to postural challenges in blood pressure (M. E. Favre & J. M. Serrador, 2019). However, very little work has investigated cerebrovascular control during exercise in females, despite a significant sex difference in prevalence of CBVD and evidence of differential cerebrovascular control (Appelros, Stegmayr, & Terent, 2009).

Exercise is a unique and regularly occurring challenge to the cerebrovasculature offering a combination of neuronal metabolic, arterial blood gas, and blood pressure challenges that can vary greatly depending on the exercise intensity. In response to incremental exercise, CBF has been shown to increase from rest and plateau at $60\%VO_{2Peak}$, followed by a decline as exercise intensity increases (Sato, Ogoh, Hirasawa, Oue, & Sadamoto, 2011), with findings consistent across different study designs (Kurt J. Smith & Philip N. Ainslie, 2017; Traystman, 2017). The decline in CBF is thought to be a result of reduction in partial pressure of carbon dioxide ($PaCO_2$) (Querido & Sheel, 2007). To date, there has only been one study that directly compared male and female's cerebrovascular response to exercise, with results indicating no significant sex-linked differences in CBF response in younger healthy adults (J. L. Ward et al., 2018). However, their protocol only reached 55% of predicted HR during low intensity exercise whereas additional research in males have shown that changes in CBF occur at greater exercise intensities (Curtelin et al., 2018; Marsden et al., 2012).

While CBF response to aerobic exercise have been shown to be consistent across male cohorts, changes in CBF in females and if there are differences in CBF responses between males and females have yet to be elucidated. Understanding cerebrovascular responses between males and females is an important first step to identify potential mechanistic differences and understanding regarding cerebrovascular control. The aim of the present study will be to directly compare CBF response in healthy males and females during graded cycle exercise. We

hypothesize that females will reach peak CBF at a lower % of maximal power output (Wmax) intensity compared to males. We also hypothesize males will decline in CBF at a lower %Wmax intensity compared to females.

**Purpose of the Study**

The present study aimed to address whether cerebrovascular responses were different between males and females during a graded exercise test (GXT) and provide better insight into the relationship between sex and cerebrovascular reactivity at differing exercise intensities.

**Research Questions**

1. Do females exhibit greater cerebral blood flow velocity (MCAv) response to different exercise intensities (%Wmax) compared to males?
    - **1.1** Do females reach their peak MCAv at a lower %Wmax than males?
    - **1.2** Do females maintain elevated MCAv at higher %Wmax than males?
2. Do females experience in cerebrovascular conductance index (CVCi) in response to MCAv increases compared to males?
    - **2.1** Do females experience greater absolute CVCi at their absolute peak MCAv than males?
    - **2.2** Do females experience greater changes in CVCi compared to males during GXT
    - **2.3** Do males and CVCi response similarly to $PETCO_2$ changes

**Alternate Hypotheses**

1. Females will exhibit greater cerebral blood flow velocity responses to different exercise intensities (%Wmax) compared to males

**1.1** Females reach their peak MCAv at a lower %Wmax than males

**1.2** Females will maintain elevated MCAv at higher %Wmax than males

**2.** Do males and females differ in cerebrovascular conductance index (CVCi) in response to MCAv increases compared to males?

**2.1** Do females experience greater absolute CVCi at their absolute peak MCAv than males?

**2.2** Do females experience greater changes in CVCi compared to males during GXT

## Significance of the Study

Pathologies in the cardio and cerebrovascular system have increased over the last few decades. Habitual exercise has been shown to mitigate by improving or maintaining microvascular function which enables the stabilization of CBF, which results in decrease of CBVD risk. While current research investigates ways to combat the effects of cardiovascular & cerebrovascular diseases, little has been done in terms of determining if there are differences between sexes. These differences could influence future training interventions aimed at mitigating these neurological disorders. This study would be the first measure cerebral hemodynamic differences between the sexes across various exercise intensities as a first step in furthering future research aimed at improving cerebrovascular health.

## Delimitations

1. The subjects will include healthy males and females between 18-30 years of age.
2. Subjects included in this study will be recreationally active (3-6 hours of activity per week).

3. Any subject with any known cardiovascular disease, musculoskeletal, and pulmonary disease will not be permitted to participate in the study.
4. Exclusion Criteria: diabetes, coronary artery disease, stroke, heart attack, sleep apnea, smoking, statins medications, hypertension, asthma, ≥ 30 body mass index (BMI), pregnancy.

**Limitations**

1. Results of our study from our sample may not apply to other populations.
2. Photoplethysmography is an estimation of brachial artery SBP, DBP, Cardiac Output, and Stroke Volume.
3. MCAv is an accurate surrogate of cerebral blood flow in the Middle Cerebral Artery.

**Assumptions**

1. Subjects will give maximal effort during graded exercise testing (GXT).
2. Subjects will be honest when answering the health and physical activity questionnaires.
3. Subjects will be fasted for 8 hours.
4. Subjects will follow the study guidelines of
5. ≥12hr without caffeine, and ≥24hr without exercise, alcohol, and the use of supplements (e.g. vitamins or other health supplements) and NSAIDs (e.g. Advil or Aleve).
6. The transcranial Doppler is a valid and reliable method for determining MCAv.

7. Changes in middle cerebral artery diameter will remain relatively constant during exercise.

8. The Equivitol Heart Rate monitor is a valid and reliable method for determining heart rate.

**Operational Definitions**

- **Cerebral Blood Flow (CBF)**: Volume of blood supply to the brain in a given period of time (ml/min).

- **Middle Cerebral Artery Velocity ($MCA_v$)**: The velocity of red blood cell flow through the middle cerebral artery.

- **Cerebrovascular Disease (CBVD):** refers to a group of pathological conditions that can lead to a cerebrovascular event, such as a stroke or aneurysm.

- **Cerebrovascular Reactivity (CR)** refers to the ability of the cerebral vessels to respond to changes in $PaCO_2$.

- **Mean Arterial Pressure (MAP)**: Average blood pressure in an individual during a single cardiac cycle.

- **Cerebral Perfusion Pressure (CPP):** Was calculated by subtracting the product of the hydrostatic column height (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 ($CVC_i$):** $MCA_v$ / CPP*100mmHg. Allows for assessment of blood flow velocity relative to perfusion pressure. Use to estimate vasodilation

- **$VO_{2Peak}$:** The oxygen consumption observed during maximum physical effort.

- **Anaerobic Threshold (AT):** The physiological point during exercise at which lactic acid starts to accumulate in the muscles, which occurs around the point during increasing intensity exercise that anaerobic processes become more dominant.

- **Stoke Volume (SV)**: The volume of blood pumped from the left ventricle per beat.

- **Heart Rate**: The rate at which the heart is beating measured by the number of contractions of the heart per minute (bpm).

- **Cardiac Output (Q)**: The product of the heart rate (HR), or the number of heart beats per minute (bpm), and the stroke volume (SV), which is the volume of blood pumped from the ventricle per beat (L/Min)

- **Arterial Partial Pressure of Carbon Dioxide ($PaCO_2$):** The measure pf the partial pressure of carbon dioxide in the arterial blood gasses.

- **Work Max (Wmax)**: The greatest amount of work that can be done during a graded exercise test.

- **Graded Exercise Test (GXT)**: Assessment used to examine the dynamic relationship between exercise and integrated physiological systems.

- **$O_2$:** Oxygen

- **$CO_2$:** Carbon Dioxide

- **Endothelial Nitric Oxide Synthase (eNOS)**: Enzymes catalyzing the production of nitric oxide (NO) from L-arginine.

# Chapter II

# Literature Review

## Introduction

Exercise is a promising, non-pharmacological intervention to help combat the negative effects of various pathologies and aging on the brain (Gaitán et al., 2019). The ability of the cardiovascular system to adapt to changes in metabolic demand is imperative for maintaining homeostasis and preventing ischemia in active and non-active tissues (Kübler, 1994). A major component of the cardiovascular system is its ability to transport oxygenated blood to the brain by way of the internal carotid & vertebral arteries. Oxygen and nutrient supply to the brain is the highest regulated in the body due to its high metabolic demand when compared to it low energy storage (Falkowska et al., 2015). Cerebral blood flow (CBF) is defined as the blood supply to (a given part of) the brain in a given time. During rest, this equates to approximately 50-55 mL per 100 g brain tissue per minute, in normotensive adults (Lassen, 1959). CBF is crucial to maintain for it being the main component in delivery of nutrients and oxygen ($O_2$) to different regions of the brain while also removing metabolites such as carbon dioxide ($CO_2$). Reductions in CBF over time may contribute to Alzheimer's and other neurodegenerative disease (Leijenaar et al., 2017). With the prevalence of Alzheimer's projected to triple by 2050 (Hebert, Weuve, Scherr, & Evans, 2013), further research in cerebrovascular response to exercise is a high priority.

Previous research has shown there are sex differences in vasodilatory responses in various vessels throughout the body during exercise (Green et al., 2016; Hicks, Kent-Braun, & Ditor, 2001; Kellawan et al., 2015). Though the research in sex differences in cardiovascular response is extensive, there has been little considered on determining if sex differences in CBF during various exercise intensities and modes are present. Graded exercise testing (GXT) is a

proven method of measuring metabolic responses to exercise at different intensities. Higher GXT performance is correlated with increased aerobic fitness levels. The aim of this study is to examine and compare the cerebral hemodynamic responses between males and females during GXT. Obtaining a greater understanding of these differences could help aid in the prevention of the detrimental effects that decreases in CBF have been shown to exhibit.

Therefore, it may be beneficial to explore if there are variations in CBF responses between males and females during GXT. The purpose of this literature review is to discuss sex-linked differences in cardiovascular response to exercise, explore cerebrovascular responses to exercise and the underlying factors that causes the response, and finally determine current gaps in the literature in regards to sex differences in CBF response to exercise.

**Sex-Linked Differences in Exercise Reponses**

There are several anatomical, physiological, and mode specific factors that affect how males and females respond to exercise. Sex differences in aerobic capacity, cardiac output, thermoregulation, and substrate utilization are among many underlying factors that affect exercise performance (Charkoudian & Joyner, 2004). It is also noted that these differences are highly dependent on exercise modality. With investigation into these differences becoming more prevalent, it is important to highlight how these factors can contribute to changes in vascular response.

**Aerobic Fitness**

When comparing solely aerobic capacity, females have been shown to exhibit 5%-15% lower $VO_{2max}$ compared to males with comparable training status (Kang, Chaloupka, Mastrangelo, & Hoffman, 2002). Reduced resting stroke volume (SV) results in lower cardiac output (Q), which in turn decreases the ability for females to reach comparable relative $VO_{2max}$

(Ferguson, Gledhill, Jamnik, Wiebe, & Payne, 2001; O'Toole, 1989). However, after normalization of stroke volume to fat free mass, these differences were eliminated in sedentary individuals, but only reduced in endurance trained athletes (Ogawa et al., 1992) Similarly, females often have lower blood volume, resulting in lower circulating hemoglobin levels with reduced oxygen-carrying capacity contributes to reduced aerobic capacity (M. J. Joyner, 1993).

**Fatiguability**

Despite this advantageous increased aerobic capacity, males have consistently demonstrated greater susceptibility to fatigue than females (Hunter, 2014). However, the mechanistic differences contributing to susceptibility are specific to contraction intensity, contraction type, and muscle groups that are activated. Specifically, in intermittent and isometric contraction of the knee-extensor muscles, sex differences in fatigability for both were still evident even after being matched for strength *post hoc* (Ansdell, Thomas, Howatson, Hunter, & Goodall, 2017). With these differences noted in large muscle group activation, it can be assumed they could be a contributing factor when comparing sex-linked differences in lower-extremity graded exercise testing.

**Exercise Intensity and Duration**

Intensity and duration of exercise plays possible the greatest role in cardiovascular response to exercise. Exercise intensity is vaguely defined as % of maximal work from low (10-35%) to moderate (35-50%) then vigorous (50-75%) and then maximal (~100%). There are numerous other ways of defining exercise intensity with % of $VO_{2max}$ or HRmax (Barbosa, Montagnana, Denadai, & Greco, 2014; Richards, Mercado, Clayton, Heigenhauser, & Wood, 2002). Short duration, high intensity (vigorous to maximal), exercise primarily involves

carbohydrate utilization, whereas long duration low intensity (low to moderate) exercise involves greater contribution of fat metabolism (Melzer, 2011).

There is evidence females heavily rely on lipolysis of adipose tissue, with less reliance on carbohydrate oxidation during endurance exercise compared to males (Arner, Kriegholm, Engfeldt, & Bolinder, 1990; Mittendorfer, Horowitz, & Klein, 2002). This difference in substrate utilization is heavily dependent on exercise intensity and duration (Michael J. Joyner, 2017) Future research is still needed conducted using females as subjects to determine the conclusive impact of, and mechanisms that underpin nutritional effects on exercise response (Devries, 2016).

Previous research suggests sex-linked mechanistic differences in cardiovascular response to changes in MAP (Frey & Hoffler, 1988; Gotshall, Tsai, & Frey, 1991). Wheatley, Snyder, Johnson, and Olson (2014) found that cardiac output were similar between males and females at submaximal exercise intensity, whereas during vigorous exercise showed reduced stroke volume in females that could not be compensated for with increased heart rate. These differences contributed to greater MAP during moderate and vigorous exercise. Interestingly, she found vascular resistance remained similar between sexes throughout the protocol. This confirms females mechanistically work in different proportion to males to maintain and regulate cardiovascular homeostasis by an increased HR while having lower resistance to flow by increased dilation of vessels. It is unknown if these mechanistic differences experienced in peripheral vessels is observed in blood flow to regions of the brain during different exercise intensities.

