The Cerebrovascular Response to Resistance Exercise in Healthy Individuals

A thesis presented in partial fulfilment of the requirements for the degree of

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Abstract

The brain is a small organ that is sensitive to chemical and pressure changes, which is why it requires tightly regulated blood flow to function optimally, particularly under varying stressors. Resistance exercise (RE) is a unique stressor that produces sinusoidal fluctuations in blood pressure, which alters the cerebral blood flow (CBF) profile to mirror that of the blood pressures. However, the brain possesses regulators that work to achieve stable CBF. These regulators include 1) partial pressure of carbon dioxide ($PaCO_2$), 2) cerebral autoregulation (CA), 3) neurovascular coupling (NVC), 4) the autonomic nervous system (ANS), and 5) cardiac output ($\dot{Q}$). CA is a known mechanism that defends against fluctuations in blood pressure, its efficiency is not as robust as previously thought, as the proposed autoregulatory range from earlier studies has been found to be much narrower. Therefore, stressors that challenge CA outside of the autoregulatory range requires investigation since the autoregulatory range being narrower, could expose the cerebral circulation to larger blood pressure perturbations and challenge stable CBF. This thesis investigated the relationship between RE and CA, focusing on cerebrovascular and cardiovascular haemodynamics during and immediately after dynamic RE in RE-trained and untrained individuals. The comparisons between RE-trained and untrained individuals would shed light on if the constant exposure to the sinusoidal fluctuations in blood pressure elicit functional adaptations that assists with maintaining stable CBF during RE. Furthermore, if functional adaptations do exist, whether that is specific to just increases in blood pressure or decreases in blood pressure or in both directions was also investigated. Additionally, this thesis explored the role of NVC in CBF regulation during RE. Transcranial Doppler (TCD) ultrasound was used to measure middle cerebral artery blood velocity (MCAv) during and after RE as a proxy for CBF. Three experimental chapters examined different aspects of RE-induced fluctuations in blood pressure and their effects on CBF regulation. **Chapter Five**: During unilateral lower body dynamic RE, using a leg extension exercise, RE-trained individuals experienced greater increases and fluctuations in mean arterial pressure (MAP) compared to untrained individuals. However, mean MCAv ($MCAv_{mean}$) did not differ between the two groups. This finding suggests that RE-trained individuals may possess cerebrovascular adaptations that help maintain stable $MCAv_{mean}$ despite greater blood pressure variability. **Chapter Six**: After completing dynamic RE, participants

immediately stood up to investigate the effects of a hypotensive stressor on MAP and $MCAv_{mean}$. The RE-trained group exhibited a greater reduction in MAP than the untrained group, yet $MCAv_{mean}$ remained similar between groups. Additionally, the rate of regulation (RoR), a metric of CA, was higher in the RE-trained group, although the time taken for $MCAv_{mean}$ to return to baseline was identical. These findings imply that RE-trained individuals may have enhanced CA responses during post-exercise hypotension. **Chapter Seven**: The role of NVC was explored by comparing MCAv in the ipsilateral and contralateral middle cerebral arteries during unilateral upper body dynamic RE, using a biceps curl exercise. The results indicated that $MCAv_{mean}$ was similar on both sides during RE, demonstrating that MCAv remains bilaterally homogeneous during dynamic RE. This suggests that, during dynamic upper body RE, NVC does not differentially modulate flow between hemispheres and that MAP has more of an influence on CBF. This thesis demonstrated that habitual RE may lead to cerebrovascular adaptations that help maintain CBF during both dynamic RE and post-exercise hypotensive recovery. It also revealed that during dynamic RE, MAP exerts a dominant influence on MCAv, potentially overriding local regulatory mechanisms such as NVC. These results have important implications for understanding how regular RE influences cerebrovascular health and the brain's ability to manage fluctuations in blood pressure during physical stress. Furthermore, the findings from this research can be applied to enhance future exercise prescription recommendations.

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To my mum and dad, thank you for nurturing my love of learning from such an early age. The passion for knowledge that you instilled in me has led me to where I am today, and I would not be the person I am without you. I appreciate all of your love, encouragement, and unwavering support throughout this PhD journey.

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List of Abbreviations

$[Ca^{2+}]$ – Calcium Concentration

$[H^{+}]$ – Hydrogen Concentration

[SID] - Strong Ion Difference

1RM - One Repetition Maximum

ABP - Arterial Blood Pressure

ACA - Anterior Cerebral Artery

ANOVA – Analysis of Variance

ANS - Autonomic Nervous System

ARI – Autoregulatory Index

AUC – Area Under the Curve

BBB – Blood Brain Barrier

Ca^{2+} - Calcium

CA - Cerebral Autoregulation

CBF - Cerebral Blood Flow

CCA - Common Carotid Artery

CO_2 – Carbon Dioxide

CPP - Cerebral Perfusion Pressure

CVCi - Cerebrovascular Conductance Index

CVR – Cerebrovascular Resistance

DBP - Diastolic Blood Pressure

DMCAv - Diastolic Middle Cerebral Artery Blood Velocity

dCA - Dynamic Cerebral Autoregulation

ECA – External Carotid Artery

ECG - Electrocardiogram

H^+ - Hydrogen

HCO_3^- - Bicarbonate

HR - Heart Rate

Hz – Hertz

ICA - Internal Carotid Artery

ICP – Intracranial Pressure

LBNP – Lower Body Negative Pressure

LBPP – Lower Body Positive Pressure

MAP - Mean Arterial Pressure

MCA - Middle Cerebral Artery

MCAv - Middle Cerebral Artery Blood Velocity

mm Hg – Millimetres of Mercury

$MCAv_{mean}$ - Mean Middle Cerebral Artery Blood Velocity

MVC - Maximal Voluntary Contraction

NIRS – Near Infrared Spectroscopy

NVC - Neurovascular Coupling

OLBNP - Oscillatory Lower Body Negative Pressure

$PaCO_2$ - Partial Pressure of Arterial Carbon Dioxide

PaO_2 - Partial Pressure of Arterial Oxygen

PCA - Posterior Cerebral Artery

PCAv - Posterior Cerebral Artery Velocity

$P_{ET}CO_2$ - Partial Pressure of End-Tidal Carbon Dioxide

PI - Pulsatility Index

PP - Pulse Pressure

PPG - Photoplethysmography

$\dot{Q}$ - Cardiac Output

RBC – Red Blood Cell

RE - Resistance Exercise

RoR - Rate of Regulation

s - Seconds

SBP - Systolic Blood Pressure

SD – Standard Deviation

SMCAv - Systolic Middle Cerebral Artery Blood Velocity

SNA – Sympathetic Nervous System Activity

SNS - Sympathetic Nervous System

TCD - Transcranial Doppler

TFA - Transfer Function Analysis

USG - Urine Specific Gravity

VM - Valsalva Manoeuvre

VA - Vertebral Artery

VO_{2max} – Maximum Oxygen Consumption

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Chapter One: Introduction

The brain is a small, high maintenance, and selfish organ. It only accounts for approximately 2% of total body mass yet receives close to 15% of cardiac output and is responsible for approximately 20% of the body's oxygen consumption (Willie et al., 2011). The high metabolic rate of the brain is due to the brain's constant neural activity. Furthermore, the brain does not have any meaningful energy stores, nor does it have an oxygen reserve, consequently making it highly susceptible to ischaemic injury. Thus, the brain is reliant on constant blood flow for energy substrate delivery and removal of waste metabolites, which highlights the need for precise cerebral blood flow (CBF) regulation (Ainslie & Duffin, 2009; Willie et al., 2011; Willie et al., 2014).

Resistance exercise (RE) is a popular form of exercise due to the many associated physiological benefits, such as increased muscle mass and strength (Deschenes & Kraemer, 2002), reduced fat mass (Lopez et al., 2022), neuroprotection (Yarrow et al., 2010), and improved mental well-being (O'Connor et al., 2010). The physiological benefits of RE extend to clinical populations, with RE used as treatment for cardiovascular disease (Paluch et al., 2024; Strasser & Schobersberger, 2011), stroke (Veldema & Jansen, 2020), and diabetes mellitus (Evans et al., 2019). Additionally, RE has been used to offset sarcopenia - the age-related decline in muscle mass (Seguin & Nelson, 2003). Furthermore, in Aotearoa New Zealand current physical activity guidelines recommended that adults (18 – 64) engage in muscle strengthening exercise at least two days a week for improved health (Ministry Of Health, 2020). Previous research investigating cerebrovascular responses during dynamic RE has mainly focused on RE-trained individuals, largely overlooking the healthy untrained population. This may be due to the assumption that RE-trained individuals are better equipped to perform high-intensity protocols safely and consistently, minimising variability in responses. However, this emphasis neglects the broader applicability of findings to the general population, which includes untrained individuals who may exhibit different cerebrovascular and hemodynamic responses due to lower baseline strength, fitness levels, and adaptations to mechanical and metabolic stress. Understanding the responses of untrained individuals is important for developing exercise guidelines that ensure safety and optimise potential cerebrovascular health across a diverse population. RE, however, induces substantial

perturbations in arterial blood pressure (ABP), with recordings of systolic (SBP) and diastolic (DBP) blood pressures reaching 480- and 350-mm Hg respectively during high-intensity dynamic RE in a trained body builder (MacDougall et al., 1985). The ABP response during RE is dependent on the muscle mass recruited (MacDougall et al., 1992), the number of repetitions within a set (Sale et al., 1993), the number of sets (Libardi et al., 2017), and the length of the rest periods between sets (Paulo et al., 2019). Despite the many benefits of RE, upon standing immediately following high-intensity RE, hypotension and cerebral hypoperfusion are evident (Moralez et al., 2012; Perry, Schlader, et al., 2014; Romero & Cooke, 2007), with syncope reported following high-intensity RE with a concurrent Valsalva manoeuvre (VM) (Compton et al., 1973). Despite the small potential for harm, RE should be encouraged for overall physical (Kraemer et al., 1988) and psychological well-being (O'Connor et al., 2010).

RE offers numerous benefits, but it also imposes a significant stress on the brain. As mentioned, RE induces rapid, sinusoidal fluctuations in blood pressure, which are reflected in CBF. Fortunately, the brain is equipped with an intrinsic regulatory mechanism that counters fluctuations in blood pressure, namely cerebral autoregulation (CA). However, the regulation of CBF is complex, and there is a myriad of regulators that work in conjunction with CA to maintain adequate CBF, including partial pressure of carbon dioxide ($PaCO_2$), neurovascular coupling (NVC), the autonomic nervous system (ANS), and cardiac output ($\dot{Q}$). Whilst CA does indeed play an important role in maintaining cerebral perfusion, recent evidence suggests that CA may not be as effective as previously thought, as the CA plateau is narrower than originally proposed by Lassen (1959).

To ensure optimal brain function, CBF must be maintained within a tightly regulated range, even when subjected to stressors such as dynamic RE. Despite the well-documented effects of aerobic exercise on CBF regulation, there is still limited understanding of the circulatory adaptations resulting from habitual RE. Furthermore, it is unclear how these adaptations may influence the within and post-RE response, especially compared to untrained and otherwise healthy individuals. Although NVC is known to contribute to CBF regulation during exercise, its role during dynamic RE remains unexplored. Much of the previous research has focused on static RE, such as handgrip exercises, to investigate NVC. However, handgrip exercises are not commonly used in typical RE sessions, with individuals who engage in RE usually

performing exercises that use larger muscle groups such as the bicep curl and leg extension. Therefore, studies utilising the handgrip exercise has limited application and relevance to real-world RE training.

Against this backdrop, the aim of this thesis was to investigate the effects of dynamic RE on cerebrovascular responses during and post-exercise. Additionally, this work examined the contribution of NVC to CBF regulation during dynamic RE. The key concepts mentioned above will be explored in detail in **Chapter Two** - a comprehensive review of the existing literature, focusing specifically on CBF, its regulators, and dynamic RE.

In **Chapter Three**, the thesis aims and objectives are outlined. **Chapter Four** outlines the methodological approach of the study, detailing participant recruitment, experimental design, data collection procedures, and the techniques used to assess cerebrovascular responses during RE. **Chapter Five**, the first experimental chapter investigated the effects of dynamic RE on mean arterial pressure (MAP) and middle cerebral artery velocity (MCAv) during exercise, comparing RE-trained and untrained individuals. **Chapter Six** extended the findings from **Chapter Five** by examining the effects of a post-exercise stand, challenging CA. **Chapter Seven** focused on the contributions of NVC to CBF regulation during dynamic RE. Finally, **Chapter Eight** offers a general discussion, summarizing the key findings, identifying common themes across the chapters, and proposing directions for future research in this field.

Chapter Two: Literature Review

The literature review focused on the key topics directly associated with the main research aims and objectives. The structure of this literature review can be divided into two parts. Part 1 delved into the cerebral circulation, including the anatomy of the cerebral vasculature and the regulators of CBF which includes 1) the $PaCO_2$, 2) ABP, 3) NVC, 4) ANS, and 5) $\dot{Q}$. The focus then shifts in part 2 to the physiological response to dynamic RE including the discussion of the blood pressure and cerebrovascular response during and post RE. Other factors such as the involvement and effect of the VM, the vascular adaptations to dynamic RE and the contributions of NVC to dynamic RE will also be explored. This literature review provides the basis for the thesis from which the main research aims, objective, and hypothesis were devised.

2.1 Cerebral Blood Flow (CBF)

The brain receives its blood supply from two primary pairs of arteries: the internal carotid arteries (ICA) and the vertebral arteries (VA). The ICAs originate from the common carotid artery (CCA) and bifurcates into the middle cerebral arteries (MCA) and anterior cerebral arteries (ACA), with the MCA being the larger of the two branches (Lee, 1995). The MCA is responsible for supplying approximately 80% of the frontal lobe and the lateral surfaces of both the temporal and parietal lobes, making it the primary contributor to the anterior circulation (Alastruey et al., 2007; Chandra et al., 2017). The VAs stem from the left and right subclavian artery, to form the left and right VA, respectively. The VAs, anastomose to create a single basilar artery, which subsequently bifurcates into the left and right posterior cerebral arteries (PCA). The PCAs supply blood to the so-called posterior circulation, which supplies the occipital lobe and the brainstem (Chandra et al., 2017). Bilaterally the PCA is connected to the MCA by the posterior communicating artery, while the left and right ACAs are linked by a single anterior communicating artery. This arrangement of cerebral arteries forms an anastomotic ring known as the Circle of Willis (Lee, 1995), see **Figure 1**, however, there are many anatomical variations.