**Exercise Mode Dependence**

Mode of exercise is also important to consider. In the forearm at rest and maximum exercise, both males and females have the same oxygen consumption relative to muscle mass ($ml \bullet min^{-1} \bullet 100ml^{-1}$ muscle)(Jahn et al., 1999). Research has shown that females have a greater resistance to fatigue of skeletal muscles during exercise (Hicks et al., 2001). One of the reasons hypothesized for this finding is due to differences in overall muscle mass. Since females on average have lower absolute muscle mass, there is less compressions of the vasculature during contraction of the muscles, resulting in lower levels of occlusion and increased flow to the muscle. Saito et al., (2008), compared sex differences in brachial artery blood flow during handgrip contractions. Subjects repeated 5 second static maximal voluntary contractions (MVC) followed by 5 second rest with a handgrip device in an intermittent pattern. Brachial artery blood flow and vascular conductance (VC) was significantly greater in females compared to males during exercise. There were no differences in average blood pressure or HR between the sexes in this experiment, due to the low amount of overall work completed by the body. The study revealed there is greater muscle perfusion and VC during the muscular relaxation phase of the intermittent MVC exercise for females. VC and blood pressure gradient determine blood flow according to Poiseuille's Law. Since there was no difference in blood pressure, we can assume that the VC was the factor that contributed to greater to the greater flow and muscle perfusion. The same VC, that was calculated from normalized flow, has not been thoroughly studied in areas of brain blood perfusion and could be explored further in future research involving exercise.

Parker et al. (2007) compared similar VC response sex differences during graded knee extensor exercise, which revealed women's femoral artery dilated to a significantly greater

extent than men across all submaximal exercise workloads. Additionally, at maximal exertion, femoral VC was lower in men than women. Collectively, when comparing sex-related differences in VC response to submaximal and maximal exercise in large muscle groups, its suggested that young women have a greater vasodilatory response compared to men. Taking VC into account could me a more accurate representation of changes in flow compared to changes in pressure.

These comparisons have not yet been made in response to exercise when measuring cerebral blood flow. These potential sex differences in vasodilatory responses in cerebrovascular in response to exercise could have important implications for future research when comparing hemodynamic responses. Due to the unlimited variation of research designs and protocols in the field of exercise physiology, cross-comparison of sex-linked differences in cardiovascular responses to exercise remains a challenge.

**Hormonal Effects to Vascular Response**

Hormones are chemical messengers that serve an important role during exercise in their ability to regulate vasodilation. Sex hormones are steroid-based whereas the pancreatic hormones, catecholamines and growth hormone are amino acid derivatives. Sex hormones play a role in vascular tone through the synthesis and release of various vasodilators like nitric oxide (NO) and vasoconstrictors like endothelin-1 ($EN_1$).

**Estrogen and Endothelial Nitric Oxide Synthase**

The term estrogen refers to three structurally similar steroid hormones: estrone, estriol, and estradiol ($E_2$). $E_2$ is the primary estrogen found within the body. These estrogens hormones, specifically $E_2$, have shown to induce the expression and activation of endothelial nitric oxide synthase (eNOS), thus enhancing NO production in human aortic endothelial cell cultures

(Hishikawa et al., 1995). The expression seen in endothelial cultures has an impact in vasculature throughout the body, including cerebral vasculature. Female cerebral arteries exhibit greater vasodilatory responses to eNOS compared to males in animal models (Geary, Krause, & Duckles, 2000). The increases in cerebrovascular reactivity preserves CBF values in younger females compared to males. This increased vasodilatory response associated with carotid artery reactivity, peripheral vascular function, and structure are negatively affected by age (Brislane et al., 2020). Estrogen levels decrease significantly in post-menopausal females. We see that incidence rates for CBVD in females is significantly less than males, but then incidence rate rises to similar levels to males post-menopause (Mosca et al., 1997; Paganini-Hill, Ross, & Henderson, 1988). This protective mechanism involving estrogens hormones could be a key factor for the disparity in CBVD between males and pre-menopausal females.

**Menstrual Cycle**

It is important to take these hormonal effects on cerebrovascular response into account when comparing males and females and attempt to control for them. Controlling for sex hormones can be accomplished by measuring female subjects during specific phases of their menstrual cycle.

In a normal 28 day menstrual cycle, the first 14 days constitute the follicular phase which involves the ovarian maturation of a primary oocyte, while the latter 14 days are referred to as the luteal phase and are associated with the preparation of the uterus for the possible implantation of a fertilized oocyte (Gardner, Shoback, & Greenspan, 2011). The follicular phase begins with menstruation, with the early follicular (EF) phase, days 1-7, being associated with the lowest levels of circulating $E_2$. With what is known about the effects of $E_2$ on the vasculature during exercise, the EF is the opportune time to test female subjects to ensure CBF differences

are not due to $E_2$. The late follicular (LF) phase, days 7-14, is when circulating $E_2$ levels are at their greatest. Measuring female subjects during the LF will help us greater understand $E_2$'s effect on CVR

**Cerebral Anatomy**

Regulation of perfusion to the brain is high due to its lack of energy stores combined with its high metabolism. Though the brain only makes up 2% of total body mass, it receives 20% of cardiac output, consumes 20% of the body's oxygen supply and 25% of the body's glucose (Traystman, 2017).

Cerebral perfusion can be divided into anterior and posterior circulation. Anterior cerebral blood flow is supplied from the internal carotid artery (ICA), which branches off from the common carotid arteries in the neck. The ICA then branches into the middle cerebral artery (MCA and the anterior cerebral artery (ACA). The MCA is the largest intra-cranial artery and supplies a portion of the frontal lobe and the lateral surface of the temporal and parietal lobes, including the primary motor cortex. The ACA supplies midline portions of the frontal lobes and superior medial parietal lobes.

Posterior circulation is supplied by the vertebral arteries (VA). The left and right VA join together at the level of the pons forming the basilar artery (BA), which connects the Circle of Willis, forming an anastomotic (cross-connection) ring. The VA delivers the remaining ~24% of global CBF to the Circle of Willis (Schöning, Walter, & Scheel, 1994; Traystman, 2017). The Circle of Willis allows for blood to flow to compensate for a lack of blood flow in one brain region in the event of a blockage.

**Cerebrovascular Response**

Cerebral perfusion pressure (CPP) can be calculated from the difference between MAP and internal cerebral pressure. Cerebral Autoregulation (CA) is the ability of the cerebral vasculature to alter resistance in response to changes in MAP, (within 50-170 mm Hg), maintaining a constant CBF (Lassen, 1959). CA works as a protective mechanism to ensure blood flow to the brain is kept constant despite large changes in CPP. Young healthy females have demonstrated greater cerebral autoregulation in the MCA to changes induced blood pressure oscillations compared to young healthy males (M. E. Favre & J. M. Serrador, 2019). During exercise, increases in cerebral activation, sympathetic nervous activity, MAP and Q , and changes in $PaCO_2$ often occur simultaneously and are responsible for driving changes in CPP. While these metabolic responses to exercise have been vastly researched, there presents a gap in the literature directly comparing them between males and females in response to exercise at greater intensities, coincidently, where the differences are likely to be the most pronounced.

Cerebrovascular Reactivity (CVR) refers to the ability of the cerebral vessels to respond to changes in arterial partial pressure of carbon dioxide ($PaCO_2$). CBF regulation is highly dependent $PaCO_2$. $CO_2$ can freely diffuse across the blood-brain barrier, thus increases in $PaCO_2$ cause the pH changes that drive an increase ventilation via central chemoreceptors (Markwalder, Grolimund, Seiler, Roth, & Aaslid, 1984; Verbree et al., 2014). This increase in ventilation, which is experienced during exercise, is due to the hypercapnic response from the chemoreceptors. Hypercapnia, or excessive $CO_2$ in the bloodstream, produces cerebral vasodilation and increases in CBF (Ito et al., 2000; Verbree et al., 2014; Wei, Kontos, & Patterson, 1980). This increase in CBF is seen at the onset of exercise. CVR can be calculated as the percent change from baseline in MCAv or CVCi relative to the percent change from baseline

in End-Tidal $CO_2$ ($PETCO_2$). There is a highly significant sex-linked difference in $CO_2$-induced CVR with the use of controlled carbegene gas, with females having a stronger vasodilatory response to changes in $PaCO_2$ than males (Kastrup, Thomas, Hartmann, & Schabet, 1997). While this research shows there is a sex-linked difference in CVR as changes in metabolic demands increase, there is still an unclear picture of where these differences begin to present.

**Cerebral Blood Flow Response to Exercise**

Our cardiovascular system, in response to exercise, is challenged with the duty of having to regulate blood flow to account of increased metabolic activity in the skeletal musculature, while ensuring vital organs such as the brain, heart, and lungs remain adequately perfused to avoid catastrophic ischemia. CBF response to exercise has traditionally been described as biphasic, with increasing flow resulting from increases in intensity until 60% $VO_{2max}$ (Herholz et al., 1987; Jorgensen, Perko, Hanel, Schroeder, & Secher, 1992). CBF then either plateaus as intensity increases (Larsen, Rasmussen, Overgaard, Secher, & Nielsen, 2008; K. J. Smith et al., 2014) or proceeds to decrease to values close to or below baseline. (K. J. Smith et al., 2012; Subudhi, Lorenz, Fulco, & Roach, 2008)

Regulation of CBF is dependent on a variety of factors such as arterial blood pressure, arterial blood gases, metabolite values, and neural pathways (Lassen, 1959). During exercise, these factors are increased at varying degrees dependent on intensity and mode of said exercise. During rhythmic-handgrip exercise, the MCAv shows increases on the contralateral side (Jorgensen, Perko, Payne, & Secher, 1993), whereas cycling shows bilateral increases in MCAv (Jorgensen, Perko, & Secher, 1992; Linkis et al., 1995). Ide, Horn, and Secher (1999) showed CBF increases during exercise in excess of the oxygen demand. 10 male and 2 female subjects completed a submaximal exercise, maintaining 30% and 60% of their measured $VO_{2max}$ for

10minutes each. $MCAV_{mean}$ increased from 60±2cm/s at rest to 65±3cm/s at 30% $VO_{2max}$, to 68±3cm/s at 60% $VO_{2max}$. This data indicated that CBF increased as exercise intensity increases, and then plateaus similar to other cardiovascular measurements during exercise due to increased metabolic response (Laughlin, 1999).

**Measurement of Cerebral Blood Flow**

There has been extensive clinical research with the use of non-invasive measurement of CBF due to by means of magnetic resonance imaging (MRI) and flow velocity measured by Transcranial Doppler Ultrasonography (TCD),with MRI as the "gold standard". Zarrinkoob et al. (2015) quantified the distribution of blood flow in the cerebral arteries, revealing the middle cerebral artery (MCA) received 21%; distal MCA, 6%; anterior cerebral artery (ACA), 12%, distal ACA, 4%; ophthalmic artery, 2%; posterior cerebral artery (PCA), 8%; and 20% to basilar artery. Uncertainty arouse if our cerebral microvasculature had similar vasoactive responses that were seen in the peripheral vasculature. Valdueza et al. (1997) measured blood flow velocity and diameter of the MCA in response to hyperventilation using MRI and TCD measurements. Participants completed 3 minutes of hyperventilation while measurements of MCAv were collected with TCD and vessel diameter and flow was recorded with MRI. MRI imaging revealed no significant changes in the diameter of the proximal MCA during normal versus hyperventilation. This revealed the relative changes in MCAv reflect relative changes in blood flow, in terms of hyperventilation.

**Cerebral Blood Flow Measurement During Exercise**

The question then arose if the diameter of cerebral arteries remained constant during exercise or if they were susceptible to similar amounts of vasodilation observed in peripheral vasculature. Verbree et al. (2017) found revealed a 2% decrease in MCA cross-sectional area

during rhythmic handgrip exercise using MRI. This elucidated limitations as measurement using TCD may underestimate CBF. Subudhi et al. (2011) revealed that increases in $PET_{CO2}$ are not observed in standard conditions, with $PET_{CO2}$ values increasing from 34±4Torr at rest to plateauing at 46±16Torr, before returning to resting values at $W_{max}$. This shows that the increases in MCAv that are observed with exercise are indicative of increased CBF and not due to other physiological factors. The use of TCD in our study will be able to show changes in CBF during large lower-extremity exercise and will provide values that show sex differences in CBF at a given intensity.

**Conclusion**

Research has shown that males and females differ in vascular control in the periphery to exercise. It is also known that there is a uniform CBF response to exercise at a given intensity. However, it is still unclear if there are sex differences in CBF response to exercise that are similar to the peripheral vasculature. A recent review by K. J. Smith and P. N. Ainslie (2017) provided a generalized overview of CBF response to with a meta-analysis of 17 studies. Of the 221 participants of the studies, 212 were male compared to 9 females. This disparity in subject demographics is one of the many reasons that more research is needed to form a greater understanding of CBF and the exercise intensity relationship and if there are differences between males and females. With the prevalence of CBVD being disproportionately greater in males than females, these potential differences in CBF response could be of great importance in exercise being an intervention for CBVD. Therefore, it is important to understand if there are differing CBF responses to exercise between males and females as it will give greater insight into the possible mechanisms of cerebrovascular control.