The distribution of CBF is not equal among the three main cerebral arteries. Approximately 46% of total CBF is directed through the MCA, 34% through the ACA, and the remaining 20% via the PCA (Zarrinkoob et al., 2015). This disproportionate distribution highlights the dominant role of the MCA in supplying blood to metabolically active and functionally critical brain regions. The MCA supplies approximately 80% of the cerebral cortex, including much of the motor cortex responsible for voluntary movement of the upper limbs, face, and trunk (Saver, 2006). Specifically, the M1 segment of the MCA, proximal to its bifurcation, is often targeted in transcranial Doppler ultrasound (TCD) due to its accessibility, relatively straight course, and role in perfusing these key functional areas. This segment also provides a stable and consistent signal for TCD measurements and reflects global changes in CBF (Willie et al., 2012).

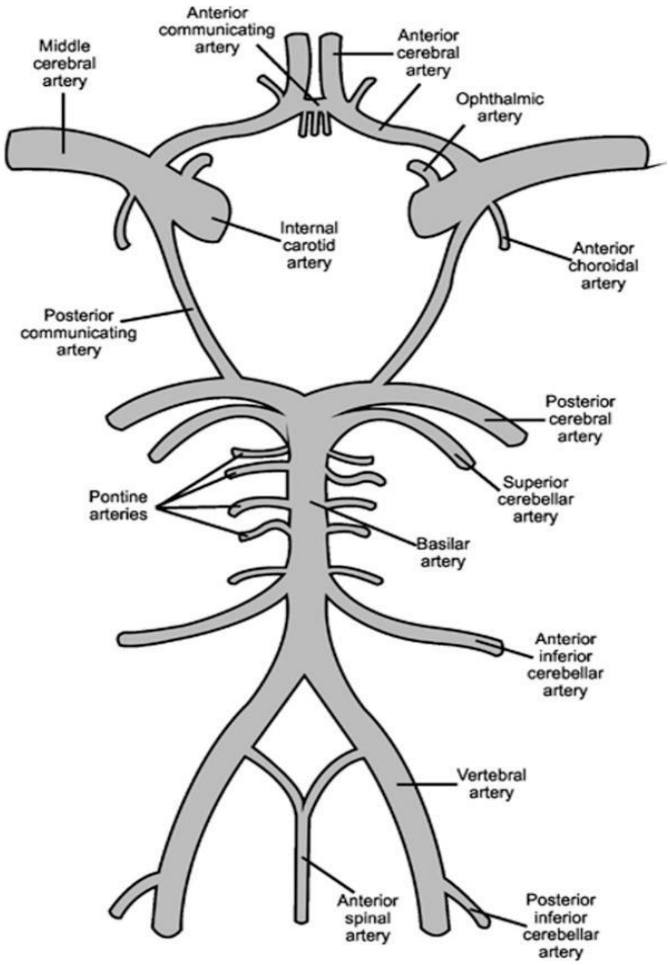

Figure 1 Diagram of the arteries forming the circle of Willis (Vrselja et al., 2014).

CBF is modulated by many physiological factors, including: $PaCO_2$, ABP, NVC, ANS activity and $\dot{Q}$ (Ainslie & Duffin, 2009) (**Figure 2**). Within these regulators exists

an order of influence, with $PaCO_2$ being the most influential on CBF, followed by MAP, whilst NVC, ANS, and $\dot{Q}$ have a lesser influence (Ainslie & Duffin, 2009; Brian, 1998; Claassen et al., 2007; Hoiland et al., 2019; Kety & Schmidt, 1948a). Identifying the exact role of each physiological factor during a multifactorial stressor such as exercise, is extremely difficult due to the way these factors interact (Willie et al., 2014). For example, during rapid changes in perfusion pressure may mask some the effects of NVC. Nevertheless, like other circulations the control of CBF is dictated by vessel resistance and the pressure gradient across the circulation.

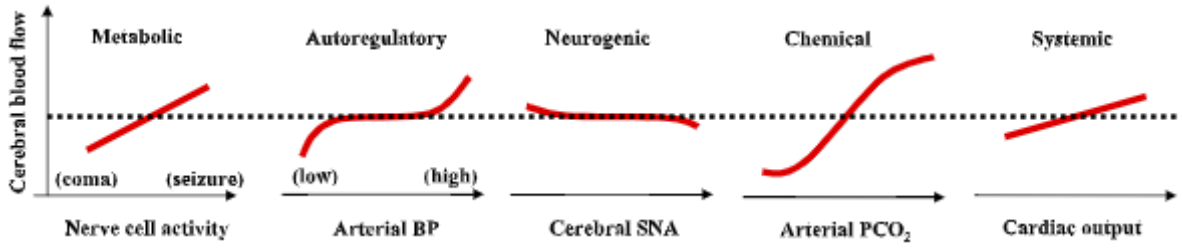

Figure 2 Influences of key physiological factors regulating CBF. Nerve cell activity, neurovascular coupling, BP, Blood pressure, SNA, sympathetic nervous activity, PCO_2, Partial pressure of carbon dioxide (Ainslie & Duffin, 2009).

Poiseuille's law governs the flow of blood through all circulations in the human body, and the brain is no exception.

$$Flow = \frac{\Delta P \pi r^4}{8 \eta L}$$

Where r = radius, ΔP = change in pressure, η = viscosity, and L = length of tube.

Poiseuille's law highlights the significant impact that minor changes in vessel radius can have on blood flow. CBF is also affected by transmural pressure, which in turn affects vessel diameter. The arteries that perfuse the parenchyma of the brain are enclosed in the skull, and subject to fluctuations in intracranial pressure (Haykowsky et al., 2003) Therefore, the difference between arterial blood pressure and the intracranial pressure (ICP) defines the cerebral perfusion pressure (CPP). Any changes in ICP as seen during the VM, and postural changes (Moncur et al., 2024), can have significant repercussions for CPP and subsequently CBF. The ability for the brain to defend itself from these changes in CPP are important as the brain has poor tolerance for ischaemia (Van Lieshout et al., 2003), with tissue remaining viable without adequate oxygen and nutrients for only a couple of minutes (Lee et al., 2000).

2.1.1 Arterial Carbon Dioxide Content

As seen in **Figure 3**, carbon dioxide (CO_2) has a profound influence on CBF. Kety and Schmidt (1945) were the first researchers to accurately measure CBF in conscious man and led to the discovery that CBF was extremely sensitive to changes in P_aCO_2. It was revealed that hypercapnia (an elevation in P_aCO_2) produced a substantial increase in CBF (Kety & Schmidt, 1948a) as seen in **Figure 3**, via a potent vasodilation of cerebral vessels, conversely hypocapnia (a reduction in P_aCO_2) significantly decreased CBF via vasoconstriction (Kety & Schmidt, 1946). During hypercapnia, the elevated CBF increases CO_2 washout, therefore limiting changes in cerebral pH (Ainslie & Duffin, 2009). Conversely, hypocapnia reduces CBF to decrease CO_2 washout. Changes in pH in the arterial vessel due to the changes in $PaCO_2$ does not change vessel diameter (Lambertsen et al., 1961). Rather, it is the change in cerebral extracellular pH that alters vascular tone (Kontos et al., 1977), as non-polar CO_2 molecules readily diffuse across the blood brain barrier (BBB), even under physiological conditions. Once across the BBB, CO_2 combines with water to form carbonic acid, which dissociates into bicarbonate (HCO_3^-) and hydrogen (H^+) ions, thereby altering extracellular pH (Lassen, 1968). The brain's sensitivity to changes in $PaCO_2$ and thus extracellular pH appears to serve as a homeostatic mechanism for regulating central pH (Chesler, 2003).

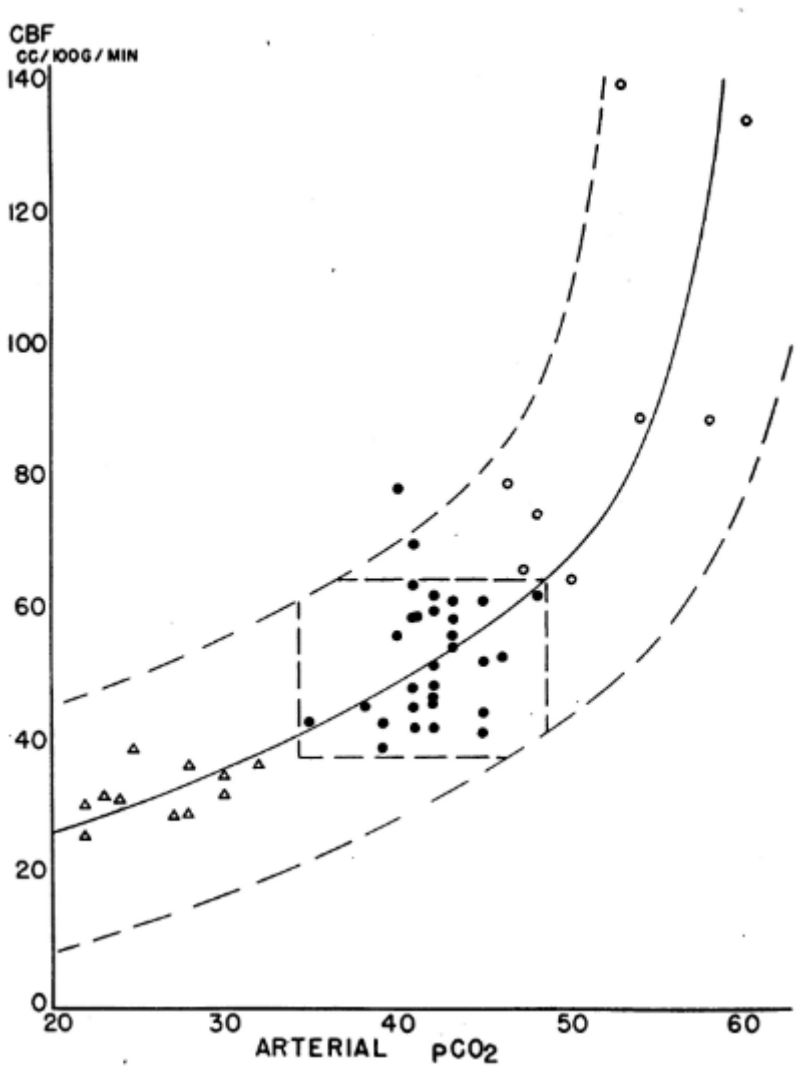

Figure 3 The relationship between cerebral blood flow (CBF) and arterial carbon dioxide (CO_2) concentration (Kety & Schmidt, 1948a). The dots represent normal ventilation, the triangles represent hyperventilation, and the open circles represent inhalation of 5 – 7% CO_2. cc/100 g/min unit measures volume of blood in cubic centimetres that passes through 100 g of brain tissue per minute.

Though the cerebral vasculature is highly sensitive to changes in $PaCO_2$, there are thresholds for both hypercapnia and hypocapnia before a change in CBF occurs. Patterson et al. (1955) found that vasodilation of cerebral vessels would not occur until >2.5% CO_2 was inspired (4.mm Hg increase in $PaCO_2$). For every 1mm Hg increase in $PaCO_2$, CBF rises by 3 – 6% (Dahl et al., 1994; Ide et al., 2003; Markwalder et al., 1984), conversely a decrease of 1 – 3% in CBF is observed every 1mm Hg decrease in $PaCO_2$. Whilst CBF may be more sensitive to increases in $PaCO_2$ than decreases, Wasserman and Patterson (1961) found that only a 2mm Hg decrease in $PaCO_2$ was the minimum threshold required to initiate vasoconstriction of cerebral vessels, while a 4.5mm Hg increase in $PaCO_2$ was required to induce vasodilation. Once the 4.5mm

Hg increase in $PaCO_2$ is surpassed, the CBF-$PaCO_2$ pattern displays that of a sigmoidal shape. The regulation of CBF via arterial blood gases occurs throughout the arterial tree from the large arteries (internal carotid and vertebral arteries) to the arterioles (Willie et al., 2014). Once chemoreceptor activation is enough to increase MAP then it becomes a pressure-dependent response (Battisti-Charbonney et al., 2011). Conversely, in hypocapnia, once the 2mm Hg decrease is reached, the decrease in CBF is smaller per unit decrease in arterial CO_2 and is not linear (Wasserman & Patterson, 1961).

The mechanism by which CO_2 regulates cerebral vascular tone remains unclear; however, it is likely that carbon dioxide producing changes in H+ ions is involved (Kontos et al., 1977). Duffin et al. (2021) highlighted that intracellular $[H^+]$ is a critical regulator of vascular smooth muscle cell function. Increases in $[H^+]$, as seen during hypercapnia, directly affect intracellular calcium concentration ($[Ca^{2+}]$) (Swietach et al., 2013), which modulates vascular smooth muscle tone and thereby CBF (Boedtkjer, 2018). Vascular smooth muscle tends to relax in acidosis and contract in alkalosis (Aalkjær & Peng, 1997), driven by $[Ca^{2+}]$ changes in response to fluctuations in $[H^+]$. A decrease in pH (increased $[H^+]$) activates ATP-sensitive and voltage-gated potassium channels, causing hyperpolarization of smooth muscle and endothelial cells and leading to vasodilation of both upstream and downstream vessel (Ainslie & Duffin, 2009; Kitazono et al., 1995; Nelson & Quayle, 1995). The regulation of intracellular $[H^+]$ involves membrane transport of strongly dissociated ions, which influences the strong ion difference ([SID]); this energy-dependent process can be affected by oxygen availability (Garneau et al., 2020; Hoiland et al., 2020). In hypercapnia, elevated $PaCO_2$ leads to a rise in extracellular pH, contributing to vasodilation through mechanisms that include increased nitric oxide (NO) release (Peebles et al., 2008). Conversely, hypocapnia decreases $PaCO_2$ and reduces $[H^+]$, causing vasoconstriction and lowering CBF (Duffin et al., 2021). Cleary et al. (2020) further emphasises the importance of vascular control mechanisms in CO_2/H^+-dependent regulation, particularly in relation to chemoreception and the drive to breathe, highlighting the complex interaction between cerebral vascular tone, brain pH, and central homeostasis.