# CHAPTER III

## Methodology

### Recruitment

Subjects were recruited at the University of Oklahoma Health and Exercise Science Department using advertisements **(Appendix A)** which informed and instructed participants to contact the PI and the Sub-Investigator. Interested individuals were then scheduled for their screening visit.

### Participants

26 healthy subjects (13 women) between 18-30 years of age took part in the study. Subjects will be moderately active according to iPAQ questionnaire **(Appendix B)**. All females participating in the study were tested during the early follicular phase of their menstrual cycle (1-7 days after the start of menstruation) to account of circulating estrogen levels and reduce variations caused by the menstrual cycle (Hashimoto et al., 1995). This study was approved by the Institutional Review Board at The University of Oklahoma Health Sciences Center.

### Screening Visit

The participants reported to the Human Circulation Research Lab at The University of Oklahoma for their screening visit at least ≥8hr fasted, ≥12hr without caffeine, alcohol, and ≥24hr without vigorous exercise or NSAIDs (e.g. Advil or Aleve). Each participant provided and completed informed consent, health insurance portability and accountability act (HIPAA) form, the 7-day physical activity questionnaire (iPAQ) **(Appendix B)**, Demographics form **(Appendix C)** and health status questionnaire **(Appendix D)**. Participants then had a venous blood sample taken by a certified member of the HCRL. Participants were then screened using the Transcranial

Doppler to determine if middle cerebral artery (MCA) signal could be found (clearly identified upward tracing). This was followed by adjustment on the recumbent cycle using a goniometer to ensure a knee flexion of 5-10° (George et al., 2000). Participants were will lastly be fitted with an ECG monitor vest and $VO_2$ mask, with their measurements recorded on the screening visit for**m (Appendix F)**. Inclusion and exclusion criteria **(Table 1)** were assessed by the screening visit **(Appendix B, D, E)**

**Table 1.** Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| ○ Age: 18-30 years old<br>○ Free of cardiovascular & metabolic diseases.<br>○ Free of any lower body skeletal muscle injuries.<br>○ Systolic Blood Pressure < 130mmHg and/or Diastolic Blood Pressure < 90mmHg.<br>○ Body mass index: BMI < 30 kg/$m^2$.<br>○ Females: In order to minimize hormonal effect, females will be tested during the early follicular phase (days 1-7) of the menstrual cycle, or during the low hormone dose phase of oral contraception use. | ○ Systolic `Blood Pressure ³ 130mmHg and/or Diastolic Blood Pressure ³ 90mmHG<br>○ Diagnosed Cardio-metabolic diseases: Diabetes; Coronary Artery Disease; stroke; heart attack;<br>○ Cardio-metabolic medications (medications prescribed muscle metabolic of cardiovascular conditions, e.g. Metformin, ACE inhibitors, Beta Inhibitors, Alpha Inhibitors, Statins, Calcium Channel inhibitors)<br>○ Current regular tobacco use (including smokeless) OR former regular tobacco user within the previous year of enrollment<br>○ Asthma, including exercise induced asthma<br>○ ³ 30 BMI<br>○ Abdominal obesity (Waist circumference of greater than 102 cm in males, and greater than 88 inches in females)<br>○ Triglyceride level of ³ 150 milligrams per deciliter of blood (mg/dL)<br>○ HDL cholesterol < 40 mg/dL in males or < 50 mg/dL in females<br>○ Fasting glucose ³ 100 mg/dL<br>○ Pregnancy<br>○ Transcranial Doppler: Subjects that are unable to get a quality $MCA_v$ signal on the TCD will be excluded from the study<br>○ Language: Subjects that do not speak English will be excluded from the study.<br>○ 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.). |

**Graded Exercise Test (GXT) Visit**

Participants reported to the Human Circulation Research Lab ≥8hr fasted, ≥12hr without caffeine, and ≥24hr without exercise, alcohol, and the use of supplements (e.g. vitamins or other health supplements) and NSAIDs (e.g. Advil or Aleve). Participants were first fitted with their Equivitol vest and were then seated on the recumbent cycle at the adjusted height from the first visit. The Transcranial Doppler (TCD) was then adjusted on the subject's head with the fitted with the $VO_2$ mask attached over the TCD headgear. Investigators then would search for $MCA_v$ signal on the participants. Once strong signal was found with clearly identified upward tracing, participants then placed their left arm in a sling and had the Non-Invasive Blood Pressure monitor attached around their left middle finger. Lastly, the subjects had a pulse oximetry ear clip ($SPO_2$) attached to their left ear. The subject then completed the GXT cycle protocol (Figure 1.).

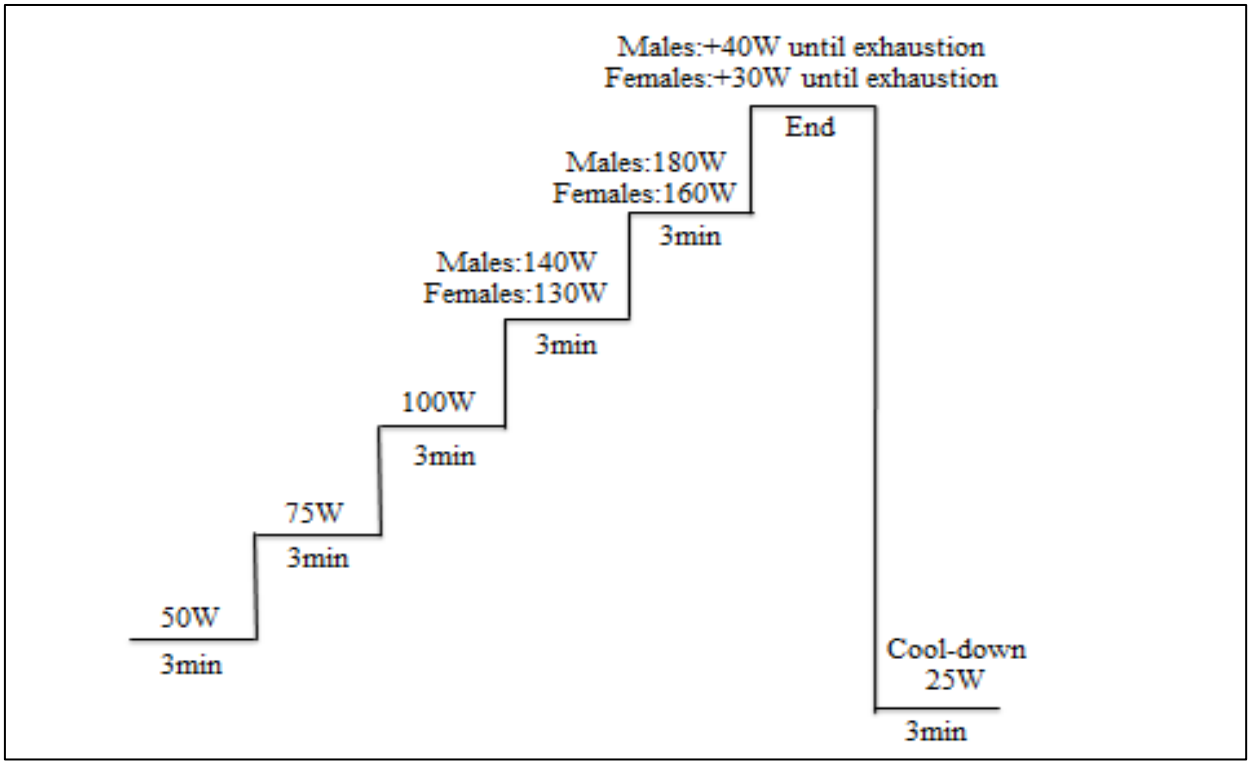



**Figure 1.** Protocol Outline. Schematic outline of incremental recumbent-cycling test to exhaustion. Each increment will be 3 min and participants will maintain 60-80rpm. The test will start at 50W and progress by 25W until 100W. Thereafter, male subjects' increments increased by 40W and Females increased by 30W.

The GXT protocol was completed on a cycle ergometer (Lode, Corival cpet, Groningen, The Netherlands). Recoding began with a 2-minute resting phase minutes for a baseline measurement. The test then increased incrementally every 3 minutes, with participants maintaining a peddle frequency of 60-80 RPM until exhaustion. The first three stages will be the same for each participant (50, 75 and 100W), the following stages will increase 30W for females and 40W for males, each stage remaining at 3 min to ensure similar time to exhaustion. Exhaustion was defined as the inability to sustain at least 60 RPM. The power output at voluntary cessation was recorded as the wattage of the highest stage completed (Wmax). The subjects were verbally encouraged throughout the testing protocol.

### Height and Weight

Height and weight were measured during the screening visit while the participant wore lightweight clothing and no shoes. To obtain a height measurement, participants were asked to stand straight against the stadiometer (Novel Products, Inc., Rockton, IL) with their arms hanging straight down and their feet together. Body weight was recorded with a standard scale (Tanita, Model BWB-800A, Japan). Each measurement was recorded to the nearest 0.5 cm and 0.1 kg.

## Cardiovascular Measurements

### Blood Pressure

Brachial artery blood pressure was measured in triplicate by an automated blood pressure monitor (HEM-705, Omron, Lake Forest, IL, USA) after a 5-minute supine rest during the screening visit. The lowest of the 3 recordings was used to determine resting blood pressure.

Mean arterial pressure (MAP) was measured by finger artery pressure photoplysmorgraphy (ADInstruments, Human Non-invasive Blood Pressure (NIBP), Colorado, USA). Finger photoplethysmography enables the non-invasive measurement of beat-to-beat arterial BP. Other hemodynamic parameters such as total vascular conductance (TVC) and cardiac output (Q) was recorded using NIBP. Though the NIBP finger artery pressure tends to underestimate absolute BP readings compared to intra-arterial measures, it does accurately represent the temporal changes of BP (Parati, Casadei, Groppelli, Di Rienzo, & Mancia, 1989). A review in which BP measurements from similar photoplysmorgraphers were compared with those from intra-arterial measurements or non-invasive intermittent BP measurements concluded

that for the assessment of beat-to-beat changes in BP and BPV, the Finapres provided a reliable alternative to invasive measures (Imholz, Wieling, van Montfrans, & Wesseling, 1998).

**Transcranial Doppler ultrasonography**

Cerebral blood flow velocity was measured using trans-cranial Doppler ultrasound (2 MHz pulsed-wave Robotic TCD probe; Neurovision, Multigon Industries, Elmsford, CA, USA) of the middle cerebral artery (MCA). Changes in cerebrovascular blood flow can be inferred from changes in blood flow velocity. To isolate the MCA, the probe was placed on the temporal bone window and readings at depths of 40-65 mm were made. Middle cerebral artery velocity ($MCA_v$) values will be collected by a continuous data collection device at 200 Hz (Powerlab/16SP ML 880; ADInstruments, Colorado, USA). This device is connected to LabChart Pro (version 7.3.7, ADInstruments, Colorado, USA) in which all data is displayed as digital hertz (Hz).

**Metabolic Gas Measurements**

$VO_2$, End-Tidal $CO_2$ ($ETCO_2$) was taken using an exercise mask (7450 Series Silicone V2™ Oro-Nasal Mask, Hans Rudolph Inc., Kansas City, Missouri, USA) and measured breath-by-breath by Gas Analyzer (CWE Inc., Gemini End-Tidal $O_2$ and $CO_2$ Analyzer, Ardmore, PA, USA). The data was collected the same as the CBF measurements.

**Heart Rate and ECG**

Heart rate, ECG, and respiration measurements was measured using multi-parameter telemetric device EQO2 (Equivital, EQ02 + SEM, Hidalgo, UK). The $EQO_2$ system offers real-time monitoring of these measurements displayed in Labchart (ADInstruments Inc, LabChart v7.3.2., Colorado Springs, Colorado, USA). Though it has some limitations in clinical settings,

the EQO2 has been proven to accurately measure ECG and HR on a beat by beat measurement (Akintola, van de Pol, Bimmel, Maan, & van Heemst, 2016)

**Blood Analysis**

Blood Analysis was completed using the point of care lipid measuring device CardioChek PA (Polymer Technology Systems, Inc., Indianapolis, United States). Participants were tested for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, 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 Level**

Activity level was estimated using the International Physical Activity Questionnaire (October 2002) Long Last 7 Days Self-Administered Format **(Appendix B)** during the first visit. Estimation was done using the Excel template from the iPAQ website.

**Power Analysis**

Sample size was determined using G*Power (version 3.1.9.2). Because this is the first study to compare cerebrovascular response (measured by $\Delta MCA_v$) to exercise intensity between males and females, we estimated sample size assuming 80% power, two-sided $\alpha=0.05$, and effect size of 0.03 based on data from similar study design (J. L. Ward et al., 2018). Given these assumptions, 30 participants (15 female) were required for the study.

**Data Acquisition and Analysis**

Data was recorded continuously and acquired via Power Lab (Powerlab/16SP ML 880; ADInstruments, Colorado, USA) at 200Hz throughout baseline and exercise. All reported variables for each exercise intensity are an averaged over the last 30s of each exercise stage.

%Wmax, was calculated from the final completed stage during the GXT. The absolute change from baseline (Δ) for any variable was calculated as the last 30s average of the variable for that work intensity – last 30s average of the same variable during baseline. CPP was calculated by subtracting the product of the hydrostatic column height (difference between the transcranial probe location and the height correction probe at heart level for finger photoplethysmography cuff) multiplied by 0.7355 from the measured MAP to obtain mmHg hydrostatic correction. Cerebrovascular conductance index was calculated as $CVC_i = MCA_v$ / CPP*100mmHg.