The onset and offset times of these responses differ significantly. There is an approximate 6 s delay between the offset of hypercapnia and changes to vascular

tone (Poulin et al., 1996). The CBF response to hypocapnia shows distinct temporal differences. There is an initial time delay of 3.9s from the onset of hypocapnia before blood flow changes begin. Following this delay, the onset response to hypocapnia (characterized by a time constant of 6.8 ± 4.7 seconds (s)) is significantly faster than the offset response (time constant of 14.3 ± 13.0 s), demonstrating an asymmetric vascular response pattern (Poulin et al., 1998). As mentioned above, CO_2 can cross the blood brain barrier (BBB) easily, whilst H^+ ions do not. Therefore, central chemoreceptors are not affected by the changes in arterial pH except for when $PaCO_2$ changes occur. The effects of CO_2 on CBF are an important mechanism to counter regulate the changes in brain H^+, which in turn stabilizes the ventilatory response to the perturbations in $PaCO_2$ (Ainslie & Duffin, 2009). Whilst hypoxia can cause cerebral vasodilation, this effect is often masked by the hypoxia-induced hyperventilation which produces hypocapnia and subsequently vasoconstriction of cerebral arterioles (Ogoh, Nakahara, et al., 2010).

2.1.2 Arterial Blood Pressure

The brain possesses an intrinsic homeostatic mechanism called CA that stabilises CBF even when blood pressure (and thus CPP) is perturbed. Lassen (1959) developed the concept of CA when he gathered data from seven different studies and calculated the now well-described autoregulatory curve (**Figure 4**). The classic autoregulatory curve demonstrated that CA had an effective ability to maintain CBF when MAP ranged between 60 to 150mm Hg. When a change in MAP is detected, CA alters cerebrovascular resistance (CVR) to maintain CBF (Whittaker et al., 2017; Willie et al., 2014) via a negative feedback loop (Tzeng & Ainslie, 2014).

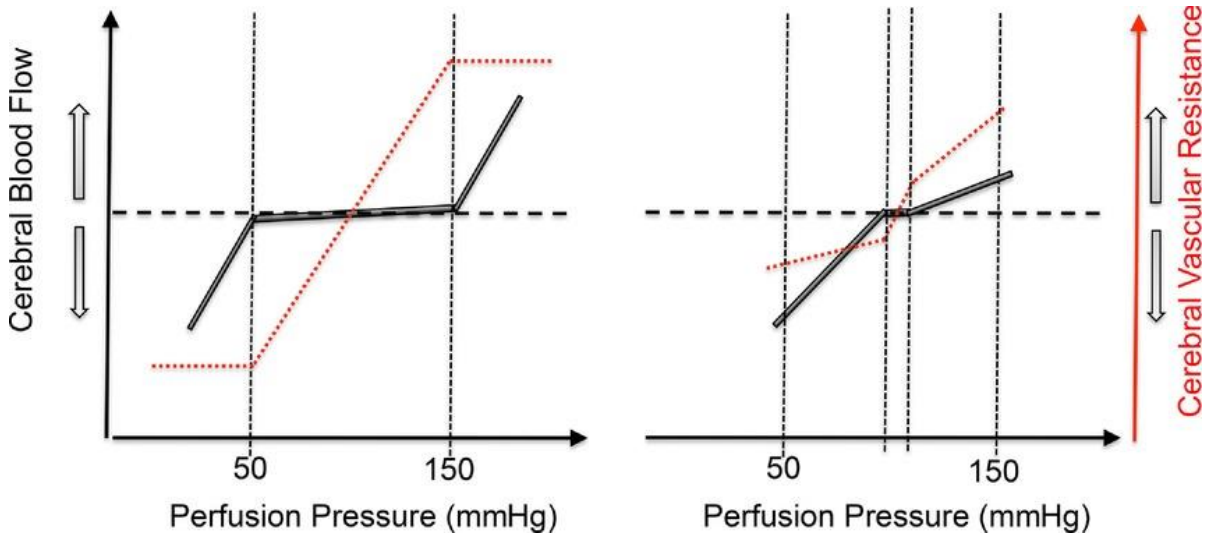

Figure 4 On the left is Lassen (1959) Classic Autoregulatory Curve, while on the right is the revised contemporary autoregulatory curve proposed by Tan (2012) describing the relationship between cerebral perfusion and CBF (Willie et al., 2014).

In cerebrovascular research CA is divided into static and dynamic. These terms describe the different time domains in which CA operates, despite the underlying mechanisms being the same. Slower (lower frequency < 0.5Hz) changes to MAP are described as being regulated by static cerebral autoregulation (sCA), and fast (higher frequency > 0.5Hz) changes to MAP being regulated by dynamic cerebral autoregulation (dCA) (Claassen et al., 2021; Tan & Taylor, 2014; Zhang et al., 1998). However, dCA is not as effective as sCA as CBF closely follows MAP during when MAP is perturbed at higher frequencies as seen in **Figure 5** (Claassen et al., 2021). CA plays a critical integrative role in regulating CBF by counteracting changes in blood pressure, which is important to the brain's homeostasis, as hypoperfusion leads to loss of consciousness and brain ischaemia (Folino, 2007; Van Lieshout et al., 2003), while hyperperfusion can lead to the deterioration of the BBB, cerebral oedema, and possible stroke (Pires et al., 2013; van Mook et al., 2005).

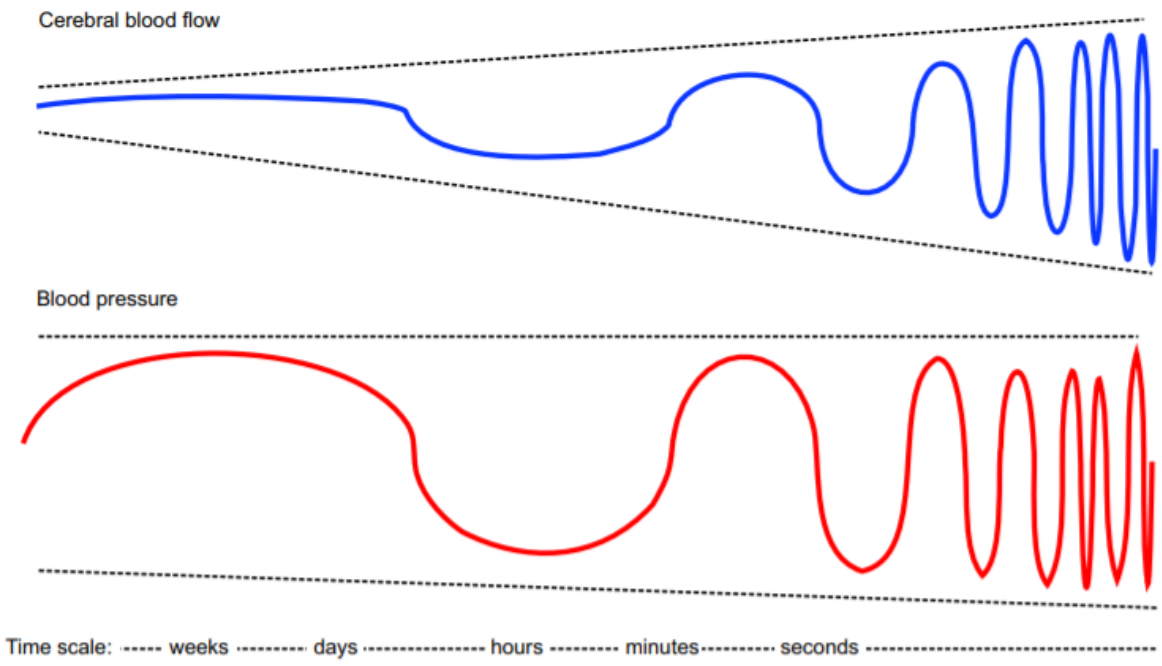

Figure 5 This figure from Claassen et al. (2021) shows the temporal changes to blood pressure and the autoregulation of cerebral blood flow (CBF). Gradual changes to blood pressure have minimal effect on CBF, however, with faster changes in blood pressure, CBF will vary proportionately with blood pressure.

CA refers to how the vascular smooth muscle responds to changes in blood pressure (Bevan & Hwa, 1985). Voltage-gated Ca^{2+} channels are sensitive to mechanical stimuli (Hill et al., 2001; Schubert & Brayden, 2005), therefore, intracellular Ca^{2+} concentrations can be altered due to stretch stimuli (Davis & Hill, 1999; Hill et al., 2001; Schubert & Mulvany, 1999). During a reduction in MAP, vascular smooth muscle relaxes in response to reduced stretch, leading to vasodilation. When the smooth muscle relaxes, Ca^{2+} channels close, leading to vasodilation (decreases vascular resistance), which is the physiological response to increase CBF and maintain tissue perfusion when perfusion pressure decreases. CBF may still decrease if perfusion pressure falls below the lower limit of autoregulation (Willie et al., 2014). According to Darcy's law ($Q = \Delta P / R$), flow (Q) is directly proportional to the pressure gradient and inversely proportional to resistance. Thus, if MAP decreases substantially, and resistance cannot be reduced any further, CBF will decline regardless of compensatory vasodilation (Panerai, 2008; Tzeng & Ainslie, 2014). When MAP is higher, vascular smooth muscle contracts, causing vasoconstriction and increasing resistance. CA response contrasts with the baroreflex, which functions systemically.

The baroreflex regulates systemic blood pressure by modifying pressure (ΔP) by altering regulators such as $\dot{Q}$ and resistance within the entire systemic circulation (e.g. total peripheral resistance), whilst CA acts locally on cerebral vessels. Per Poiseuille's Law (see **Section 2.1**), flow is proportional to r^4, even a small change in radius results in a significant change in flow, counteracting the effects of the ΔP. As highlighted by Fog (1939a, 1939b) small arteries such as pial arteriolar and arteries contribute significantly to the regulation of CBF during changes in MAP and when vasodilation of these vessels cannot maintain adequate flow in the brain, this is the lower limit of CA (Kontos et al., 1978; MacKenzie et al., 1979). Larger intracranial arteries have now been shown to be involved with the regulation of CBF (Olufsen et al., 2002). Tzeng et al. (2011) reported that blocking Ca^{2+} channels of the brain causes large cerebral vessels to dilate, thus decreasing MCAv and increasing pressure-driven blood flow, highlighting the importance of Ca^{2+} in dynamic autoregulation.

Baroreflex regulation of blood pressure and CA are interconnected (Rosenberg et al., 2022). The baroreceptors situated in the carotid sinus and aortic arch detect changes in blood pressure and send afferent nervous impulses to the brainstem. The brainstem controls ANS which indirectly affects CBF by altering systemic vascular resistance and $\dot{Q}$ (Ogoh & Tarumi, 2019). There is evidence of a reciprocal cooperation between baroreflex sensitivity and CA, that is, in individuals with lower baroreflex sensitivity CA sensitivity is greater (Ogoh, Tzeng, et al., 2010; Tzeng et al., 2010). During hypotension, baroreflex-mediated increases in heart rate (HR) and systemic vascular resistance provide a protective mechanism to defend against temporal reductions in MAP, which assists with maintaining an adequate perfusion gradient across vital organs, including the brain (Levine et al., 1994). CA and the ANS influence local arterial vessel radius to further assist with maintaining CBF during acute hypotension (Willie et al., 2014; Zhang et al., 2002). During reductions in MAP and concurrent reduction in CBF during lower body negative pressure (LBBP), the baroreflex response and CA work together and protect the brain from cerebral hypoperfusion and the onset of presyncope symptoms and syncope (Rosenberg et al., 2022). There are two phases to the physiological response to acute hypotension (Ogoh et al., 2008). For example, during the sit-to-stand manoeuvre, Phase I was defined as to the time after the sit-to-stand manoeuvre where the changes in middle cerebral artery blood velocity mean ($MCAv_{mean}$) are independent of any baroreflex

corrections (1-7 s after the sit-to-stand) (Deegan et al., 2009; Sorond et al., 2009; van Beek et al., 2008). Phase II refers to when the baroreflex mechanism starts and continues for 4 s (Ogoh et al., 2008). The rate of change in cerebrovascular conductance index (CVCi) observed during Phase I is reflective of dCA capacity, as these changes occur independent of arterial baroreflex regulation (Aaslid et al., 1989). Therefore, to accurately measure dCA independent of baroreflex intervention, Phase I needs to be measured.

2.1.2.1 Static Cerebral Autoregulation

For most early studies investigating CA, Lassen's proposed autoregulatory curve was adopted. However, Lassen's autoregulatory curve was a combination of seven different data sets, which included a total of 11 different clinical cohorts. Therefore, the autoregulatory curve was more of a depiction of inter-subject values of individuals with differing health conditions, rather than being an accurate representation of MAP-CBF relationship in a heterogenous group of individuals or reflective of normal function in healthy controls. CA can be impaired by cerebral pathologies such as stroke, trauma, and ischemia (Brodie et al., 2009; Georgiadis et al., 2001; Reinhard et al., 2005; Schwarz et al., 2002). Heistad and Kontos (1983) conducted a reanalysis of the data sets from Lassen's study, however, they did not include all the data, deciding to exclude certain clinical cohorts. A total of 376 participants from Lassen's study were included, although it was unclear which clinical cohorts were excluded from the analysis. The results from Heistad and Kontos (1983) reanalysis found that for every 10mm Hg decrease in MAP, CBF decreased by 2 - 7%, while a 10mm Hg increase in MAP produced a 7% increase in CBF. Another reinvestigation of the CA curve was conducted by Lucas et al. (2010) using pharmacological manipulation of MAP. The results indicated that the relationship between MAP-CBF was more pressure-passive, as the authors found that there was a 0.8% change in MCAv for every 1mm Hg change in MAP, independent of changes in partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), which is measured as a proxy for $PaCO_2$. Lucas et al. (2010) did not see a plateau region in their study; however, this may be due to the stepwise changes in MAP being outside the plateau range (Tzeng & Ainslie, 2014). These data are supported by Zhang et al. (2009), who examined the effects of steady-state phenylephrine induced increases in MAP on

MCAv and found that an increase in blood pressure by ~37% (~30mm Hg) above baseline increased MCAv by ~11%. Tan (2012) reported that the autoregulatory range might only be 5mm Hg either side of baseline measures of blood pressure (see **Figure 4**), which is much narrower than the range suggested by Lassen (1959). The brain presents a pressure-passive component during steady-state changes in MAP, a plateau may still be present where CBF is well maintained within a specific MAP range, however, this plateau range seems to be much smaller than initially proposed by Lassen (Tan, 2012). These data indicate that any changes to MAP outside of the 5mm Hg either side of the baseline measures will translate into the cerebral circulation, resulting in a commensurate change in CBF, elucidating that CA is not as effective as it was once believed.

2.1.2.2 Dynamic Cerebral Autoregulation

Dynamic CA can be described as the regulation of CBF in response to abrupt and transient (i.e. seconds) changes to MAP (Aaslid et al., 1989). Technological advances such as the development of transcranial Doppler (TCD) ultrasonography and the finger photoplethysmography (Finapres) has enabled the dynamic examination of the cerebral pressure-flow relationship (van Beek et al., 2008). Aaslid et al. (1989) conducted the first experiment investigating dCA using TCD, by inducing abrupt hypotension induced by rapid thigh-cuff deflation. This method consisted of inflating bilateral thigh cuffs to 20mm Hg above the participant's systolic blood pressure for 2 minutes. Upon rapid deflation a hypotension ensued. Aaslid et al. (1989) found that dCA appears more efficient at offsetting transient increases in blood pressure rather than decreases. However, the study induced blood pressure changes through thigh cuff release, which resulted in a sudden drop in blood pressure followed by recovery. The increase in blood pressure observed corresponded to the recovery phase after the thigh cuff release, which blood pressure returned to or slightly exceeded baseline values. This does not represent hypertension, but rather than an overshoot in blood pressure. Using the modified Oxford method with nitroprusside and phenylephrine injections to manipulate MAP Tzeng et al. (2010) reported similar findings and confirmed that dCA exhibits an asymmetrical response. Subsequent investigations of spontaneous fluctuations at rest (Panerai, Barnes, et al., 2023) and non-pharmacological methods to perturb MAP such as squat stand (Brassard,

Ferland-Dutil, et al., 2017; Labrecque et al., 2021; Panerai et al., 2018) have supported this asymmetrical response. This asymmetric response is referred to hysteresis and reflects the greater capacity of dCA to counteract rising MAP.

Aside from the direction of change, the rate of change in MAP is also important (Tzeng & Ainslie, 2014). The brain operates as a high pass filter (Hamner et al., 2004) in which low-frequency changes to ABP are more efficiently defended, however, high-frequency changes are transferred directly to the cerebral circulation (Diehl et al., 1998; van Beek et al., 2008; Zhang et al., 1998). Regulation in the high-frequency range is not as effective because there is a time lag of ~5s (Zhang et al., 1998) before the cerebrovascular response is initiated to offset the changes in blood pressure. Activities such as standing up (Sorond et al., 2009; Thomas et al., 2009), the VM (Pott et al., 2000; Tiecks Frank et al., 1995), and dynamic RE (Edwards et al., 2002; Romero & Cooke, 2007) generate rapid changes in blood pressure that are unable to be buffered by dCA which is reflected in a concurrent change in CBF.

The reduction in phase angle and low-frequency power after exercise confirms the temporarily disturbed CA. Smail et al. (2023) observed a transient disturbance in CA immediately after 4 sets of 10 reps of squats at 70% of 1 repetition max (1RM). The authors found that 10 minutes after exercise, an elevation in gain and normalised gain was observed in the 0.10Hz squat-stand manoeuvre because of the inability to buffer blood pressure during systole. This temporary disturbance did not remain as CA metrics returned to normal after 45 minutes, however, the findings of the study are in accordance with the findings of Koch et al. (2005).

2.1.4 Effects of $PaCO_2$ on Cerebral Autoregulation

The regulators of CBF interact, with carbon dioxide being the most influential, (Ainslie et al., 2005), however the effects of $PaCO_2$ on CA can vary. Aaslid et al. (1989) and Czosnyka et al. (1993) reported that dCA was compromised during hypercapnia. The plateau seen in the autoregulation curve shortens and is shifted to the right, whilst the upper limit of the curve is shifted left, thus decreasing the range and efficiency of CA (Meng & Gelb, 2015). The brain can become pressure-passive when the hypercapnic stimulus produces chemoreceptor-induced increases in MAP (Battisti-

Charbonney et al., 2011). Perry, Lucas, et al. (2014) reported that during a hypercapnic conditions (fraction of inspired CO_2 = 5%) with a superimposed steady-state increase in MAP during lower body positive pressure at 20mm Hg and 40mm Hg, sCA was impaired with increases in MAP translated to MCAv. The vasomotor tone of cerebral vessels is the main factor regulating CA (Aaslid et al., 1989), with the dilatory effect of $PaCO_2$ contributing to the impairment of CA (McCulloch et al., 2000). Conversely, hypocapnia is reported to have a restorative effect on dCA (Aaslid et al., 1989), and sCA during isoflurane anaesthesia (McCulloch et al., 2005). Meng and Gelb (2015) illustrated a widening of the autoregulatory plateau and the upper limit of the CA during hypocapnia, although the authors reported that the lower limit of CA remains the same. The studies collectively show that hypercapnia impairs dCA.

2.1.5 Neurovascular Coupling (NVC)

Neurovascular coupling involves increasing local CBF to match increased neuronal activity (functional hyperaemia) (Attwell et al., 2010; Bélanger et al., 2011; Iadecola & Nedergaard, 2007). NVC is believed to have both feedback and feedforward mechanisms. The feedback mechanism is driven by the need to clear by-products of brain activity, for example, lactate, CO_2, amyloid-β-peptide, and tau (Hosford & Gourine, 2019). Furthermore, the metabolic by-products of brain activity include potent vasodilators such as adenosine, CO_2, H+, and lactate, which could potentially mediate the blood flow response (Freeman & Li, 2016). The feedforward mechanism states that an increase in CBF occurs due to the increases in neurovascular signalling pathways resulting in a release of vasoactive by-products of synaptic activity such as potassium (K^+), nitric oxide (NO), and prostanoids (Attwell et al., 2010). Due to the tight regulation of CBF, it may be that the two mechanisms work not independently of each other, but in tandem to ensure adequate blood flow.

Rosengarten et al. (2003) investigated the effects of hypercapnia and normocapnia on NVC using visual stimuli and reported that hypercapnia affects NVC regulation in two ways 1) by slowing down the initial rapid increase in CBF, 2) though the initial rapid increase in CBF slowed down, hypercapnia led to a greater absolute increase in CBF in the stimulated brain areas. These findings suggest that the initial slower CBF response under hypercapnia may paradoxically contribute to more

distribution of blood flow. Maggio et al. (2013) found that hypercapnia impaired NVC but not CVR. The authors concluded that the direct effect that CO_2 has on neural activity was far greater than vasodilation related to pH. Caldwell et al. (2021) reported similar findings as the authors found that NVC kinetics were slower in hypercapnia versus hypocapnia, which indicates the importance of cerebrovascular tone on NVC responsiveness and that it is the movement of CO_2 across the BBB to alter perivascular pH, rather than arterial pH, that affects acute CBF regulation in humans.

2.1.6 Autonomic Nervous System (ANS)

The cerebral vasculature is innervated by adrenergic and cholinergic fibres of various extrinsic and intrinsic origins (Edvinsson, 1975; Gulbenkian et al., 2001), however, the neural regulation of the cerebral circulation remains contentious (Ainslie & Brassard, 2014; Brassard, Tymko, et al., 2017; Gulbenkian et al., 2001; Heistad & Marcus, 1978; Strandgaard & Sigurdsson, 2008; van Lieshout & Secher, 2008). The most common method used to investigate ANS contribution to CA is through pharmacological blockade. Studies found that α-adrenergic blockade impaired CA (Hamner et al., 2010; Ogoh et al., 2008). However, β-blockade did not have an effect on CA during cycling exercise at moderate and high-intensities (Ogoh et al., 2007). Similarly, Seifert et al. (2009) reported that β-blockade (Propranolol) had no effect on MCAv during rest, however, during exercise Propranolol decreased $\dot{Q}$ which led to a decrease in MCAv. Zhang et al. (2002) induced a ganglionic autonomic blockade by administering trimethaphan to examine the cross-spectral relationship between ABP and the fluctuations in CBF via oscillatory lower body negative pressure (OLBNP). The authors found that ganglionic autonomic blockade altered dCA, as ABP and MCAv both decreased, whilst transfer function analysis (TFA) gain was doubled, and phase was decreased at low frequencies. Thus, indicating that CA had been reduced. However, the ganglionic blockade suggested that during hand grip exercise sympathetic activation vasoconstriction occurs in the large feed arteries of the brain (e.g. middle cerebral artery). This implies that SNA plays a protective role for the cerebral microcirculation. Although MAP rapidly increased from phase III (see Section **2.3.1** for descriptions of VM phases) back toward baseline levels, no Phase IV blood pressure overshoot was observed. Despite the reduced phase IV MAP response during blockade, MCAv increased by 55%, indicative of a loss of vasoconstrictor ability, indicating that the sympathetic nervous system (SNS) restrains MCAv during rising

MAP. Though still unclear, it is speculated that during the higher MAPs the SNS become present and that is to protect the cerebral vasculature from hyperperfusion.

While α-adrenergic blockade, β-blockade and ganglionic autonomic blockade provides insights into the overall role of the SNS, Hamner et al. (2012) investigated the specific contributions of the parasympathetic nervous system. Hamner et al. (2012) studied the effect of cholinergic blockade using glycopyrrolate on the pressure-flow relationship during OLBNP at six different frequencies (0.03 – 0.08Hz). The authors reported that systemic cholinergic blockade impaired CA, as an increase in transfer function coherence was shown between MAP and CBF. This demonstrates that the parasympathetic nervous control has an active and special role in CA.

2.1.7 Cardiac Output (Q̇)

The contribution of Q̇ to CBF regulation is contentious as the mechanism involved are not fully understood. The influence of Q̇ on CBF is both direct and indirect through its effects on MAP and CVR. When referencing Poiseuille's Law, Q̇ is not considered a determinant of flow, as the law states that flow is dependent on CPP and resistance. However, Q̇ is the total blood flow generated by the heart and in the closed cardiovascular system, changes in Q̇ can alter steady-state CBF by mediating changes in regional vascular resistance (Koller & Toth, 2012). Previous studies have demonstrated a linear relationship between Q̇ and CBF, where changes in Q̇ can modulate MCAv, even when MAP and $PaCO_2$ levels were held constant during LBNP and volume expansion (Ainslie & Duffin, 2009). Furthermore, at rest and during exercise, Q̇ has a linear relationship with CBF, and its regulation is independent of CA (Ogoh, Brothers, et al., 2005). However, Deegan et al. (2010) demonstrated that during sudden hypotension, Q̇ does not impact dCA. Increased shear stress, resulting from elevated pulsatile pressure (associated with increased stroke volume) and/or greater blood flow, can induce shear-stress-mediated vasodilation due to increases in steady-state pressure flow in the cerebral circulation (Ainslie & Duffin, 2009) This vasodilation is an indirect consequence of increased cardiac output, which enhances flow and thus raises shear stress on the endothelium, prompting a physiological response in cerebrovascular endothelial cells, such as nitric oxide release, reducing CVR in arterioles and thereby elevating CBF (Rubanyi et al., 1986; Treib et al., 1996).

In summary, while $\dot{Q}$ can influence CBF under specific conditions, this influence is secondary to the primary regulators of CBF, such as MAP and$PaCO_2$.

2.2 Aerobic Exercise

Most research that has investigated CBF regulation during exercise employed an aerobic exercise at a steady-state intensity, mainly using cycling as the modality (Brugniaux et al., 2014; Smith et al., 2012; Subudhi et al., 2008). Aerobic steady-state exercise is characterised by an initial increase in blood pressure, that eventually plateaus or continues to increase slowly throughout the exercise (Jorgensen, Perko, & Secher, 1992) . CBF increases during exercise until approximately 60 – 70% of maximal workload, before decreasing back to resting levels at higher intensities, with the overall exercise intensity-CBF relationship resembling and inverted-U (see cycling response in **Figure 6**) (Smith & Ainslie, 2017). The inverted-U shape is due to hyperventilation as indicated in **Figure 6** with the changes in $P_{ET}CO_2$. However, this is not consistent between exercise modalities. Pott et al. (1997) observed that during rowing at 75% of VO_{2max}, $MCAv_{mean}$ and MAP increased, however, the haemodynamic profile resembled that of dynamic RE (discussed below in **Section**). Therefore, the inverted-U shape is usually observed during aerobic exercise above 65% VO_{2max} when MAP is not being rapidly perturbed. Furthermore, even though $MCAv_{mean}$ increased during rowing, the mean was taken across the exercise, which may not reflect the true sinusoidal $MCAv_{mean}$ response. Lyngeraa et al. (2013) investigated the effects of running on MCAv and found that during running, an oscillatory pattern is observed in MAP and MCAv. The rhythmic oscillations are attributed to the interference between pressure waves generated by cardiac contraction and locomotion (Palatini, Mos, Mormino, et al., 1989). The authors concluded that running increases MAP and therefore MCAv. However, the authors did not measure $PaCO_2$ or $P_{ET}CO_2$ and only took the average across the duration of the exercise instead of MCAv and MAP during each stride. Furlong et al. (2020) compared MCAv between cycling and running, during a step increment test from 35% to 95% of VO_{2max}. The typical MCAv inverted-U shape seen in previous studies was present during cycling, with the peak being at 65% of VO_{2max} then returning to baseline at higher intensities. However, during running MCAv continued to increase up to 95% of VO_{2max} despite the slight decrease in $P_{ET}CO_2$ after 65% of VO_{2max}. The increase in MCAv after 65% of VO_{2max} was observed in participants with higher aerobic fitness, with the lower fit participants showing the

inverted-U shape when running (See **Figure 6** below). Collectively, these studies provide preliminary evidence that different forms of aerobic exercise may influence cardiovascular and cerebrovascular haemodynamics in distinct ways. The haemodynamic responses diverge even further within RE and are discussed below in **Section 2.3.2** and . Due to the differences in haemodynamic profiles between aerobic and RE exercise, adaptations can manifest in different ways. Therefore, more research is required to further understand how the haemodynamic profile of habitual RE effects CBF and how the cerebral vasculature adapts. More people now engage in RE, subsequently, it is becoming more important to understand how RE not only affects systemic haemodynamics, but also cerebrovascular haemodynamics and if chronic exposure to these exercises can impact systemic and cerebral health.