Statistical analyses were performed using SAS (SAS 9.1, Cary, NC) software. All data are reported as means ± SD with significance set at $P < 0.05$. Student's *t*-test for independent groups and Tukey post hoc analysis were used to compare baseline differences between male and female groups. An autoregressive, random-coefficients model (PROC MIXED) using a continuous predictor (either absolute workload or workload as a percentage of maximal workload attained), fitting a random intercept and slope with workload as the within-individual factor and sex as the between-individual factor, was used to determine differences between subject groups in outcome variables (MCAv, CVCi, CPP, and TVC). Figures and tables were created using Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, WA, US).

# CHAPTER IV

## Results

### Baseline Characteristics

In total, 26 healthy subjects (13 females) participated in the study. Subject characteristics are shown in Table 1. There were no significant between group differences in resting blood glucose levels (men: 94.1 ± 7.4 mg/dL; women: 90.0 ± 7.5 mg/dL, p=0.24), triglycerides (men: 74.8 ± 17.5 mg/dL; women: 72.4 ± 23.9 mg/dL, p=0.97), or low-density lipoprotein cholesterol levels (men: 63.7 ± 23.2 mg/dL; women: 64.4 ± 21.4 mg/dL, p=0.39). However, high-density lipoprotein cholesterol was significantly higher in women (men: 50.8 ± 10.2 mg/dL; women: 63.8 ± 10.0 mg/dL, p = 0.002).

**Table 4.** Subject Characteristics

| | Men (n = 13) | Women (n = 13) |
|---|---|---|
| Age (years) | 24.6 ± 3.5 | 23.7 ± 3.7 |
| Height (cm) | 178.5 ± 6.8 | 171.5 ± 5.4* |
| Weight (kg) | 79.9 ± 7.6 | 63.9 ± 7.4* |
| BMI (kg/m$^2$) | 25.1 ± 2.1 | 21.7 ± 2.2* |
| Systolic Blood Pressure (mmHg) | 120.5 ± 7.6 | 110.4 ± 8.8* |
| Diastolic Blood Pressure (mmHg) | 71.0 ± 6.6 | 71.5 ± 11.4 |
| IPAQ Fitness Score (METs) | 3833.46 ± 2822.3 | 4871.2 ± 3699.6 |
| Baseline MCAv (cm/s) | 61.9 ± 11.1 | 68.7 ± 18.3 |
| Baseline Heart Rate (bpm) | 73.1 ± 7.2 | 86.3 ± 8.9* |

Values are group averages ± SD; n, no. of subjects. BMI, body mass index; IPAQ, International Physical Activity Questionnaire; MCAv, middle cerebral artery velocity;
* Significant difference between men and women, $p < 0.05$.

**Absolute Metabolic and Cardio-Cerebrovascular Response**

The absolute response values across the GXT are summarized in Table 3.

**Table 6.** Absolute Metabolic and Cerebrovascular Response Across GXT

| | Exercise Intensity (%Wmax) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | p value |
| MCAv (cm/s) | | | | | | | | | | | | 0.06 |
| Men | 61.58 | 66.97 | 71.30 | 74.57 | 76.77 | 77.92 | 77.99 | 77.07 | 74.98 | 71.87 | 67.17 | |
| Women | 68.97 | 74.41 | 78.87 | 82.36 | 84.42 | 86.42 | 86.99 | 86.58 | 85.21 | 82.86 | 79.53 | |
| CVCi (cm/s/100mmHg) | | | | | | | | | | | | < 0.01 |
| Men | 92.73 | 93.77 | 93.86 | 93.02 | 91.23 | 88.51 | 84.85 | 80.25 | 74.71 | 68.23 | 61.29 | |
| Women | 95.51 | 96.64 | 97.03 | 96.68 | 94.86 | 93.74 | 91.15 | 87.82 | 83.76 | 78.94 | 73.39 | |
| CPP (mmHg) | | | | | | | | | | | | < 0.01 |
| Men | 67.74 | 72.44 | 77.15 | 81.85 | 86.56 | 91.26 | 95.97 | 100.67 | 105.38 | 110.09 | 113.08 | |
| Women | 75.96 | 79.39 | 82.82 | 86.26 | 89.95 | 93.12 | 96.55 | 99.98 | 103.42 | 106.85 | 110.28 | |
| $P_{ETCO2}$ (mmHg) | | | | | | | | | | | | |
| Men | 40.24 | 43.15 | 45.37 | 46.91 | 47.77 | 47.77 | 47.94 | 46.22 | 44.34 | 41.77 | 38.52 | 0.61 |
| Women | 38.75 | 41.66 | 43.90 | 45.47 | 46.19 | 46.43 | 46.14 | 45.02 | 43.23 | 40.76 | 37.62 | |
| CO (L/min) | | | | | | | | | | | | < 0.01 |
| Men | 8.46 | 10.18 | 11.90 | 13.62 | 15.34 | 17.06 | 18.78 | 20.50 | 22.22 | 23.94 | 25.66 | |
| Women | 7.00 | 7.92 | 8.83 | 9.75 | 10.61 | 12.05 | 12.49 | 13.41 | 14.32 | 15.24 | 16.15 | |
| MAP (mmHg) | | | | | | | | | | | | < 0.01 |
| Men | 87.21 | 91.91 | 96.32 | 101.32 | 106.02 | 110.73 | 115.43 | 120.13 | 124.84 | 129.54 | 134.25 | |
| Women | 94.02 | 97.45 | 100.88 | 1043.31 | 108.01 | 111.07 | 114.61 | 118.04 | 121.47 | 124.90 | 128.34 | |
| TVC (L/min/mmHg) | | | | | | | | | | | | 0.01 |
| Men | 0.10 | 0.12 | 0.13 | 0.14 | 0.15 | 0.16 | 0.17 | 0.17 | 0.18 | 0.19 | 0.19 | |
| Women | 0.08 | 0.09 | 0.09 | 0.10 | 0.10 | 0.11 | 0.11 | 0.12 | 0.12 | 0.13 | 0.13 | |
| $VO_2$ (L/min) | | | | | | | | | | | | < 0.01 |
| Men | 0.36 | 0.56 | 0.79 | 1.02 | 1.26 | 1.49 | 1.73 | 1.96 | 2.19 | 2.43 | 2.66 | |
| Women | 0.29 | 0.43 | 0.60 | 0.77 | 0.96 | 1.13 | 1.32 | 1.50 | 1.69 | 1.91 | 2.12 | |

MCAv, middle cerebral artery velocity; CVCi, cerebrovascular conductance index; CPP, cerebral perfusion pressure; PETCO2, end-tidal carbon dioxide; CO, cardiac output; MAP, mean arterial pressure; TVC, total vascular conductance; $VO_2$, oxygen uptake.

**MCAv Response**

MCAv were similar at baseline between the sexes (MCAv, men: 61.9 ± 11.1 cm/s; women: 69.3 ± 17.1 cm/s, p=0.10). In both sexes there was a main effect of exercise intensity ($p < 0.0001$) increasing until ~60-65% Wmax and declining from peak MCAv at exercise intensities greater than 70%Wmax. There was a trend for women to maintain a higher MCAv at higher exercise intensities however, sex and Wmax interaction was not significant ($p = 0.06$) Table 2.).

ΔMCAv response changes with exercise intensity ($p < 0.0001$) with a trend for women to maintain a higher ΔMCAv at exercise intensities > 65% Wmax) when compared to men (Sex and Wmax interaction, $p = 0.06$).

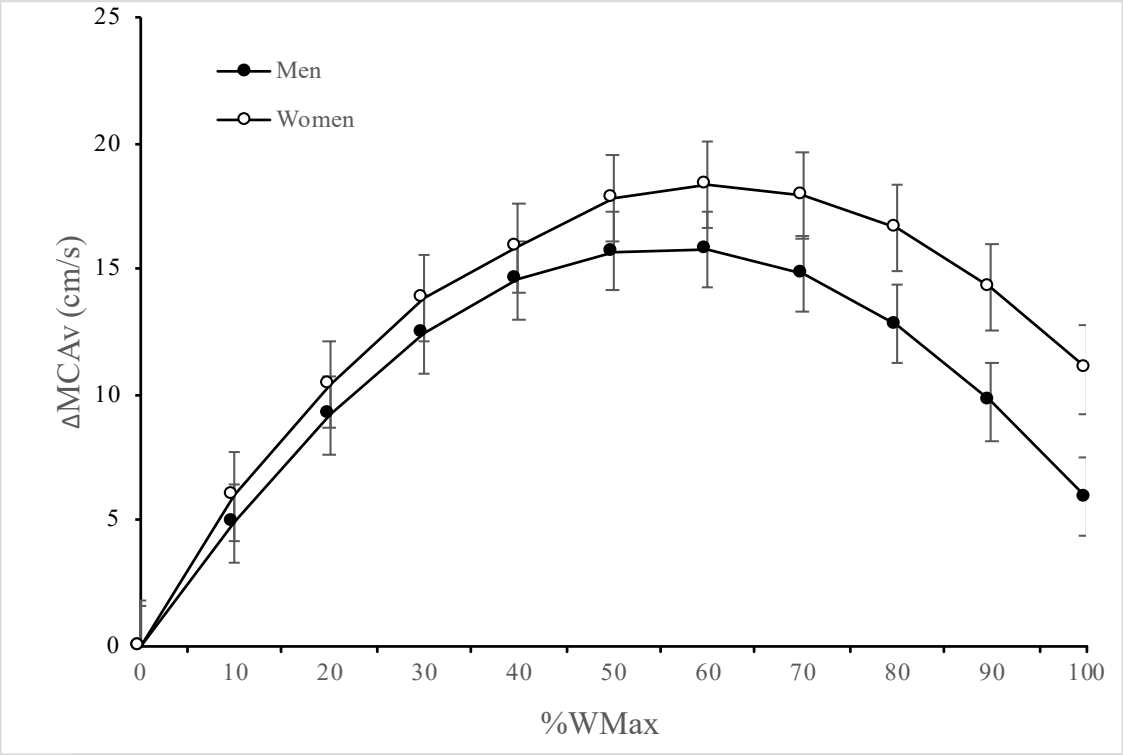



**Figure 3.** Change (Δ) in MCAv, middle cerebral artery velocity, relative to rest expressed as group means ± SD at percentage of maximal workload (%Wmax). *Significant difference between men and women $p < 0.05$

**Cerebral Perfusion Pressure Response**

Absolute CPP were similar between men and women at baseline (CPP, men: 67.7 ± 18.5 mmHg; women: 74.2 ± 17.0 mmHg, p=0.12) and increased with exercise intensity reaching a maximum at 100 %Wmax ($p < 0.0001$). There was also a significant sex and exercise intensity interaction ($p = 0.002$) as exercise intensity increased (Table 2.). However, posthoc analysis indicates absolute CPP were not different between the sexes even at 100% Wmax (CPP, men: 114.8 ± 18.4 mmHg; women: 111.6 ± 17.0 mmHg, p=0.38) (Table. 2).

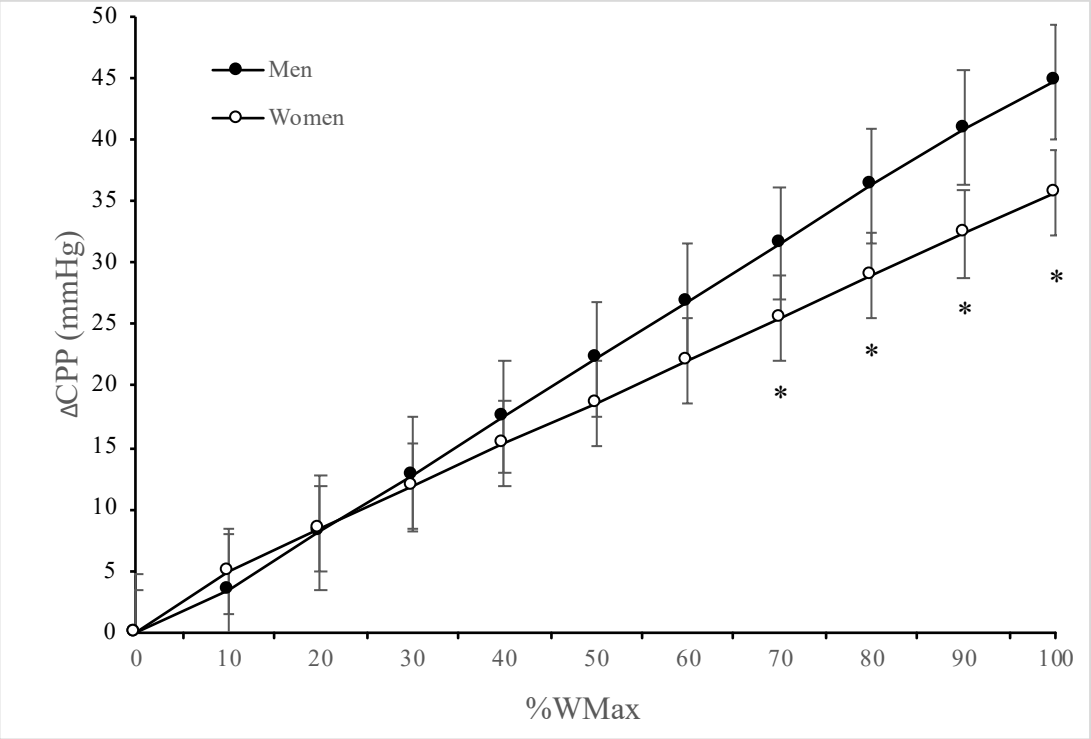



**Figure 5.** Change (Δ) in CPP, cerebral perfusion pressure, relative to rest expressed as group means ± SD at percentage of maximal workload (%Wmax). * Significant difference between men and women $p < 0.05$

ΔCPP which would be indicative to the pressor response was also found to significantly increase from baseline with increases in exercise intensity ($p < 0.0001$). Similarly to absolute CPP there was a significant sex and Wmax interaction ($p = 0.0002$) where ΔCPP increased greater in men when compared women at exercise intensities ≥ 70% Wmax reaching peak values at 100%Wmax. From baseline to ~ 60% Wmax no significant interaction was found ($p = 0.44$) between sex (ΔCPP, men: Δ26.9 ± 8.5 mmHg; women: Δ 22.1 ± 5.3 mmHg, p=0.10). However, there was a significant interaction observed ($p< 0.01$) between ΔCPP at workloads at 70% Wmax (men: Δ45.7 ± 8.4 mmHg; women: Δ 37.3 ± 5.3 mmHg, p=0.03) (figure 2).

**Cerebrovascular Conductance Index**

Absolute CVCi were similar between men and women at baseline (CVCi, men: 93.3 ± 17.2 cm/s/100mmHg; women: 104.0 ± 23.3 cm/s/100mmHg, p=0.20). There was also a main effect of exercise intensity on CVCi (p=0.01), with a significant sex by exercise intensity interaction ($p = 0.005$) where women maintained a greater CVCi at higher exercise intensities compared to men. However, Bonferroni post hoc analysis revealed there was no significant differences between the sexes even at maximal exercise (100% Wmax, CVCi, men: 61.2 ± 17.2 cm/s/100mmHg; women: 73.4 ± 19.8 cm/s/100mmHg . p=0.10) (Table 2).

ΔCVCi from baseline changed with exercise intensity ($p = 0.016$) however was the greatest changes were observed at Wmax > 65%. There was a significant interaction observed between sex and exercise intensity ($p = 0.005$) with women maintaining a greater ΔCVCi at higher exercise intensities (100% Wmax, ΔCVCi, men: -31.5 ± 7.2 cm/s/100mmHg; women: -22.5 ± 10.9 cm/s/100mmHg. $p<0.01$) (Figure 3).

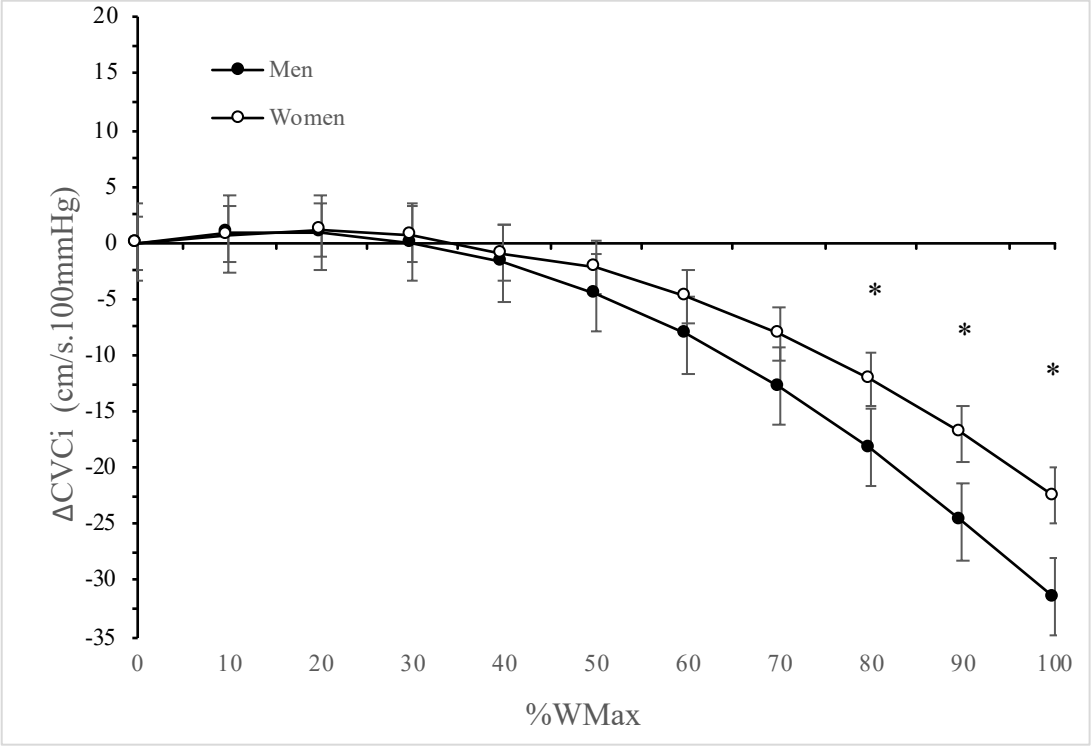



**Figure 7.** Change (Δ) in CVCi, cerebrovascular conductance index, relative to rest expressed as group means ± SD at percentage of maximal workload (%Wmax). *Significant difference between men and women $p < 0.05$

**Oxygen Uptake**

There no significant difference in oxygen uptake between men and women at baseline ($VO_2$, men: 0.36 ± 0.25 L/min; women: 0.30 ± 0.17 L/min, p=0.37). As expected $VO_2$ increased with linearly with exercise intensity ($p < 0.0001$). There was a sex by exercise interaction as men increased $VO_2$ to a greater extent with increase in %Wmax ($p < 0.0001$) (Table 2).

**Heart Rate Response**

Interestingly, women were observed to have a greater HR than men at baseline (HR, men: 73.1 ± 7.2 bpm; women: 86.3 ± 8.9 bpm, $p<0.01$) at all exercise intensities to ~80% Wmax (HR, men: 157.6 ± 7.2 bpm; women: 164.1 ± 8.9 bpm, p=0.05). However, men and women did

not differ in HR at 100% Wmax (HR, men: 178.7 ± 7.2 bpm; women: 183.5 ± 8.9 bpm, p=0.14) (Table 2).

**End Tidal $CO_2$ Response**

At baseline end tidal $CO_2$ was similar between the sexes ($P_{ETCO2}$, men: 40.2 ± 4.26 mmHg; women: 38.7 ± 4.54 mmHg, p=0.19). $P_{ETCO2}$, changed with exercise intensity in a parabolic fashion increasing to a maximal value ~ 50% Wmax, and declining at higher exercise intensities ($p < 0.0001$). However, there was no differences between the sexes or sex by exercise intensity interactions ($p > 0.05$) (Table 2). Similarly, there was no significant interaction observed in Δ $P_{ETCO2}$ response between men and women at any exercise intensity ($p > 0.05$) (figure 4.)

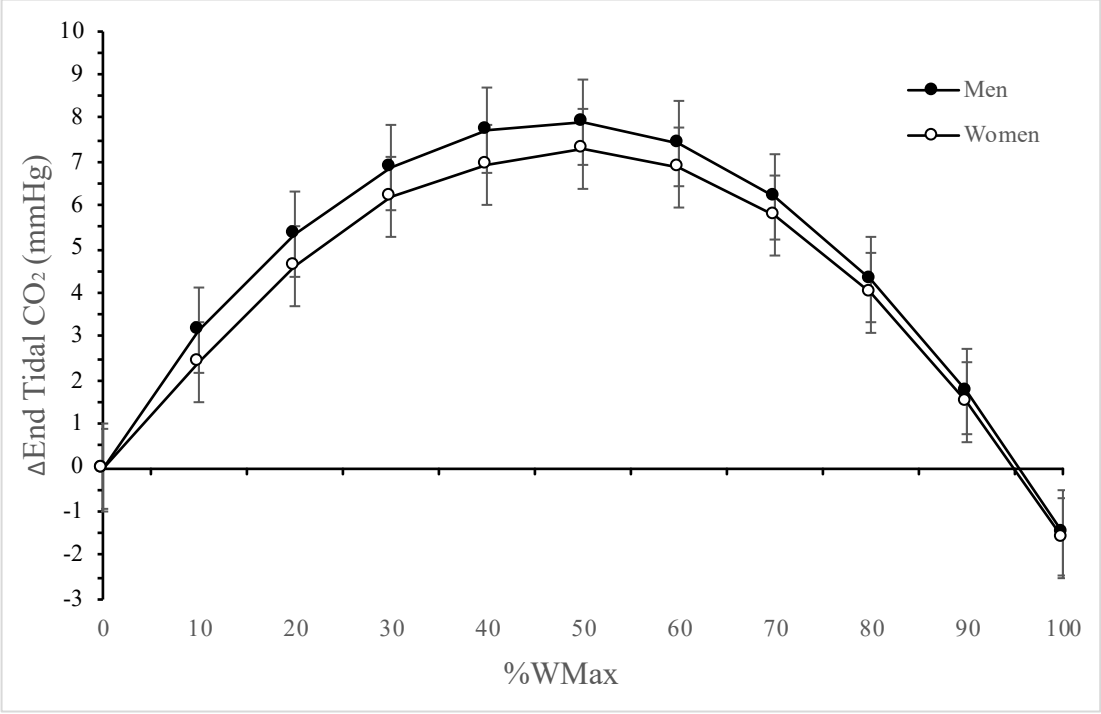



**Figure 9.** Change (Δ) in $\Delta ETCO_2$, end-tidal carbon dioxide, relative to rest expressed as group means ± SD at percentage of maximal workload (%Wmax). *Significant difference between men and women $p < 0.05$

# CHAPTER V

## Discussion

### Principal Findings:

The purpose of this study was to compare CBF response in healthy males and females during graded cycle exercise to determine if sex-linked differences in vascular responses to exercise experiences in peripheral vasculature were observed in the brain. The novel findings were: 1) There was no significant difference in MCAv and MCAv response between men and women throughout graded-exercise testing. 2) Men had significantly greater CPP response at exercise intensities values of ≥ 70% Wmax and greater compared to women. 3) Women maintained significantly greater cerebrovascular conductance compared to men at exercise intensities values of ≥ 80% Wmax and greater compared to men.

To our knowledge, no previous studies have directly compared sex-liked differences in cerebrovascular response to maximal exertion. The hypothesis was designed to identify if sex-linked differences are present in cerebrovascular response to GXT similar to that observed in the peripheral vasculature. Partly contrary to our hypothesis, we found males and females reach their peak MCAv at 60% Wmax. Additionally, our data revealed the underlying mechanism for maintaining CBF at maximal exertion differs between males and females. Female subjects maintained flow by sustained vascular conductance while male subjects maintained flow by significant increases in CPP. Interestingly, said mechanism appears to be independent of $ETCO_2$ levels based off of data in Figure 5. Alternatively, female subjects could have experienced greater vasodilatory response to similar $ETCO_2$ values as males.

**Cerebrovascular Response**

MCAv displayed a parabolic relationship, increasing during low to moderate intensity exercise and decreasing toward baseline values at higher exercise intestines as commonly observed in other laboratories (Kurt J. Smith & Philip N. Ainslie, 2017; Subudhi et al., 2011). Though not significant, there was a trend for females to have greater absolute MCAv values throughout the entire GXT (Table 2) , similar to (Peltonen et al., 2015; J. L. Ward et al., 2018). Though multiple studies have measured CBF and CVCi response (Kathleen B. Miller, Howery, Harvey, Eldridge, & Barnes, 2018; Jaimie L. Ward et al., 2018), only a select few separated male and female data (Ward et al., 2018) and less have directly compared them (Joshi & Edgell, 2019; Petersen, Petersen, Andresen, Secher, & Juhler, 2016). Although, our data did not achieve significance ($p = 0.06$), there appears to be a divergence in the ΔMCAv between males and females at exercise intensities greater than 70% Wmax (Figure 1). These data suggest that CBF responses between males and females to exercise are more similar when compared to responses in the periphery (Parker et al., 2007; Saito, Iemitsu, Otsuki, Maeda, & Ajisaka, 2008), however, the regulation of vessel diameter and pressure to achieve similar CBF response vary between sexes.

Cerebral perfusion pressure (CPP) is determined by the difference between cerebral arterial blood pressure and intra-cranial pressure, both of which can be affected by changes in cerebral hydrostatic pressure (Ogawa et al., 1992). Because subjects, head was in a consistent upright position there should be no substantial changes in intra-cranial pressure (Petersen et al., 2016), thus CPP ~ cerebral arterial pressure can be calculated if the hydrostatic column affect is accounted for (see Methods, data acquisition and analysis section). CPP increased in a linear fashion as exercise intensity increased in both sexes (Table 2). However, when ΔCPP is

examined, men had greater values at exercise intensities ≥ 60% Wmax (Figure 2). As ΔCPP would be indicative of the exercise pressor response changing arterial pressure (ΔMAP), these findings are consistent with observations of a lower exercise pressor response in young women during both submaximal and maximal cycling (Ogawa et al., 1992). The exercise pressor response is the sum of carotid baroreflex resetting, mechano- and metaboreflexes increasing sympathetic outflow to the peripheral circulation (Laughlin et al., 2012). Evidence of a sex difference in baroreflex resetting (Kim, Deo, Fisher, & Fadel, 2012) is minimal but there is strong evidence that females have an attenuated mechano and metaobreflexes when compared to males. For example, Ives et al., measured leg blood flow and central hemodynamics during three minutes of passive leg extension in young males and females. Females were found to have a lower cardiac output and blood pressure response to the passive leg movement indicating an attenuated mechanoreflex in the females (Ives, McDaniel, Witman, & Richardson, 2013). In studies where metaboreflex activation is isolated via active limb occlusion post-exercise, females have shown to have a lower muscle sympathetic nerve activity and a blunted blood pressure response compared to males (Ettinger et al., 1996; Jarvis et al., 2011). Post exercising limb occlusion is a technique that traps metabolites derived from the active muscle stimulating the III and IV afferents and the metaboreflex without contributions from mechanoreflex or central command (Fisher, Young, & Fadel, 2015). These data are congruent with observations of lower sympathetic nerve activity and catecholamine release during exercise in females (Gustafson & Kalkhoff, 1982; Katayama et al., 2018). Therefore, the difference in ΔCPP observed in the current study is due to attenuated meachno and metaboreflex responses in females. Further, as exercise intensity increases and sympathetic outflow to drive blood pressure increases the sex difference widens (Figure 2.).