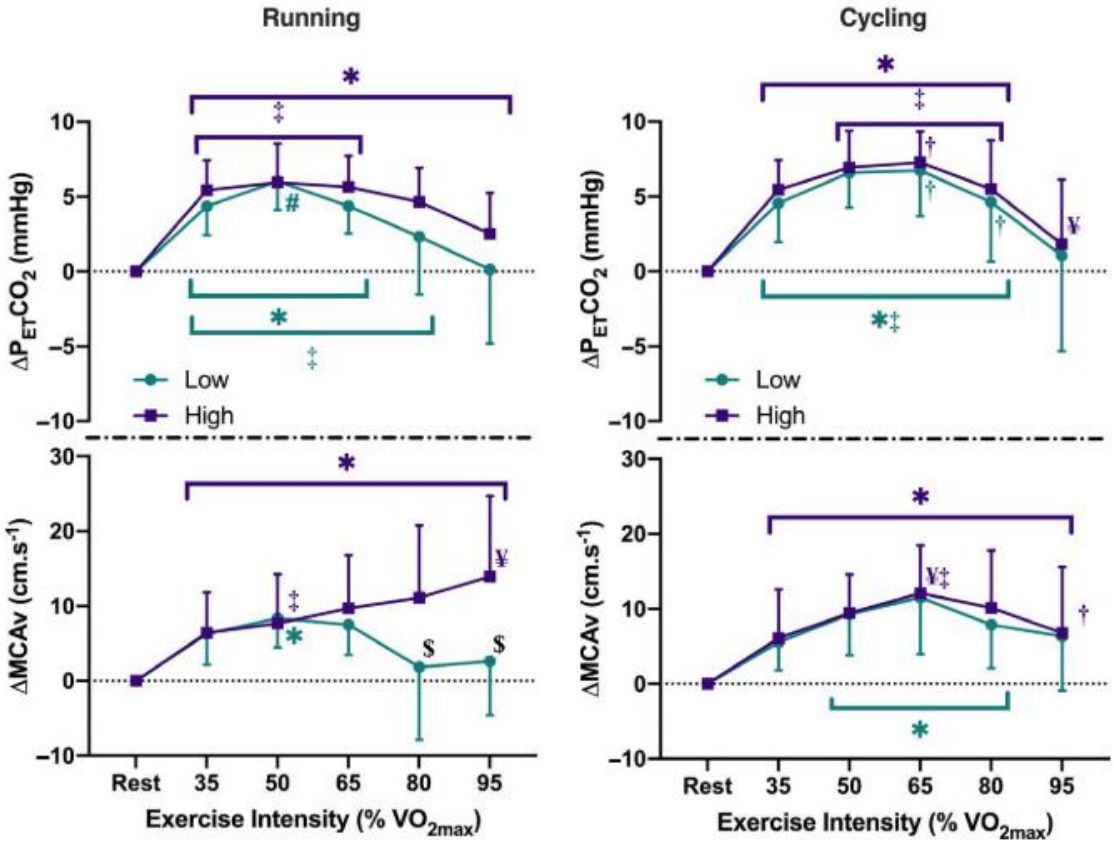

Figure 6 Comparison of change in partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) (top panels) and change in middle cerebral artery blood velocity (MCAv) from rest (bottom panels) during incremental running (left) and cycling (right) exercise (3-min stages at 35%, 50%, 65%, 80%, 95% VO2max), between participants characterized as high (male: >45 mL/min/kg; female: >40 mL/min/kg) or low fitness (male: <40 mL/min/kg; female: <35 mL/min/kg) (Furlong et al., 2020).

2.3 Resistance Exercise

RE can be divided into two different modalities, static and dynamic. Static RE, also known as isometric exercise, is a sustained muscle contraction (e.g., 30 seconds) with no change in muscle length or joint angle (Perry & Lucas, 2021). Dynamic RE consists of concentric and eccentric muscle contractions performed repeatedly in a cyclic manner. The completion of one contraction cycle in dynamic RE is termed a repetition (rep), and a set is a number of reps performed consecutively without rest (Schoenfeld, 2010). During both static and dynamic RE exercise the VM can dominate the within and post-exercise haemodynamic response (Pott et al., 2003). As such, the role of the VM is an important consideration when investigating the haemodynamic response to RE.

2.3.1 Valsalva Manoeuvre

A Valsalva manoeuvre is a forced expiration against a closed glottis (Junqueira Jr, 2008) which increases intrathoracic pressure (Tiecks Frank et al., 1995). A person would engage in a VM when performing any activity that requires bracing e.g. coughing (Chao et al., 2007), defecation (Sikirov, 1990) or childbirth (Vaziri et al., 2016). The VM can also be used clinically in the treatment of supraventricular tachycardia (Appelboam et al., 2015; Gaudart et al., 2021) and as an assessment for ANS function (Low, 2003). There are four distinctive phases of the VM. Phase I is characterised with the initial increase in blood pressure at strain onset with Phase IIa defined by the first decrease in blood pressure that immediately follows as venous return is impeded by the elevated intrathoracic pressure. The reduction in blood pressure triggers the baroreflex which causes vasoconstriction and increases HR (phase IIb) (Remmen et al., 2005). Once the strain is terminated, there is a rapid decrease in MAP (phase III) (Tiecks Frank et al., 1995), and the overshoot observed in blood pressure is the defining characteristic of phase IV as the now restored cardiac output is ejected into a constricted arterial tree.

The role of the VM during RE is complicated (see **Figure 7**). Current recommendations indicate the VM should be avoided during RE in healthy adults (Garber et al., 2011) as it exacerbates the within-exercise MAP. The VM is recruited when lifting weights ≥80% of maximal voluntary contraction (MVC) or during repetitive efforts when approaching fatigue (MacDougall et al., 1992). The VM associated

increase in intrathoracic pressure assists in stabilising the spine and the trunk that allows for an increase in lifting capacity and safety (Hackett & Chow, 2013). However, engaging in the VM during heavy exercise can lead to symptoms like light-headedness or dizziness (Gaffney et al., 1990; MacDougall et al., 1985).

Perry, Mündel, et al. (2014) investigated the effects of graded VMs on cerebrovascular response at the intensities of 30%, 60%, and 90% at a duration of 5 s and 10 s and found that higher intensity during 10 s VMs elicited syncope in healthy individuals. The greatest Phase III reduction in MCAv being observed following 90% VM with a simultaneous reduction in MAP. Furthermore, engaging in the VM whilst standing can exacerbate the reduction in MAP and therefore MCAv when compared to a seated and supine position (Pott et al., 2000; Singer et al., 2001).

Perry et al. (2020) study on cerebrovascular haemodynamics during isometric RE with and without the VM reveals that during isometric RE the VM initially limits the increase in $MCAv_{mean}$. However, after the strain is released, the VM challenges the regulation of MCAv, resulting in lower MCAv compared to exercise alone. The VM induces phase-dependent changes in MCAv, and MAP is reduced when combined with static RE. Combining the VM with resistance exercise helps maintain stable blood flow, reducing the usual increase in MCAv seen after the manoeuvre (Phase IV). Though engaging in the VM is not recommended, it may protect the cerebral vasculature by reducing the transmural pressure which results in a smaller increase in CPP during high-intensity RE (Haykowsky et al., 2003). The use of the VM exacerbates the fluctuations in MAP and increases the risk of intracranial aneurysm (Vlak et al., 2011). However, the most common risk involved with RE is post-exercise hypotension and syncope (Halliwill et al., 2014).

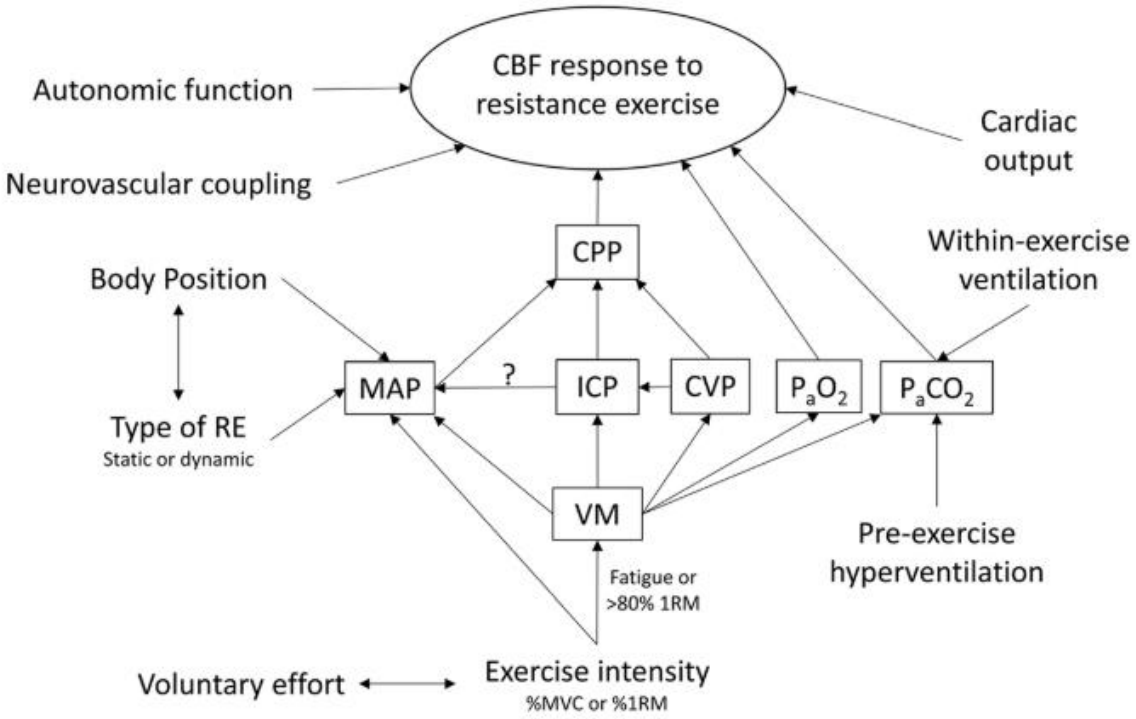

Figure 7 Summary of the physiological regulators of cerebral blood flow (CBF) during RE. RE resistance exercise, CPP cerebral perfusion pressure, MAP mean arterial blood pressure, ICP intracranial pressure, CVP central venous pressure, $PaCO_2$ the partial pressure of arterial carbon dioxide, PaO2 the partial pressure of arterial oxygen, VM Valsalva manoeuvre, MVC maximal voluntary contraction and 1RM one repetition maximum (Perry & Lucas, 2021).

2.3.2 Blood Pressure Response – During Static Resistance Exercise

Static and dynamic RE elicit diverse blood pressure responses. As seen in **Figure 8**, at the onset of static RE, an intensity dependent gradual increase in MAP is observed, which continues to rise throughout the effort (McNeil et al., 2015). The initial increase in MAP at exercise onset is mediated by elevated SNS activity, which increases HR and systemic vasoconstriction to non-active musculature (Grotle et al., 2020). This is followed by a continued, intensity-dependent rise in MAP, driven by sustained sympathetic activation and mechanical compression of blood vessels in the contracting muscles, while dCA works to maintain stable cerebral perfusion despite the elevated blood pressure (Perry & Lucas, 2021).

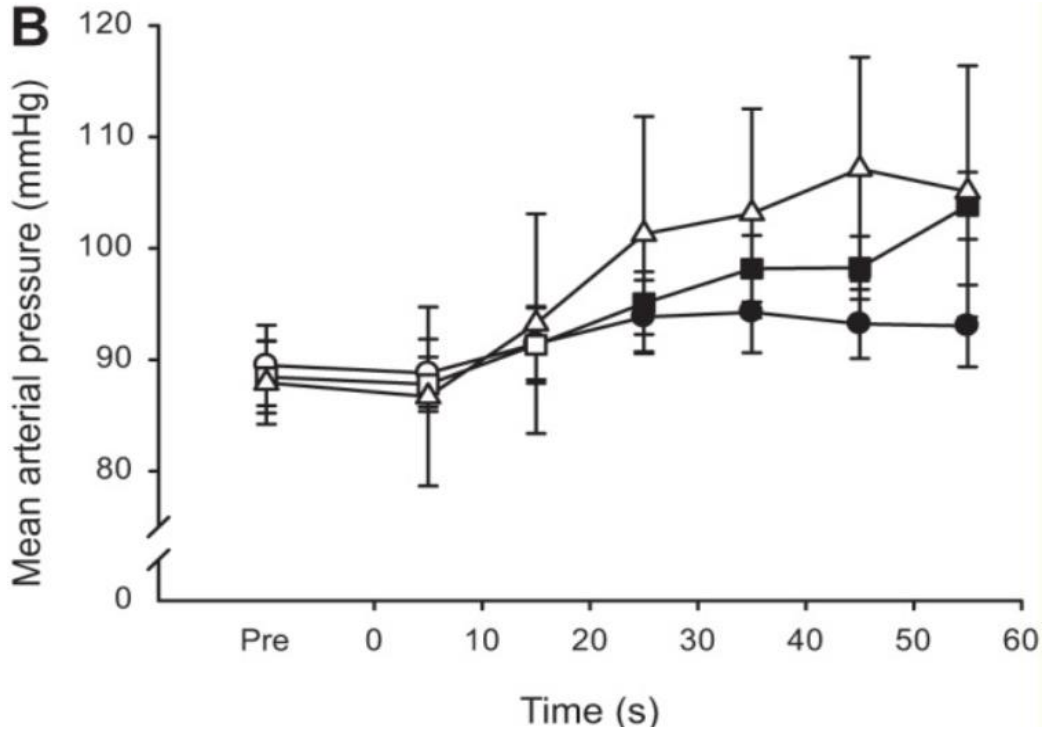

Figure 8 Static Resistance Exercise MAP Profile (McNeil et al., 2015), MAP during continuous isometric contractions at various levels maximal torque. Contractions were performed at 30 (O), 60 (□), and 100% (Δ) of MVC torque. Solid symbols indicate data points that are significantly different from Pre ($P < 0.05$).