Though our results did not reveal significant difference in cerebral blood flow response, male subjects exhibited a greater reduction in CVCi (Table 2). ΔCVCi displayed a curvilinear decay from baseline measures as exercise intensity increases reaching a nadir in both groups at 100% Wmax (Figure 3). This is the typical CVCi – exercise intensity relationship observed by others, however, past investigations delineating this relationship consisted of predominately male subjects (Kurt J. Smith & Philip N. Ainslie, 2017; Subudhi et al., 2011). The interesting finding in our data is that as exercise intensity increases, ΔCVCi differs between the sexes with females displaying a greater CVCi. The two main mechanisms that seems to be regulating vascular tone during exercise are the influences of arterial blood gases (e.g. $ETCO_2$) and dynamic cerebral autoregulation responding to changes in blood pressure. To the best of our knowledge there have been no investigations have successfully manipulating each of these factors individually during exercise, let alone, comparing responses differences between the sexes. However, there have been many investigations that have examined cerebrovascular responses to changes in pressure or arterial $CO_2$ in isolation. 4D-MRI analysis of the major cerebral arteries during a hypercapnic has found young males to have a greater cerebral vascular reactivity than young females (K. B. Miller et al., 2019). However, this finding is not consistent especially in studies that have measured CBF with TCD (Fan et al., 2019; Madureira, Castro, & Azevedo, 2017; Peltonen et al., 2015). In our study the $\Delta P_{ETCO2}$ responses were similar between the sexes as exercise intensity increased (Figure 4.). Therefore, sex differences observed as exercise intensity increased are not likely driven by changes in $ETCO_2$. Similarly, sex differences in cereboautoregulation and in response to changes in blood pressure of conflicting results. In spontaneous and included blood pressure oscillations, Farve et al., (2019) females demonstrating significantly improved cerebral autoregulation compared to males regardless of menstrual cycle phase (Michelle E. Favre &

Jorge M. Serrador, 2019). Conversely, in moderately endurance trained athletes Laberecque et al., observed females to have an attenuated autoregulatory response in to similar blood pressure oscillations conducted in the Farve et al., (2019) study (Labrecque et al., 2019).

Our data suggest the greater ΔCVCi observed in females is more related to cerebral autoregulation of pressure the during GXT at higher exercise intensities and does not appear to be regulated by $ETCO_2$ levels. Further investigation into the underlying mechanism could include measurement of venous blood gas measurements for further evaluation of metabolite towards maximal exertion, where we have shown these differences in cerebral autoregulation are at their greatest. This highlights a significant finding in our study, where both sexes maintained a similar cerebral blood flow response (there is a trend for females to have a higher response) as exercise intensity increased, however, how that response was achieved appears to be very different. Males through significantly greater increases in CPP towards maximal exertion changed ΔMCAv whereas women altered flow with attenuated changes in CPP and less vasoconstriction indicating the mechanisms for maintaining cerebral flow differ between males and females especially during higher exercise intensities.

**Implications and Further Research**

Maintaining sufficient cerebral perfusion and cerebrovascular reactivity is crucial for the preservation of cognitive function. Our study further emphasizes the effect of sex on exercise induced vasodilatory response in the cerebrovasculature. Ward et al., (2018) revealed females experience a delay in cerebrovascular response from rest to the onset of moderate-intensity exercise as they age, with additional research showing in reduction cerebral blood flow in post-menopausal women can be corrected by estrogen replacement therapy (Farid et al., 1999). Our data suggests further investigation into female cerebrovascular response to maximal exertion is

warranted due to the most significant differences in CVCi occurring near 100% Wmax. Additionally, our data supports the idea that a factor for increased risk for stroke and CBVD in males is due to reduced cerebrovascular function compared to females at maximal exertion, for which CBF decline is compensated by significant increases in CPP. The results of our study further prove the need for increased research in sex-linked differences in cerebrovascular responses near maximal exertion.

With aerobic exercise training being a proven, non-pharmaceutical, intervention for improving vascular response to exercise (Hirai et al,. 2015), future research should explore the effect of mode-specific exercise interventions for maintaining cerebrovascular function. Specifically, a recent study by Timo et al., (2019) comparing young and older men found ten 1-minute interval exercise bouts at 60% Wmax promoted acute increases in CBF compared to one 10-minute continuous bout at 60% Wmax in older men. With more investigation into the potential of various exercise modes/protocols/intensities for maintaining cerebrovascular health, the results of our study highlight the crucial necessity of inclusion for female subjects.

**Methodological Considerations**

There are a number of methodological considerations that should be acknowledged when interpreting the data from this investigation. First, all female participants in our study were observed during the early follicular phase of the menstrual cycle to reduce the influence of circulating estrogen (Gardner et al., 2011). While recent literature revealed aspects of cerebrovascular control are not menstrual cycle phases (M. E. Favre & J. M. Serrador, 2019), many other physiological responses during exercise are modulated by hormonal fluctuation(Sims & Heather, 2018). Therefore, testing females in the early follicular phase is a conservative approach to identifying differences in vascular control between the sexes.

Second, measurement of cerebral blood flow through use of transcranial doppler ultrasound operates on the assumption that the cerebral vessel remains at a constant diameter, and that changes in cerebral blood velocity is indicative of changes in overall cerebral blood flow. Older studies have supported this assumption (Valdueza et al., 1997; Serrador et al., 2000); though more recent studies using high resonance imaging (Verbree et al., 2014; Wilson et al., 2011) challenged the assumption due to changes in vessel diameter in response to changes in arterial pressure of $CO_2$. More specifically, there is conflicting evidence as to whether exercise induces changes in MCA diameter (Hoiland & Ainslie 2016). However, the changes experienced during exercise in larger vessels like the MCA is likely to be minimal (Giller et al., 1985). For the purposes of our study, TCD provide a simple, non-invasive, measurement of cerebral blood flow which could be monitored beat-by-beat during GXT.

Third, the GXT protocol used in this investigation was designed similarly to Kim et al., (2016) which allowed for similar time to exhaustion between groups with the first three 3 minute stages consistent for all subjects (50W, 75W and 100W respectively), with subsequent stages increasing 30W for females and 40W for males. Addition of a 25W stage following baseline recording, prior to 50W stage, could have been beneficial for participants whom were unable to complete stages above 100W, and thus resulting in shorter GXT time to failure. Use of a recumbent cycle ergometer for our GXT protocol was necessary to maintain fidelity of the ultrasound signal requisite for measuring $MCA_V$. Further investigation is needed to fully understand the $MCA_V$ response among different exercise protocols as well as various exercise intensities.

## Conclusion

In summary, young females were able maintain MCAv in response to GXT through increased CVCi, while young males were able to sustain similar MCAv values through significant increases in CPP. Additionally, the similar $ETCO_2$ values between groups suggests either the sex-linked mechanistic differences in cerebrovascular response GXT independent of $ETCO_2$, or that young females experience a greater vasodilatory response to similar $ETCO_2$ values. This study opens the door for future research aimed at elucidating mechanisms for cerebrovascular response while also reiterating the importance of inclusion of female participants.

# APPENDIX A

## Recruitment Flyer

COLLEGE OF ARTS AND SCIENCES
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE
The UNIVERSITY of OKLAHOMA

## Differences in cerebrovascular responses to submaximal and maximal exercise between men and women

Are you interested in helping us find out if **blood flow to the brain** in response to **exercise** differs between men and women?

---

Recreationally active men and women are needed for a study to investigate whether the cerebral blood flow response is similar between men and women during a graded exercise test.

---

Time commitment: Only 2 short visits (~4 hours total), 3rd optional visit for women

What will be measured: Cerebral Blood Flow, Oxygen Uptake ($VO_2$), Cardiovascular and Metabolic response

Eligibility: males and females aged 18-30; recreationally active (3-6 hours of activity per week); no ongoing injuries or health risk factors





**If interested, please contact:**

Principal Investigator: Dr. Mikhail Kellawan ; kellawan@ou.edu; (405) 325-9028

OR Joe Shelley; josephshelley@ou.edu; (405) 397-0040

*The University of Oklahoma is an equal opportunity institution (IRB# 10121).*

Joe Shelley (405) 397-0040 JosephShelley@ou.edu

# APPENDIX B

# INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

# INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

# (October 2002)

# LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

### FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instrumalests that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The developmalest of an international measure for physical activity commalesced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measuremalest properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

## Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

## Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommalesd using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

## Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective.* Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

## INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you

breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

Yes ☐

☐

No → *Skip to PART 2: TRANSPORTATION*

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing upstairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ days per week

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ hours per day _____ minutes per day

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ days per week

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ hours per day _____ minutes per day

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ days per week

☐ No job-related walking → Skip to PART 2: TRANSPORTATION

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day** _____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ days per week

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ hours per day _____ minutes per day

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ days per week

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ hours per day _____ minutes per day

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ days per week

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK,***

HOUSE MAINTENANCE, AND CARING FOR FAMILY

13. How much time did you usually spend on one of those days **walking** from place to place?

**_____ hours per day _____ minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ days per week

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ hours per day _____ minutes per day

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ days per week

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ hours per day _____ minutes per day

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ days per week

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION,***

SPORT AND LEISURE-TIME PHYSICAL ACTIVITY

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

**_____ hours per day _____ minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ days per week

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ hours per day _____ minutes per day

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ days per week

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ hours per day _____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ days per week

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day** _____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ hours per day _____ minutes per day

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ hours per day _____ minutes per day

**This is the end of the questionnaire, thank you for participating.**

# APPENDIX C

## Demographics Form

PI: J. Mikhail Kellawan IRB Number: 10121 Short Title: CBF-GXT-SEXDIFF

**Visit Date:**____/____/_____ Subject Initials: ☐☐☐

## DEMOGRAPHICS

| |
|---|
| **First Name*:** |
| **Middle Name (or initial):** |
| **Last Name*:** |

**Birthdate*:** ☐☐ / ☐☐ / ☐☐☐☐
Month Day Year

**Gender*:** (check one)
- ☐ **Male**
- ☐ **Female**
- ☐ **Unknown or Not Reported**

**Ethnicity*:** (check one)
- ☐ **Hispanic**
- ☐ **Non-Hispanic**
- ☐ **Unknown or Not Reported**

**Race*:** (check all that apply)
- ☐ **American Indian or Alaska Native**
- ☐ **Asian**
- ☐ **Black or African American**
- ☐ **Native Hawaiian or Other Pacific Islander**
- ☐ **White or Caucasian**
- ☐ **Unknown or Not Reported**

**Contact Information*:**

| | | |
|---|---|---|
| **Address:** | | **Unit #:** |
| **City:** | **State:** | **Zip:** |
| **Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Alternate Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Email address:** |
| **Preferred method of contact:** | | |

**Emergency Contact*:**

| | | |
|---|---|---|
| **Name:** | | |
| **Address:** | | **Unit #:** |
| **City:** | **State:** | **Zip:** |
| **Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Alternate Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other | **Email address:** |
| **Preferred method of contact:** | | |

*indicates required field

**Form Completed By**: _____ **Date**: _____

# APPENDIX E

## Medical History

Subject ID: _____ Sex: M / W Date: / /

## Medical History (General)

| Body System | Have you ever had any conditions affecting these body systems? | *Only complete if 'Yes' for Diagnosed Condition* | | | |
|---|---|---|---|---|---|
| | | Diagnosis/Condition/Surgery | Onset Date | Is it a current problem? | Are you currently taking a prescribed medication?* |
| **Cardiovascular** | | | | | |
| ☐ Heart Attack | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Stroke | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Hypertension | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Coronary Artery Disease | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Other Cardiovascular | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Your 1st Degree Relatives (e.g. mother, brother, daughter) | ☐ Yes ☐ No | List family members, their diagnosis, and approximately when they were diagnosed: | | | |
| **Lungs** | | | | | |
| ☐ Asthma | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Exercise-Induced Bronchospasm | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Obstructive Lung Disease | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Other | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| **Musculoskeletal** | | | | | |
| ☐ Knee | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Hips | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| ☐ Back | | | | | |
| ☐ Other | | | | | |
| **Head/Eyes/Ears/ Nose/Throat/Neck** | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| **Endocrine/Metabolic** | | | | | |
| Diabetes | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |

| | | | | | |
|---|---|---|---|---|---|
| High blood sugar | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| Liver | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| Thyroid | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| Kidney | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |
| Pituitary Gland | ☐ Yes ☐ No | | | ☐ Yes ☐ No | ☐ Yes ☐ No |

**ADDITIONAL NOTES:** _____

_____

_____

## Additional Questions (all subjects)

| Have you recently experienced any of the following? | Yes | No | When? |
|---|---|---|---|
| Pain in the neck, jaw, or arms? | | | |
| Dizziness or fainting? | | | |
| Swelling in the ankles? | | | |
| Rapid heart rate while at rest? | | | |
| Leg pain or cramping while walking, relieved with rest? | | | |
| Has a doctor ever told you that you have a heart murmur? | | | |
| Unusual fatigue with usual activities? | | | |

*Please list all Medications or Supplements You Take*

| **Medications/Supplements** |
|---|
| Prescribed medications: |
| Are you taking hormone replacement (e.g., estrogen) therapy? |
| Do you take supplements (aspirin, vitamins, etc.)? |

Do you have any reason you believe you should not participate in this research study? ☐ Yes ☐ No

Explain:

Are you currently enrolled in any other research studies or have you participated in any other research studies in the past 30 days? ☐ Yes ☐ No

If yes, when was your last study visit (MM/DD/YYYY)?

If yes, what is the date of your next visit (MM/DD/YYYY)?

## Female Subjects Only ☐ N/A - subject is male

Subject currently pregnant? ☐ Yes ☐ No
Subject plans to become pregnant? ☐ Yes ☐ No

**Currently using birth control?** ☐ Yes ☐ No

**If yes, method of birth control** *[Select All That Apply]:*

| | | |
|---|---|---|
| ☐[1] Oral Contraceptives | ☐[5] NuvaRing | ☐[10] Post-menopausal for ≥ 1 year |
| ☐[2] Hormonal Injections | ☐[6] Intrauterine device | ☐[11] Tubal ligation, bilateral oophorectomy, or hysterectomy |
| ☐[3] Hormonal Implants (i.e. Implanon) | ☐[7] hormonal Intrauterine device | ☐[12] Abstinence |
| ☐[4] Contraceptive Patches | ☐[8] non-hormonal Barrier method | ☐[13] Other (specify in Reproductive field) |
| | ☐[9] Spermicide | |
| **Start Date of Birth Control (MM/DD/YY):** | Brand Name: _____ | |

**What is the date do you expect you next period?** _____

**Do you have a regular menstrual cycle (last 3 cycles consecutive)**? ☐ Yes ☐ No

**Past Menstrual History**

**Start Date of LAST menstrual cycle (MM/DD/YY):**_____

**End Date of LAST menstrual cycle (MM/DD/YY):**_____

**Have you ever consulted a doctor about menstrual problems (specifically, about irregular or missing periods)?**

_____

**Have you ever consulted a doctor about any problems relating to your hormonal system? If so, please explain.**

_____

**For HCRL Staff Only**

**Form Verified by:**_____ **Date:** _____

# APPENDIX F

## Screening Visit Data Collection Form

**Subject Initials** ☐☐☐ **Subject ID** ☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

## Screening Visit Data Collection Form - Demographics

Gender: ☐ Male ☐ Female

If female, first day of last menses: **Date:** ☐☐ / ☐☐ / ☐☐

Age: ☐☐ years *(refer to birthday on the Demographics form from previous section)*

**10 Hours fasted?** (Y) (N) **NSAIDS Today?** (Y) (N) **Smoked today?** (Y) (N) **Alcohol in last 24 hours?** (Y) (N)

## Vital Sign Measurements

Height: ☐☐☐.☐ cm Weight: ☐☐☐.☐ kg BMI: ☐☐.☐ $kg/m^2$

Time of Collection: _____ AM

$$\textbf{BMI} = \frac{\textbf{(weight in kilograms)}}{\textbf{height in meters}^2}$$

Waist Circumference: ☐☐☐ cm Hip Circumference: ☐☐☐ cm

1. Systolic Blood Pressure: ☐☐☐ mmHg Diastolic Blood Pressure: ☐☐☐ mmHg
2. Systolic Blood Pressure: ☐☐☐ mmHg Diastolic Blood Pressure: ☐☐☐ mmHg
3. Systolic Blood Pressure: ☐☐☐ mmHg Diastolic Blood Pressure: ☐☐☐ mmHg

Lowest recorded Blood Pressure (Systolic/Diastolic): _____/_____

**Subject Initials** ☐☐☐ **Subject ID** ☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

## Laboratory Results

**Blood draw completed:** ☐ Yes ☐ No **Time:** ___ : ____ (24 hour format)

| TEST | Results #1 | Results #2 | Average |
|---|---|---|---|
| **Glucose** | ☐☐☐ mg/dL | ☐☐☐ mg/dL | ☐☐☐ mg/dL |
| **Triglycerides** | ☐☐☐ mg/dL | ☐☐☐ mg/dL | ☐☐☐ mg/dL |
| **HDL** | ☐☐☐ mg/dL | ☐☐☐ mg/dL | ☐☐☐ mg/dL |
| **LDL** | ☐☐☐ mg/dL | ☐☐☐ mg/dL | ☐☐☐ mg/dL |

## Study Protocol Measurements

*Transcranial Doppler $MCA_v$ Signal Strength*: **Strong** ☐ **Weak** ☐ **Not Found** ☐

**Equivitol Vest Size (Circle one)**: (1) (2) (3) (4) (5) (6) **Lode Bike Seat Height:** ☐☐☐

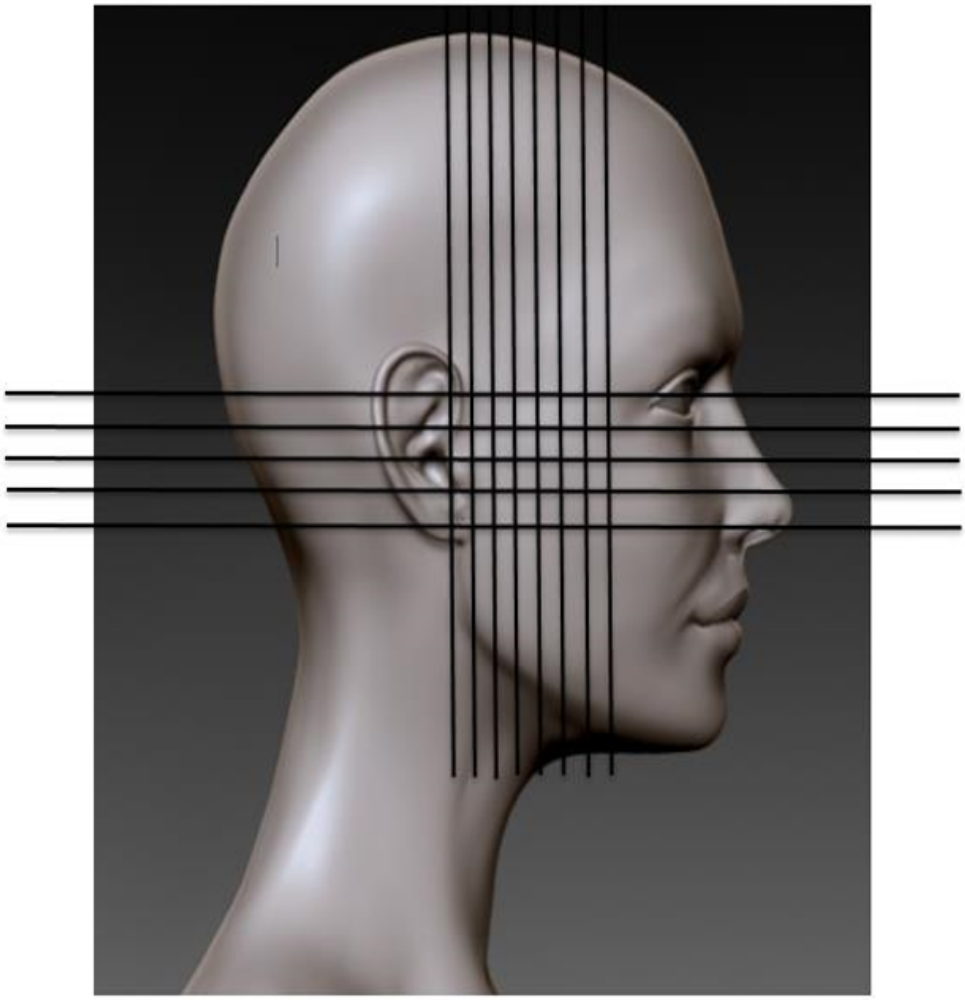
**$VO_2$ Mask Size** (Circle one): (Extra Small) (Small) (Medium) (Large) (XL)

**Form Completed By:**_____ **Date:**_____

**PI: Signature:**_____ **Date:**_____

# Transcranial Doppler Placement Location

(shade area where strongest signal is found)



# APPENDIX G

## SAS Data Output

*MCAv Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 1361.27410100 | |
| **1** | 2 | 1118.90477655 | 0.00004545 |
| **2** | 1 | 1118.85241194 | 0.00000060 |
| **3** | 1 | 1118.85158858 | 0.00000000 |

Convergence criteria met but final Hessian is not positive definite.

***Estimated G matrix is not positive definite.***

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 221.25 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 27.3253 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1118.9 |
| **AIC (Smaller is Better)** | 1124.9 |
| **AICC (Smaller is Better)** | 1125.0 |
| **BIC (Smaller is Better)** | 1118.9 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 68.9718 | 4.2924 | 0 | 16.07 | . |
| **RelW** | | 0.5922 | 0.04237 | 133 | 13.98 | <.0001 |
| **Sex** | m | -7.3949 | 5.9639 | 24 | -1.24 | 0.2270 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW2** | | -0.00487 | 0.000423 | 133 | -11.50 | <.0001 |

## *MCAv Model*

### *The Mixed Procedure*

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **RelW2*Sex** | m | -0.00044 | 0.000239 | 133 | -1.86 | 0.0657 |
| **RelW2*Sex** | w | 0 | . | . | . | . |

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 133 | 195.35 | <.0001 |
| **Sex** | 1 | 24 | 1.54 | 0.2270 |
| **RelW2** | 1 | 133 | 160.10 | <.0001 |
| **RelW2*Sex** | 1 | 133 | 3.44 | 0.0657 |

## *MCAv Post Hoc*

### *The Multtest Procedure*

| P-Value Adjustment Information | |
|---|---|
| **P-Value Adjustment** | Bonferroni |
| **P-Value Adjustment** | Hommel |

| p-Values | | | |
|---|---|---|---|
| **Test** | **Raw** | **Bonferroni** | **Hommel** |
| 1 | 0.0794 | 0.2382 | 0.0794 |
| 2 | 0.0566 | 0.1698 | 0.0794 |
| 3 | 0.0382 | 0.1145 | 0.0794 |

*Delta_MCAv Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **3** | 1 | 1063.38363884 | 0.00000061 |
| **4** | 1 | 1063.38362819 | 0.00000000 |

Convergence criteria met but final Hessian is not positive definite.

***Estimated G matrix is not positive definite.***

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 21.0925 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 26.6896 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1063.4 |
| **AIC (Smaller is Better)** | 1069.4 |
| **AICC (Smaller is Better)** | 1069.5 |
| **BIC (Smaller is Better)** | 1063.4 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 0.5601 | 1.7301 | 0 | 0.32 | . |
| **RelW** | | 0.5860 | 0.04186 | 133 | 14.00 | <.0001 |
| **Sex** | m | -1.0155 | 2.1758 | 24 | -0.47 | 0.6449 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW2** | | -0.00482 | 0.000418 | 133 | -11.52 | <.0001 |
| **RelW2*Sex** | m | -0.00044 | 0.000236 | 133 | -1.85 | 0.0661 |
| **RelW2*Sex** | w | 0 | . | . | . | . |

## *Delta_MCAv Model*

### *The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 133 | 195.98 | <.0001 |
| **Sex** | 1 | 24 | 0.22 | 0.6449 |
| **RelW2** | 1 | 133 | 160.74 | <.0001 |
| **RelW2*Sex** | 1 | 133 | 3.43 | 0.0661 |

## *Delta_MCAv Post Hoc*

### *The Multtest Procedure*

| P-Value Adjustment Information | |
|---|---|
| **P-Value Adjustment** | Bonferroni |
| **P-Value Adjustment** | Hommel |

| p-Values | | | |
|---|---|---|---|
| **Test** | **Raw** | **Bonferroni** | **Hommel** |
| 1 | 0.0198 | 0.0595 | 0.0198 |
| 2 | 0.0051 | 0.0152 | 0.0101 |
| 3 | 0.0010 | 0.0030 | 0.0030 |

*CVCi Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **3** | 1 | 1227.19902167 | 0.00000003 |
| **4** | 1 | 1227.19899780 | 0.00000000 |

Convergence criteria met but final Hessian is not positive definite.