2.3.3 Blood Pressure Response – During Dynamic Resistance Exercise

Dynamic RE produces sinusoidal fluctuations in blood pressure, as seen in **Figure 9**. The sinusoidal fluctuations in blood pressure are attributed to the cyclic nature of muscle contractions, throughout the movement. The blood pressure profile seen in **Figure 9** can be attributed to the mechanical compression of the arteries of the contracting musculature during the concentric phase which raises blood pressure. During the eccentric phase blood pressure declines as the arteries become decompressed (MacDougall et al., 1985). Blood pressure peaks at the greatest joint angle which corresponds to the transition from the eccentric phase to the concentric phase (MacDougall et al., 1992). The two significant factors that influence MAP during dynamic-RE are exercise intensity (MacDougall et al., 1992; McCartney et al., 1993) and the muscle mass recruited (Lewis et al., 1985; McCartney et al., 1993; Mitchell et al., 1980; Palatini, Mos, Munari, et al., 1989). Exercise intensity can increase by increasing load or reps (Mangine et al., 2015). Increasing either the load or number of repetitions increases the likelihood of engaging the VM. As mentioned above, at

intensities >80% of MVC the VM is unavoidable. Similarly, the VM may also be recruited in the latter repetitions of a set as the lifter begins to fatigue (MacDougall et al., 1992). Whilst the VM can act to stabilise the trunk during lifting, the utilisation of the VM exacerbates the within-exercise MAP response (MacDougall et al., 1992). Thus, extreme hypertension can be observed during large muscle mass exercise at high-intensity. Indeed, using direct arterial measurement MacDougall et al (1985) reported blood pressures of 480/350mm Hg for an individual and a cohort average of 320/250mm Hg during bilateral leg press in trained body builders.

The recruitment of larger muscle masses produces the greatest increase in blood pressure, as there is a greater demand for oxygen, which increases $\dot{Q}$, HR, and increased contractility, thus increasing blood pressure (Joyner & Casey, 2015). Increases in blood pressure during RE are credited to both an increase in systolic and diastolic pressures (Libardi et al., 2017; MacDougall et al., 1992; Niewiadomski et al., 2012; Poton & Polito, 2016). The number of repetitions within a set (Sale et al., 1993), within succeeding sets of the same exercise (Libardi et al., 2017), and when rest periods between sets are reduced (Paulo et al., 2019) also contribute to increase in MAP during RE. Though static and dynamic RE have different blood pressure responses, this thesis focuses on the effects of dynamic RE, therefore the response to dynamic RE will be presented in henceforth.

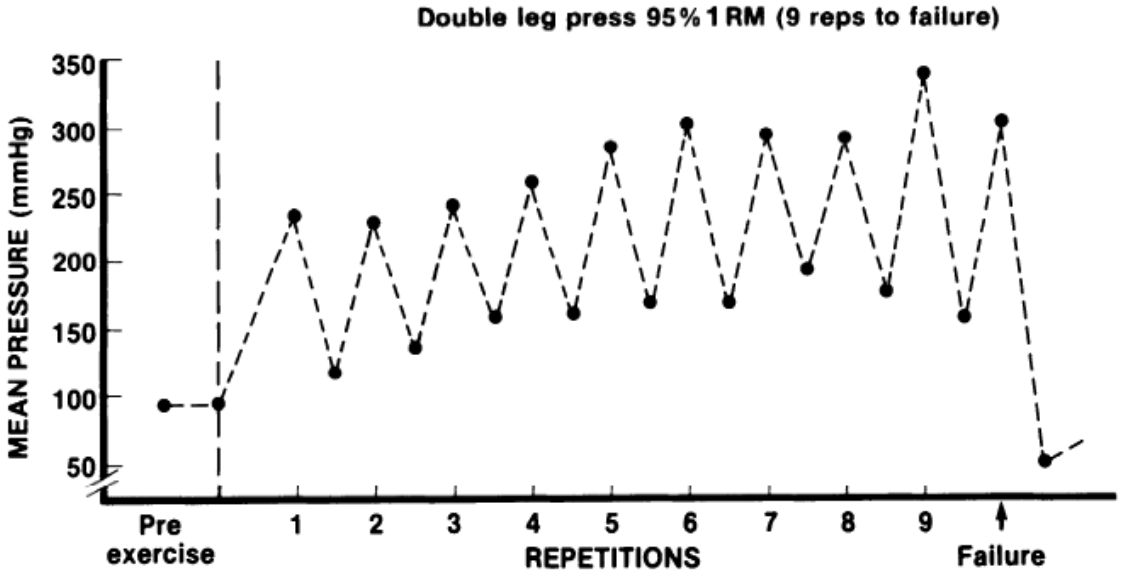

Figure 9 Dynamic Resistance Exercise MAP Profile (MacDougall et al., 1985), double leg-presses to failure at 90% of 1 repetition maximum (1RM).

High-intensity RE has been shown to elevate ICP, likely due to a combination of elevated MAP and muscle contraction-induced mechanical effects (Pott et al., 2003; Wilson, 2007). When the VM is superimposed on high-intensity RE, ICP is further elevated via increased intrathoracic and central venous pressures (Greenfield et al., 1981; Wilson et al., 1991), which can act to buffer the rise in transmural pressure across the wall of intracranial blood vessels. As described in section **2.3.1**, the VM is recruited at intensities >75% 1RM (MacDougall et al., 1992; MacDougall et al., 1985). This rise in ICP may serve to attenuate the increase in transmural pressure, potentially protecting the cerebral vasculature from excessive mechanical stress during acute hypertensive responses to RE. However, the recruitment of the VM during RE adds complexity to the interpretation of cerebrovascular responses, as both MAP and ICP are elevated concurrently and thus the exact CPP during RE is unclear. Given this, the present thesis deliberately employed moderate RE intensities and instructed participants to avoid the VM by maintaining paced breathing throughout exercise, further described in section **4.2.4**. This was done to reduce confounding influences on ICP and CPP, allowing for clearer interpretation of cerebrovascular responses without the additional effects of VM.

2.3.4 Cerebrovascular Response – During Dynamic Resistance Exercise

During the concentric phase of a bilateral leg press at 95% of 1RM to failure, a four-fold increase in blood pressure has been observed (MacDougall et al., 1985), which exceeds the proposed upper cerebral autoregulation limit (Lassen, 1959). The rapid fluctuations observed in blood pressure during dynamic RE are too fast for CA to counteract, reflecting the high-pass filter nature of the cerebral vasculature (Hamner et al., 2019). Therefore, changes in MCAv closely reflects what is observed in MAP during the leg press (Edwards et al., 2002; Moralez et al., 2012; Romero & Cooke, 2007), leg extension (Koch et al., 2005) and squatting with additional load (Perry, Schlader, et al., 2014). Although blood pressure reaches extreme values during RE, it is the magnitude and rate of change in MAP that determines the cerebrovascular response (Edwards et al., 2002; Koch et al., 2005).

Regarding the change in MCAv during RE in RE-trained individuals, the results of past studies are inconsistent, as some report an increase (Koch et al., 2005; Moralez et al., 2012; Perry, Schlader, et al., 2014; Romero & Cooke, 2007), a decrease

(Dickerman et al., 2000), or no change (Edwards et al., 2002). Edwards et al. (2002), Moralez et al. (2012) and Romero and Cooke (2007) all used the leg press exercise to challenge CBF regulation, at an intensity of 80 – 100% of 1RM. Despite these intensities the authors suggest that no VM was recruited, Edwards et al. (2002) working intensity of 75% of predicted MVC for 10 reps could entice the use of the VM in the latter reps of the set. However, the participants of this study only performed one set of 10 reps at 75% of predicted MVC and VM was not reported. Recruiting the VM during high-intensity loads in elite level resistance trained individuals saw a 25% decrease in $MCAv_{mean}$ (Dickerman et al., 2000), however, the authors did not report $PaCO_2$ or $P_{ET}CO_2$ as a proxy. As CO_2 is a potent regulator of MCAv, it is unclear what is driving the reduction in $MCAv_{mean}$. Moreover, previous studies investigating the cerebrovascular response to dynamic RE have typically reported the mean value of MCAv and MAP across the exercise set which does not take into consideration the nature of the response i.e. the zenith and nadir of each wave. Perry, Schlader, et al. (2014) study on hemodynamic responses to upright RE in RE-trained males found that $MCAv_{mean}$ and MAP were elevated during exercise, however, it was only the increase in MAP that was dependent on the load lifted and number of repetitions. Though $MCAv_{mean}$ did follow the pattern of MAP, the magnitude of increase did not match that of MAP. Perry, Schlader, et al. (2014) reported that the peak (zenith) $MCAv_{mean}$ was not different between loads lifted (30, 60 and 90% of the 6-repetition maximum). However, the magnitude of these changes (e.g. zenith to nadir difference) was not reported, nor was this data reported for MAP. The reporting of the zenith, nadir, and zenith to nadir difference could provide a more accurate representation of the haemodynamic variability occurring during RE exercise rather than using a simple mean of a given variable. The inclusion of these data may also help describe the haemodynamic change within-exercise (e.g. across a set of RE) and between individuals.

Braz et al. (2014) demonstrated that the overriding influence of $P_{ET}CO_2$ on CBF persists during RE. The authors observed that when $P_{ET}CO_2$ was clamped at baseline, $MCAv_{mean}$ was elevated during fatiguing static handgrip exercise. In contrast, when $P_{ET}CO_2$ was allowed to fluctuate naturally, these elevations in $MCAv_{mean}$ were not observed. This finding is particularly relevant because hyperventilation, a common pre-exercise breathing pattern used by some individuals before high-intensity lifts

(Compton et al., 1973) can lead to a reduction in $P_{ET}CO_2$. This is often followed by the VM, which may further impact CBF regulation during exercise. Romero and Cooke (2007) demonstrated that hyperventilation decreases $P_{ET}CO_2$ by ~8% which decreased exercise MCAv by ~39% during the leg press exercise at 80% of 6RM, absent of an immediate VM. Hyperventilation produces hypocapnia which improves dynamic CA (Aaslid et al., 1989). As a result, it is suggested that hyperventilation before exercise may reduce absolute CBF during RE and potentially enhance dCA, allowing changes in MAP to be more effectively buffered (Perry & Lucas, 2021). Hyperventilation and engaging in the VM changes the CBF-blood pressure relationship during RE, with the VM potentially providing a temporary protective mechanism by limiting the rise in MCAv.

2.3.5 Blood Pressure Response – Post Dynamic Resistance Exercise

Upon termination of RE a reduction in mean, systolic, and diastolic blood pressures is observed (Brown et al., 1994; Compton et al., 1973; de Vos et al., 2008; Fisher, 2001; Moralez et al., 2012; Romero & Cooke, 2007), with an increase in the pulsatility index (PI) (Lefferts et al., 2014). Following cessation of RE there is an increase in blood flow to the active musculature via functional hyperaemia (Sjøgaard et al., 1988), aided by a reduced transmural pressure (Rossberg & Peňaz, 1988). Contraction intensity (Walløe & Wesche, 1988) and frequency (Corcondilas et al., 1964) have also been seen to increase the extent of the hyperaemia. Perry, Schlader, et al. (2014) found load dependent hypotension immediately following upright squatting with the highest relative RE intensity generating the lowest absolute blood pressures. Furthermore, MAP time to recovery and time below baseline were larger following more intense RE. Studies investigating the effects of dynamic RE on hemodynamic responses have often used the lower limb exercise such as the leg press (Edwards et al., 2002; Moralez et al., 2012; Romero & Cooke, 2007), with only Perry, Schlader, et al. (2014) using the upright exercise of a squat. The leg press exercise puts the participant in a semi-recumbent position, which assists venous drainage, as the feet are positioned at or above heart level (Perry & Lucas, 2021), such that hypotension is not seen when the participant remains in a semi-recumbent position (Edwards et al., 2002). The upright position in combination with greater

exercise intensities exacerbates temporary post-exercise hypotension regardless of contraction type (Perry & Lucas, 2021; Perry, Schlader, et al., 2014).

2.3.6 Cerebrovascular Response – Post Dynamic Resistance Exercise

Like the within response to RE, cerebrovascular responses following RE continues to be dominated by rapidly changing MAP, as cerebral hypoperfusion sufficient to cause syncope has been observed after heavy dynamic RE (Compton et al., 1973), attributed to a VM associated acute reduction in $\dot{Q}$, that initiates a rapid decline in MAP and CBF. Additionally, pre-exercise hyperventilation can critically reduce CBF throughout RE, exacerbating the risk of syncope (Romero & Cooke, 2007). Post-exercise, the magnitude of the reduction in MAP and $MCAv_{mean}$ are dependent on the intensity of exercise (load lifted as % of 1RM), but not on the number of repetitions (Perry, Schlader, et al., 2014). A recent study shows that dCA is modified by body position with reduced effectiveness when standing (Favre et al., 2019), compounding the effect of hypotension following upright exercise. The decrease in $MCAv_{mean}$ observed is credited to a selective decrease in diastolic blood velocity following exercise (Perry, Schlader, et al., 2014), also seen in pre-syncope (Schondorf et al., 1997).

Pre-exercise hyperventilation, despite improving dCA, decreases pre- and within-exercise MCAv (Compton et al., 1973; Romero & Cooke, 2007), which contributes to the increased risk of post-exercise syncope. Previous literature investigating the effects of acute RE on dCA found that immediately (<30 s) after exercise, dCA is temporarily disturbed (Koch et al., 2005). The authors found that immediately after exhaustive dynamic RE there was an increase in MCAv and PI, despite a reduction in MAP upon termination of exercise. The magnitude of the CBF reduction post-exercise is dependent on the load lifted when upright and closely follows MAP, with the largest and longest decrease in CBF seen after lifting the highest relative load (Perry, Schlader, et al., 2014). In the absence of hypotension, CBF is seen to decrease below baseline after RE in a semi-recumbent position, this further emphasizing that it is the change in MAP, not absolute MAP, that drives the CBF response (Edwards et al., 2002).

There are similarities between post-exercise hypotension following RE and orthostatic intolerance. Orthostatic intolerance is typified by venous pooling (Smit et al., 1999), which increases local venous pressure in the lower extremities but reduces central venous pressure (Harms et al., 1999), This decrease in central venous pressure, coupled with a reduction in systemic vascular resistance (Wieling et al., 2007) can lead to insufficient cerebral perfusion and symptoms of dizziness or syncope. This results in a rapid relocation of blood into the lower limbs with sudden decreases in MAP which exceeds the baroreflex control of vascular tone (Thomas et al., 2009). Compton et al. (1973) reported syncope after high-intensity upright Olympic style lifting (clean and jerk). The syncope observed could be attributed to the movement being done in an upright position with long straining periods due to the multi-phase nature of the clean and jerk. Furthermore, when in the upright position, the combination of pre-exercise hyperventilation, exercise-induced functional hyperaemia to muscles below heart level, and release of strain, jeopardises maintenance of CBF after RE (Perry, Schlader, et al., 2014; Romero & Cooke, 2007). Moralez et al. (2012) reported that during dehydration before dynamic RE, participants reported greater severity for light-headedness, when compared to being hydrated. Even though the dehydrated trial had a greater decrease in MCAv which decreased into the “symptomatic threshold” immediately after standing, MAP for both conditions was not significantly different. Pre- and within-exercise hyperventilation, and dehydration both contribute to post-exercise cerebral hypoperfusion, however, the rapid reduction in MAP likely underpins post-exercise syncope. It appears that being in the supine or seated position diminishes the likelihood of RE induced syncope as post-exercise MCAv and MAP reductions are lessened.

2.3.7 Neurovascular Coupling – During Resistance Exercise

During unilateral static RE, blood flow differs regionally and reflects the anatomical location of the corresponding or active motor areas. During a right-hand contraction, a 19% increase in the contralateral MCAv was observed, compared to no changes seen in the ipsilateral MCAv (Jorgensen, Perko, & Secher, 1992; Jorgensen, Perko, Hanel, et al., 1992; Linkis et al., 1995). Increases in blood flow to premotor and motor sensory areas have been observed during low-intensity static hand grip

(Friedman et al., 1991) and leg extension (Rogers et al., 1990), with no changes in global hemisphere flow. These local increases in blood flow are mediated by NVC and reflect elevated metabolism in active motor areas (Claassen et al., 2021). During the slow and continuous increases in MAP during static RE without the VM, the effect of NVC can be observed (Fernandes et al., 2016; Hirasawa et al., 2016; Imms et al., 1998). The slow progressive increases in MAP seen during static RE can be effectively countered by CA. The main variable that drives CBF during dynamic RE is MAP, however, during static RE NVC is the primary driver of CBF.

Whilst the effects of static RE on brain blood flow and NVC have been examined, no studies investigating the effects of dynamic RE on the contribution of NVC to CBF. As previously stated, dynamic RE elicits sinusoidal fluctuations in MAP which is too fast for CA to counteract. Furthermore, the MCA provides blood supply to 80% of the anterior circulation which includes the motor cortex (Alastruey et al., 2007; Chandra et al., 2017), making the MCA an important target when investigating NVC during exercise. Measurement of blood flow (or a proxy e.g., MCAv) bilaterally during unilateral RE would elucidate the contribution of NVC during dynamic RE by comparing active and non-active brain areas during a background of rapidly changing MAP.

2.3.8 Circulatory Adaptations to Dynamic Resistance Exercise

The circulatory adaptations to regular aerobic exercise have been well documented with increases in central arterial compliance, aerobic power, and maximal $\dot{Q}$ (Green et al., 2011; Hellsten & Nyberg, 2011). However, the circulatory adaptations to RE have not been thoroughly investigated. Habitual resistance training elicits vascular adaptations, including a reduction in central arterial compliance (increase in arterial stiffness) (DeVan et al., 2005; Kawano et al., 2006; Miyachi, 2013; Miyachi et al., 2004) and it is possible that these vascular adaptations extend to the cerebral circulation.

Miyachi (2013) conducted a meta-analysis examining the effects of RE intensity on arterial stiffness. This meta-analysis included eight studies and found that, overall, RE was associated with an ~11% increase in arterial stiffness. Notably, this increase was primarily observed in young individuals with low baseline levels of arterial stiffness.

More importantly, the meta-analysis highlighted that the increase in arterial stiffness was intensity-dependent, with high-intensity RE increases arterial stiffness, while moderate-intensity RE did not. The reduction in central arterial compliance observed with RE has been linked to higher MCA pulsatility at rest, suggesting a reduction in the pulsatile buffering capacity of the central arteries (Nakamura & Muraoka, 2018). This indicates subtle changes in the cerebral vasculature. As cerebrovascular compliance contributes to CA (Tzeng et al., 2011), there is a possibility that repeated hypertensive stimuli may alter cerebrovascular function. The true extent of these adaptations and potential improvements in CA may become evident under conditions of high perfusion pressures, or when the brain acquires a more effective range for autoregulation (Perry & Lucas, 2021).

The chronic effects of dynamic RE on CA has been investigated by Perry et al. (2019) using a cross-sectional approach. It was reported that aerobically trained and resistance trained individuals demonstrated similar dCA capacity during forced MAP oscillations during repeated squat stands at 0.10Hz and 0.05Hz. The study compared RE-trained against endurance trained and untrained with no differences in CA between groups. It is possible that the CA operates at a higher operating point in RE-trained individuals. Roy et al. (2022) conducted further analysis of the same dataset and participants from Perry et al. (2019), applying different analytical methods to assess CA, measuring CA using absolute ($\Delta MCAv_T/\Delta MAP_T$) and relative ($\%MCAv_T/\%MAP_T$) changes in MCAv and MAP with respect to time during repeated squat stands. The authors found that sensitivity to directional changes in blood pressure is present in the sedentary and endurance groups but absent in the RE-trained group during 0.10Hz frequency. Furthermore, they found that endurance athletes had a higher relative $\Delta MCAv_T/\Delta MAP_T$ during MAP decreases at 0.10Hz, indicating a reduced ability of dCA to adjust CBF during acute reductions in MAP. As discussed above, given the hysteresis pattern dCA exhibits, directional assessment of dCA may reveal specific adaptions. Indeed, these data indicate that the modality of exercise does influence CA and supports the hysteresis-like patterns in endurance trained and untrained participants but not in RE-trained participants during 0.10Hz squat-stand manoeuvres. Other studies found no difference in CA between RE-trained and endurance-trained (Perry et al., 2019) and healthy individuals (Brassard, Ferland-Dutil, et al., 2017), during hypertensive and hypotensive challenges of the squat-stand manoeuvre. These

inconsistencies highlight the need for further investigation into the direction-specific regulation of MAP by CA across different exercise modalities.

In a training study Thomas et al. (2021) found that RE, not endurance exercise, induced changes in cerebrovascular function. The authors conducted a randomised cross-over intervention consisting of 3 months endurance exercise, 3 months of RE, with a 3-month washout period separating the interventions. The resistance training programme included 3 weeks working on muscular endurance (60 – 70% 1RM), 3 weeks on muscular hypertrophy (70 – 75% 1RM), and 3 weeks on muscular strength (80 – 90% 1RM). The participants engaged in both upper body and lower body RE, alternating days. Cerebrovascular outcomes (MCAv and posterior cerebral artery velocity (PCAv)) were measured pre- and post- intervention on weeks 0, 12, 24, and 36. They reported that 3 months of RE, decreased pulsatility in the extracranial arteries and increased CVR in the intracranial vascular bed. The authors did not test the cerebrovascular response during RE, however, during the post-exercise acute (aerobic) exercise response test, MCAv was lower following the RE intervention compared to pre-RE intervention. During spontaneous blood pressure fluctuations there were no differences in CA post RE and endurance exercise interventions. Thomas et al. (2021) and Perry et al. (2019) used TFA as a way to measure CA, but with different methods of perturbing MAP. Thomas et al. (2021) assessed CA during spontaneous fluctuations in blood pressure, whereas Perry et al. (2019) measured CA using driven oscillations in MAP produced by the squat-to-stand manoeuvre. Similarly, Roy et al. (2022) also used the squat-to-stand manoeuvre, but assessed CA using both the absolute ($\Delta MCAv_T/\Delta MAP_T$) and relative ($\%MCAv_T/\%MAP_T$) changes in MCAv and MAP over time. These methodological differences complicate the ability to reach a consensus on the vascular adaptations that may result from habitual RE training. Although the studies share a common interest in measuring CA, the different techniques used to assess it could significantly influence the conclusions drawn. As there is currently no gold standard for measuring CA, this lack of methodological consistency presents a challenge in interpreting and comparing results within the field.

The inconsistencies pertaining to the results relating to dCA may be due to the different methods of measuring dCA. A systematic review by Burma et al. (2024) identified eight different methods of measuring dCA which includes using the autoregulatory index (ARI), TFA, rate of regulation (RoR), rate of recovery, mean flow

index in response to CPP, mean flow index in response to MAP, and the ratio between MCAv/MAP as a percentage or absolute values. The TFA method has been the most frequently used. TFA holds the assumption that dCA acts as a linear system and requires an input signal and output signal to determine dCA (Kostoglou et al., 2024). TFA measures coherence (fraction of MAP linearly relating to MCAv), gain (amplitude change in MCAv for a given change in MAP), and phase (difference in timing between MCAv and MAP waveforms) (Panerai, Brassard, et al., 2023). Though TFA is commonly used, there are still discrepancies in the techniques to induce the driven changes for TFA, which include repeated squat-stands, deep-breathing, oscillatory lower body negative pressure, and sit-to-stand (Burma et al., 2024). The systematic review by Burma et al. (2024) found the squat-stand manoeuvre to be the best at producing driven changes to MAP and had a consistently high coherence compared to the other techniques. However, currently no gold standard measurement of dCA exists, making comparisons between data sets difficult. Furthermore, there is no normative data for comparisons between cohorts.

2.4 Summary

To date there have been few studies investigating the cerebrovascular response during dynamic RE, with past literature reporting conflicting results on the MCAv response during dynamic RE and failing to come to a consensus. Much of the previous research investigated cerebrovascular response during dynamic RE using RE-trained individuals neglecting the healthy untrained population. Comparing the difference between the two cohorts would distinguish possible differences in the cerebrovascular response to dynamic RE that could inform possible adaptations from repeated exposure to the fluctuations in blood pressure induced by RE. Moreover, these data could then be used to inform safe practice for those new to RE. More recently studies have investigated the adaptations that occur in response to dynamic RE and the consequences of those adaptations on cerebrovascular health. More specifically functional adaptations of the cerebral vasculature in habitually trained RE individuals that may act to counter the rapid perturbations in blood pressure seen during RE. However, most of the studies investigating the chronic adaptations to dynamic RE have not examined the within RE response. As suggested by Perry and

Lucas (2021), the cerebrovascular adaptations to RE may be elucidated during RE itself. However, there is no current data supporting this hypothesis for within and post RE.

CBF regulation is influenced by more than just dCA; NVC also plays a significant role in adequately perfusing active brain areas. Previous studies have primarily used static RE to explore the contribution of NVC to CBF regulation, with little focus on dynamic RE. Investigating potential differences between the contralateral and ipsilateral sides of the brain during unilateral dynamic RE could provide valuable insights into the regional CBF responses. This could be particularly useful for guiding safe RE prescription in clinical populations, where one side of the body may be weakened or paralysed (e.g. stroke).

This literature review highlighted the complex nature of CBF regulation. The contribution of NVC to CBF needs to be investigated to further understand if homogenous flow exists during dynamic unilateral RE. Also, it is now known that CA is not as effective as once believed, as the rapid changes in MAP elicited by dynamic RE are too fast for CA to counteract, thereby challenging CA. A common stressor such as dynamic RE can elicit these rapid sinusoidal fluctuations to MAP, which challenges the cerebral circulation. Whether the brain adapts to repetitive exposures to these fluctuations in MAP and therefore MCAv is not clear. Furthermore, if vascular adaptations do occur whether it is present during RE, or post-exercise regulation needs to be investigated further.

Chapter Three: Research aims and hypotheses

The research presented in this thesis builds upon the existing gaps in the current literature as indicated in the literature review (**Chapter Two**). Namely, the need for further investigation into the cerebrovascular response during dynamic RE and the subsequent stand following dynamic RE. Furthermore, research was required to determine the contribution of NVC to CBF regulation during dynamic RE. Therefore, the aim of this thesis was to investigate the cerebrovascular response during and immediately following dynamic RE. More specifically, the objectives for this thesis were to investigate the:

1) Effect of habitual RE training on the cerebrovascular response to dynamic RE induced sinusoidal fluctuations in blood pressure (**Chapter Five**),
2) Effect of habitual RE training on the cerebrovascular response to orthostasis induced post-dynamic RE hypotension (**Chapter Six**), and
3) Cerebral haemodynamic response to unilateral dynamic upper body RE in healthy individuals (**Chapter Seven**).

Each Experimental Chapter has hypotheses aligning with each of the objectives stated above.

Chapter Four: Methods and Techniques

This thesis examined the effects of RE on CBF, therefore, accurate and continuous measures of both CBF and MAP were needed to determine the relationship between RE and CBF. This chapter describes the main equipment used for data collection, as well as a description of the study design, and the RE utilised. This chapter is separated into two parts, the first detailing the two primary devices used for data collection: the TCD for the non-invasive measurement of blood velocity in intracranial arteries, and the Finometer for the non-invasive measurement of ABP. The second part explains the general methods used throughout the three experimental chapters. There are methods and statistical analyses that are unique to each experimental chapter. As such, these unique methods are discussed in the respective experimental chapters (Chapters **Five**, **Six** and **Seven**).

4.1 Techniques and Rationales

4.1.1 Measurement of Cerebral Blood Flow

The measurement of CBF is challenging, with existing methods for measuring absolute CBF being expensive and invasive having poor temporal resolution. For example, the Kety-Schmidt method for measurement of global CBF by tracking nitrous oxide gas uptake in the brain requires blood samples for calculation (Kety & Schmidt, 1948b). In addition, the Xenon clearance technique involves participants inhaling radioactive xenon, and detectors track the xenon washout from brain tissue to estimate flow (Lassen, 1985). Similarly, Positron Emission Tomography uses a radioactive tracer to produce detailed, time-averaged images of regional blood flow in the brain, reflecting metabolic activity and allowing researchers to assess functional changes in specific areas (Kuttner et al., 2021). These methods provide important CBF measurements, especially during the early studies of CBF regulation. However, the TCD allows non-invasive, high temporal resolution monitoring of blood velocities within the intracranial cerebral arteries, capturing beat-to-beat changes which has permitted the investigation of dynamic responses in CBF.

Within this thesis, TCD (DWL, Compumedics, Germany) was used to assess blood velocity in the middle cerebral artery (MCAv) as a proxy for CBF (Aaslid et al., 1989). An ultrasound frequency of ≤ 2 MHz is used for TCD which allows the

penetration of the bones of the skull (Aaslid, 1986; DeWitt & Wechsler, 1988). Using a low-frequency transducer probe to insonate the artery of interest through a thin bone window also known as the “acoustic” window is needed for adequate insonation of intracerebral arteries (Willie et al., 2011). A common location used for insonation is the temporal window located above the zygomatic arch. The position of the temporal window permits measurements of large basal cerebral arteries such as the MCA, the ACA, and PCA (Aaslid, 1986; DeWitt & Wechsler, 1988). The bone is thin at the temporal window such that the ultrasound waves can penetrate the skull and permit the measurement of intracranial blood velocity in the arteries previously described. Most importantly, as the TCD can measure beat-to-beat changes in blood velocity, an accurate account of the cerebrovascular profile during RE can be captured.