***Estimated G matrix is not positive definite.***

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 340.36 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 57.0226 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1227.2 |
| **AIC (Smaller is Better)** | 1233.2 |
| **AICC (Smaller is Better)** | 1233.4 |
| **BIC (Smaller is Better)** | 1227.2 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 95.5114 | 5.3958 | 0 | 17.70 | . |
| **RelW** | | 0.1502 | 0.06121 | 133 | 2.45 | 0.0154 |
| **Sex** | m | -2.7773 | 7.4536 | 24 | -0.37 | 0.7127 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW2** | | -0.00371 | 0.000611 | 133 | -6.08 | <.0001 |
| **RelW2*Sex** | m | -0.00098 | 0.000345 | 133 | -2.84 | 0.0052 |
| **RelW2*Sex** | w | 0 | . | . | . | . |

*CVCi Model*

*The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 133 | 6.02 | 0.0154 |
| **Sex** | 1 | 24 | 0.14 | 0.7127 |
| **RelW2** | 1 | 133 | 52.39 | <.0001 |
| **RelW2*Sex** | 1 | 133 | 8.08 | 0.0052 |

*CVCi Post Hoc*

*The Multtest Procedure*

| P-Value Adjustment Information | |
|---|---|
| **P-Value Adjustment** | Bonferroni |
| **P-Value Adjustment** | Hommel |

| p-Values | | | |
|---|---|---|---|
| **Test** | **Raw** | **Bonferroni** | **Hommel** |
| 1 | 0.3463 | 1.0000 | 0.3640 |
| 2 | 0.3545 | 1.0000 | 0.3640 |
| 3 | 0.3640 | 1.0000 | 0.3640 |

*Delta_CVCi Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **3** | 3 | 1195.58121689 | 0.00000004 |
| **4** | 1 | 1195.58121456 | 0.00000000 |

Convergence criteria met but final Hessian is not positive definite.

***Estimated G matrix is not positive definite.***

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 84.0988 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 57.0391 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1195.6 |
| **AIC (Smaller is Better)** | 1201.6 |
| **AICC (Smaller is Better)** | 1201.7 |
| **BIC (Smaller is Better)** | 1195.6 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | -0.3941 | 3.0660 | 0 | -0.13 | . |
| **RelW** | | 0.1489 | 0.06121 | 133 | 2.43 | 0.0163 |
| **Sex** | m | 0.1988 | 4.0157 | 24 | 0.05 | 0.9609 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW2** | | -0.00370 | 0.000611 | 133 | -6.05 | <.0001 |
| **RelW2*Sex** | m | -0.00099 | 0.000345 | 133 | -2.86 | 0.0049 |
| **RelW2*Sex** | w | 0 | . | . | . | . |

*Delta_CVCi Model*

*The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| Effect | Num DF | Den DF | F Value | Pr > F |
| RelW | 1 | 133 | 5.92 | 0.0163 |
| Sex | 1 | 24 | 0.00 | 0.9609 |
| RelW2 | 1 | 133 | 52.07 | <.0001 |
| RelW2*Sex | 1 | 133 | 8.18 | 0.0049 |

*Delta_CVCi Post Hoc*

*The Multtest Procedure*

| P-Value Adjustment Information | |
|---|---|
| P-Value Adjustment | Bonferroni |
| P-Value Adjustment | Hommel |

| p-Values | | | |
|---|---|---|---|
| Test | Raw | Bonferroni | Hommel |
| 1 | 0.3739 | 1.0000 | 0.4064 |
| 2 | 0.3888 | 1.0000 | 0.4064 |
| 3 | 0.4064 | 1.0000 | 0.4064 |

*CPP Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **3** | 1 | 1178.66249211 | 0.00000002 |
| **4** | 1 | 1178.66247565 | 0.00000000 |

Convergence criteria met but final Hessian is not positive definite.

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 3.037E-9 |
| **subj(Sex)** | | 310.52 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 47.3539 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1178.7 |
| **AIC (Smaller is Better)** | 1186.7 |
| **AICC (Smaller is Better)** | 1186.9 |
| **BIC (Smaller is Better)** | 1178.7 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 75.9586 | 5.1204 | 0 | 14.83 | . |
| **RelW** | | 0.3432 | 0.02396 | 134 | 14.32 | <.0001 |
| **Sex** | m | -8.2235 | 7.2089 | 24 | -1.14 | 0.2652 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW*Sex** | m | 0.1273 | 0.03311 | 134 | 3.85 | 0.0002 |
| **RelW*Sex** | w | 0 | . | . | . | . |

*CPP Model*

*The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 134 | 604.24 | <.0001 |
| **Sex** | 1 | 24 | 1.30 | 0.2652 |
| **RelW*Sex** | 1 | 134 | 14.80 | 0.0002 |

*CPP Post Hoc*

*The Multtest Procedure*

| P-Value Adjustment Information | |
|---|---|
| **P-Value Adjustment** | Bonferroni |
| **P-Value Adjustment** | Hommel |

| p-Values | | | |
|---|---|---|---|
| **Test** | **Raw** | **Bonferroni** | **Hommel** |
| 1 | 0.8547 | 1.0000 | 0.8547 |
| 2 | 0.7468 | 1.0000 | 0.8547 |
| 3 | 0.6439 | 1.0000 | 0.8547 |

*Delta_CPP Model*

*The Mixed Procedure*

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 1.2E-11 |
| **subj(Sex)** | | 56.9259 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 47.3631 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1140.5 |
| **AIC (Smaller is Better)** | 1146.5 |
| **AICC (Smaller is Better)** | 1146.6 |
| **BIC (Smaller is Better)** | 1140.5 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 1.5233 | 2.5898 | 0 | 0.59 | . |
| **RelW** | | 0.3428 | 0.02396 | 134 | 14.31 | <.0001 |
| **Sex** | m | -2.8485 | 3.5984 | 24 | -0.79 | 0.4364 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW*Sex** | m | 0.1278 | 0.03311 | 134 | 3.86 | 0.0002 |
| **RelW*Sex** | w | 0 | . | . | . | . |

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 134 | 603.72 | <.0001 |
| **Sex** | 1 | 24 | 0.63 | 0.4364 |
| **RelW*Sex** | 1 | 134 | 14.91 | 0.0002 |

*Delta_CPP Post Hoc*

*The Multtest Procedure*

| P-Value Adjustment Information | |
|---|---|
| **P-Value Adjustment** | Bonferroni |
| **P-Value Adjustment** | Hommel |

| p-Values | | | |
|---|---|---|---|
| **Test** | **Raw** | **Bonferroni** | **Hommel** |
| 1 | 0.0263 | 0.0790 | 0.0263 |
| 2 | 0.0119 | 0.0358 | 0.0238 |
| 3 | 0.0052 | 0.0156 | 0.0156 |

*HR Model*

*The Mixed Procedure*

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 68.6291 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 39.2063 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1118.7 |
| **AIC (Smaller is Better)** | 1124.7 |
| **AICC (Smaller is Better)** | 1124.9 |
| **BIC (Smaller is Better)** | 1118.7 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 86.0988 | 2.6847 | 0 | 32.07 | . |
| **RelW** | | 0.9746 | 0.02180 | 134 | 44.70 | <.0001 |
| **Sex** | m | -13.0323 | 3.7455 | 24 | -3.48 | 0.0019 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW*Sex** | m | 0.08195 | 0.03012 | 134 | 2.72 | 0.0074 |
| **RelW*Sex** | w | 0 | . | . | . | . |

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 134 | 4546.98 | <.0001 |
| **Sex** | 1 | 24 | 12.11 | 0.0019 |
| **RelW*Sex** | 1 | 134 | 7.40 | 0.0074 |

*VO2 Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 178.00920715 | |
| **1** | 3 | 105.11899207 | 0.00095412 |
| **2** | 1 | 105.11121176 | 0.00000301 |
| **3** | 1 | 105.11118549 | 0.00000000 |

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 0.08270 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 0.06735 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 105.1 |
| **AIC (Smaller is Better)** | 111.1 |
| **AICC (Smaller is Better)** | 111.3 |
| **BIC (Smaller is Better)** | 105.1 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 0.2226 | 0.09835 | 0 | 2.26 | . |
| **RelW** | | 0.01833 | 0.000904 | 134 | 20.28 | <.0001 |
| **Sex** | m | 0.1010 | 0.1367 | 24 | 0.74 | 0.4669 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW*Sex** | m | 0.005039 | 0.001248 | 134 | 4.04 | <.0001 |
| **RelW*Sex** | w | 0 | . | . | . | . |

*VO2 Model*

*The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 134 | 1115.54 | <.0001 |
| **Sex** | 1 | 24 | 0.55 | 0.4669 |
| **RelW*Sex** | 1 | 134 | 16.29 | <.0001 |

*VO2 Post Hoc*

*The Multtest Procedure*

| P-Value Adjustment Information | |
|---|---|
| **P-Value Adjustment** | Bonferroni |
| **P-Value Adjustment** | Hommel |

| p-Values | | | |
|---|---|---|---|
| **Test** | **Raw** | **Bonferroni** | **Hommel** |
| 1 | <.0001 | 0.0002 | 0.0002 |
| 2 | 0.0004 | 0.0013 | 0.0009 |
| 3 | 0.0015 | 0.0045 | 0.0015 |

*$ETCO_2$*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 388.92850763 | |
| **1** | 3 | 242.46580605 | 0.00068389 |
| **2** | 1 | 242.45829646 | 0.00000176 |
| **3** | 1 | 242.45827582 | 0.00000000 |

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 7.13E-13 |
| **subj(Sex)** | | 0.3643 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 0.1187 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 242.5 |
| **AIC (Smaller is Better)** | 250.5 |
| **AICC (Smaller is Better)** | 250.7 |
| **BIC (Smaller is Better)** | 242.5 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 5.2864 | 0.1847 | 0 | 28.62 | . |
| **RelW** | | 0.04434 | 0.002793 | 133 | 15.88 | <.0001 |
| **Sex** | m | 0.2036 | 0.2504 | 24 | 0.81 | 0.4241 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW2** | | -0.00046 | 0.000028 | 133 | -16.45 | <.0001 |
| **RelW2*Sex** | m | -8.13E-6 | 0.000016 | 133 | -0.52 | 0.6061 |
| **RelW2*Sex** | w | 0 | . | . | . | . |

*$ETCO_2$*

*The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 133 | 252.05 | <.0001 |
| **Sex** | 1 | 24 | 0.66 | 0.4241 |
| **RelW2** | 1 | 133 | 305.01 | <.0001 |
| **RelW2*Sex** | 1 | 133 | 0.27 | 0.6061 |

*TVC Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **3** | 1 | -498.57857796 | 0.00002880 |
| **4** | 1 | -498.57886235 | 0.00000000 |

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 0.000927 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 0.001626 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | -498.6 |
| **AIC (Smaller is Better)** | -492.6 |
| **AICC (Smaller is Better)** | -492.4 |
| **BIC (Smaller is Better)** | -498.6 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 0.07794 | 0.01229 | 0 | 6.34 | . |
| **RelW** | | 0.000561 | 0.000140 | 134 | 4.00 | 0.0001 |
| **Sex** | m | 0.02516 | 0.01692 | 24 | 1.49 | 0.1500 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW*Sex** | m | 0.000479 | 0.000194 | 134 | 2.47 | 0.0148 |
| **RelW*Sex** | w | 0 | . | . | . | . |

*TVC Model*

*The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 134 | 68.12 | <.0001 |
| **Sex** | 1 | 24 | 2.21 | 0.1500 |
| **RelW*Sex** | 1 | 134 | 6.09 | 0.0148 |

*MAP Model*

*The Mixed Procedure*

| Iteration History | | | |
|---|---|---|---|
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **3** | 1 | 1179.59800677 | 0.00000028 |
| **4** | 1 | 1179.59771060 | 0.00000000 |

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 0 |
| **subj(Sex)** | | 322.99 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 47.3587 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 1179.6 |
| **AIC (Smaller is Better)** | 1185.6 |
| **AICC (Smaller is Better)** | 1185.8 |
| **BIC (Smaller is Better)** | 1179.6 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 94.0181 | 5.2132 | 0 | 18.03 | . |
| **RelW** | | 0.3432 | 0.02396 | 134 | 14.32 | <.0001 |
| **Sex** | m | -6.8108 | 7.3407 | 24 | -0.93 | 0.3627 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW*Sex** | m | 0.1272 | 0.03311 | 134 | 3.84 | 0.0002 |
| **RelW*Sex** | w | 0 | . | . | . | . |

*MAP Model*

*The Mixed Procedure*

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 134 | 603.86 | <.0001 |
| **Sex** | 1 | 24 | 0.86 | 0.3627 |
| **RelW*Sex** | 1 | 134 | 14.77 | 0.0002 |

*CO Model*

*The Mixed Procedure*

| Covariance Parameter Estimates | | |
|---|---|---|
| **Cov Parm** | **Subject** | **Estimate** |
| **Intercept** | | 7.56E-13 |
| **subj(Sex)** | | 2.8876 |
| **AR(1)** | subj(Sex) | 0 |
| **Residual** | | 16.8984 |

| Fit Statistics | |
|---|---|
| **-2 Res Log Likelihood** | 943.9 |
| **AIC (Smaller is Better)** | 949.9 |
| **AICC (Smaller is Better)** | 950.0 |
| **BIC (Smaller is Better)** | 943.9 |

| Solution for Fixed Effects | | | | | | |
|---|---|---|---|---|---|---|
| **Effect** | **Sex** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Intercept** | | 7.0010 | 1.0236 | 0 | 6.84 | . |
| **RelW** | | 0.09153 | 0.01431 | 134 | 6.40 | <.0001 |
| **Sex** | m | 1.4584 | 1.3902 | 24 | 1.05 | 0.3046 |
| **Sex** | w | 0 | . | . | . | . |
| **RelW*Sex** | m | 0.08042 | 0.01977 | 134 | 4.07 | <.0001 |
| **RelW*Sex** | w | 0 | . | . | . | . |

| Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **RelW** | 1 | 134 | 177.58 | <.0001 |
| **Sex** | 1 | 24 | 1.10 | 0.3046 |
| **RelW*Sex** | 1 | 134 | 16.54 | <.0001 |

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