The TCD operates via a similar principle to other ultrasounds. The TCD probe is fixed in the same position over the acoustic window, via a headset. The ultrasound probe emits sound waves that are reflected off moving red blood cells (RBC), which are then detected by the transducer. The resultant Doppler shift is proportional to the velocity of the RBCs (Aaslid, 1986; DeWitt & Wechsler, 1988). When using the TCD the diameter of the vessel is not known, therefore, the TCD is measuring the velocity of RBCs within the insonated artery, not absolute volumetric flow. The calculation of true blood flow would require both the cross-sectional area of the artery and the blood velocity (**See Chapter 2 Section 2.1**). Since TCD cannot measure arterial diameter, it assumes that the diameter remains stable over time. Consequently, blood velocity serves as a proxy for blood flow only if the vessel diameter is indeed constant. Changes in arterial diameter would directly impact the relationship between velocity and flow (Ainslie & Hoiland, 2014), potentially leading to inaccurate estimations of true CBF. Furthermore, the large intracranial arteries are typically insonated using TCD, as these arteries deliver oxygenated blood to large regions of the brain. However, this means that the TCD has poor spatial resolution as the measurements are confined to these large feed arteries.

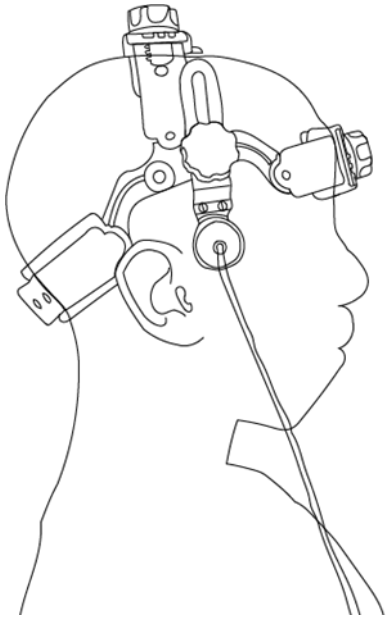

Figure 10 A lateral view of the transcranial Doppler ultrasound (TCD) on the acoustic window located above the zygomatic arch of the participant, held in place with the headset.

TCD uses spectral analysis and through a two-dimensional format presents three-dimensional Doppler data (Lyden & Nelson, 1997). On the horizontal scale, time is represented, whilst on the vertical scale frequency shift (velocity). Signal intensity is displayed as the colour or relative brightness of the trace. A 'spectral envelope' relating to the maximum blood velocity throughout a cardiac cycle is produced (Fodale et al., 2007). This is easy to create, even if the signal-to-noise ratio is low. Furthermore, TCD can be used in curved vessels, as the section most directly in line with the ultrasound beam has the greatest Doppler shift. Measurements are then made from the 'spectral envelope' (Moppett & Mahajan, 2004).

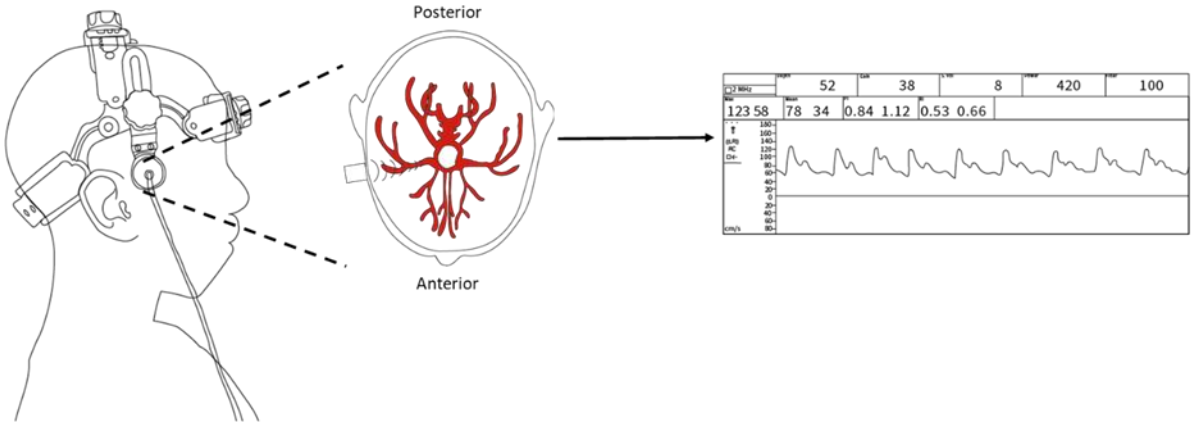

Figure 11 A horizontal cross-section of the skull, demonstrating the insonation of the Middle Cerebral Artery (MCA) when in use and the trace seen on the interfaced computer.

The TCD provides many advantages such as being easy to operate, inexpensive, and providing beat-to-beat measurements of intracranial blood velocity, however, there are some drawbacks to this method which are discussed in **Chapter Eight, Section 8.2**

4.1.2 Insonation of the Middle Cerebral Artery

Given its dominance in supplying the lateral cerebral hemispheres and regions involved in voluntary motor control of the face, upper limbs, and trunk, the MCA is the most appropriate and informative site for assessing cerebrovascular responses during RE. The MCA was the artery insonated in this thesis using the TCD technique. This section is a summary of the protocol used to insonate the MCA with guidance from Aaslid (1986); Aaslid et al. (1982), Moppett and Mahajan (2004) and Willie et al. (2014). First, an adjustable headset was placed on the participant's head to ensure that it was the right size and the right location for the probes. The transducer probe position on the participants differed because of the anatomical differences in the location of the MCA and the dimensions of the MCA itself. As described above (Section **4.1.1**) an important anatomical landmark for the insonation of the MCA is the temporal window which is located above the zygomatic arch. The probe was attached to the headset and situated in the middle of the temporal window approximately perpendicular to the estimated location of the MCA, with the depth set at 50 mm (Aaslid et al., 1982).

To improve the conductance and therefore the signal of the Doppler, ultrasound gel is applied on the transducer probe and the skin (Afzal et al., 2022). The DWL programme used for the measurement of MCAv for this thesis provided audible and visual cues that assisted in the location of the participant's MCA. The audible cue for the MCA was its unique high-pitched sound. The visual cues are the 1) red band in the M-mode indicating that blood is moving toward the probe. Blood flow in the MCA moves towards the probe and thus the blood velocity is described as positive by Panerai (2009) and 2) and the shape of the Doppler spectra waveform. When an audible or visual cue appeared, the probe head was adjusted until a better signal intensity was secured, which was reflected in the spectral envelope (see **Figure 12**) The movement of blood toward the probe was indicated by the red band in the M mode as seen in **Figure 12**. In the presence of laminar flow, the velocity of blood through a vessel is parabolic, with the fastest velocity in the middle of the vessel and the slower

velocities closer to the vessel wall (Levick, 2013) and the position of the probe is adjusted until the highest velocity has been established. Occlusion of the ipsilateral common carotid artery (CCA) can be used to confirm that the MCA has been located as the CCA is an upstream vessel of the MCA. Occlusion of the CCA would be reflected by a decrease in blood flow in the MCA during compression. Once the MCA was confirmed, the depth of the probe was reduced to track the M1 segment, which ranges between 45 – 60mm (Bathala et al., 2013), which is another identifier of the MCA. The probe was fixed into position once the MCA was insonated, this allowed for a constant insonation angle. The MCA was located during the familiarisation session, and the depth, gain, position, and angle of the probe were recorded for the subsequent trials. Furthermore, with the participant's consent, a photo was taken of the headset position and the probe position on both sides, to ensure that the probes were in the same position for the experimental trials.

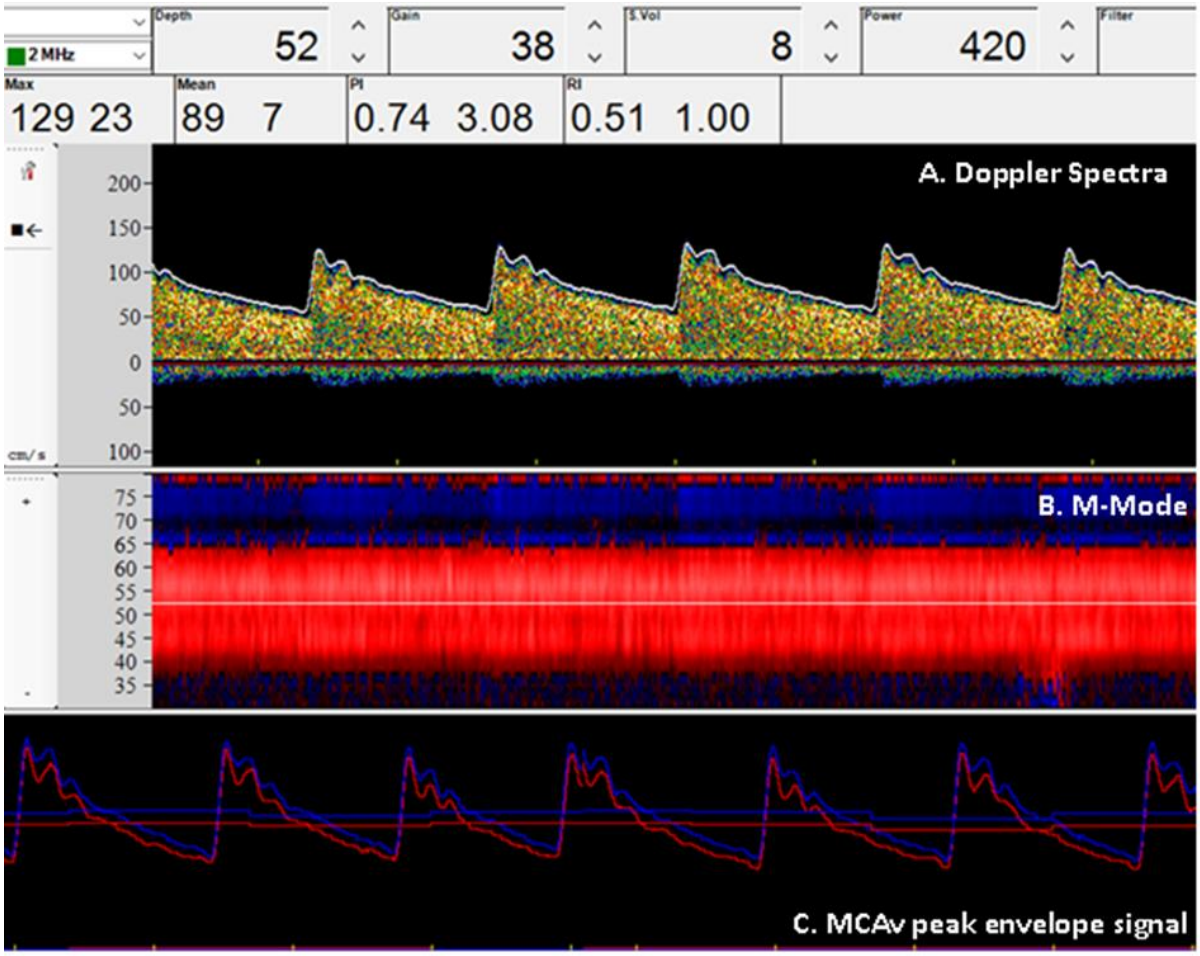

Figure 12 The right middle cerebral artery (MCA) is insonated with the transcranial Doppler ultrasound (TCD) probe. A: The Doppler spectrogram produced by the TCD B: M-mode Doppler. C: MCA peak envelope signal which can be exported for offline analysis (n = 1).

4.1.3 Calculation of Mean, Systolic, and Diastolic MCAv

The MCAv peak envelope signal seen in **Figure 12** above produced by the TCD was exported into the recording software, LabChart v8.1.13 ADInstruments, Australia. Using the velocity envelope the systolic MCAv (SMCAv) was identified as the maximum velocity for each cardiac cycle, and diastolic MCAv (DMCAv) was identified as the minimum velocity for each cardiac cycle. The $MCAv_{mean}$ was calculated using the mean waveform of the raw MCAv trace in LabChart.

4.1.4 Cerebrovascular Conductance

The cerebrovascular conductance index (CVCi) was calculated using the equation: $MCAv_{mean}$ / MAP. CVCi is used in the thesis because it contributes to the estimated changes in cerebrovascular tone. Lautt (1989) reported that changes in flow occur due to changes in vascular tone, conductance is more responsible for the change in vascular tone than resistance. For the thesis, cerebrovascular conductance was used to reflect changes in vessel tone using the calculation above.

4.1.5 Pulsatility Index

The Gosling PI for the MCA was calculated as SMCAv - DMCAv / $MCAv_{mean}$ (Gosling & King, 1974). PI was calculated as it provides information on the structural, functional, and haemodynamic conditions of the cerebral circulation and vasculature (Gao et al., 2019).

4.1.6 Measurement of Arterial Blood Pressure

The method chosen to measure ABP for this thesis is a non-invasive method using a Finapres (FInger Arterial PRESure), known as the Finometer (Finapres Medical Systems, The Netherlands). The Finometer provides beat-to-beat measures of finger blood pressure that are used to recreate a waveform like that of an intra-arterial recording (Carlson et al., 2019). The Finometer apparatus uses finger photoplethysmography (PPG), an optical measurement method to measure blood pressure (Chung et al., 2013), with the volume clamp method (or vascular unloading) first introduced by Penaz (1973). When the volume clamping method of Penaz is paired with the Physiocal criteria of Wesseling et al. (1986), this method provides reliable, non-invasive, and continuous measures of ABP.

4.1.7 Beat-to-beat arterial blood pressure

The Finapres begins with standardised step-wise increases in finger cuff pressure in a pulsatile manner and is then held constant until one beat is detected per step. At the final pressure step, the pressure inside the cuff increases beyond systolic pressure, depending on if the cuff pressure exceeds 100mm Hg. The unloading state of the arteries is determined by the maximal PPG pulsation during the maximal cuff pressure with the criteria to avoid venous pulsation (Boehmer, 1987). This unloading state also reflects MAP, and therefore the set point. Once this set point is established, the Physiocal begins to operate. The physiocal procedure occurs at regular time intervals up to 70 beats, this is where the set point is checked, and there is an interruption in the blood pressure tracing. The set point is adjusted if needed (Imholz et al., 1998).

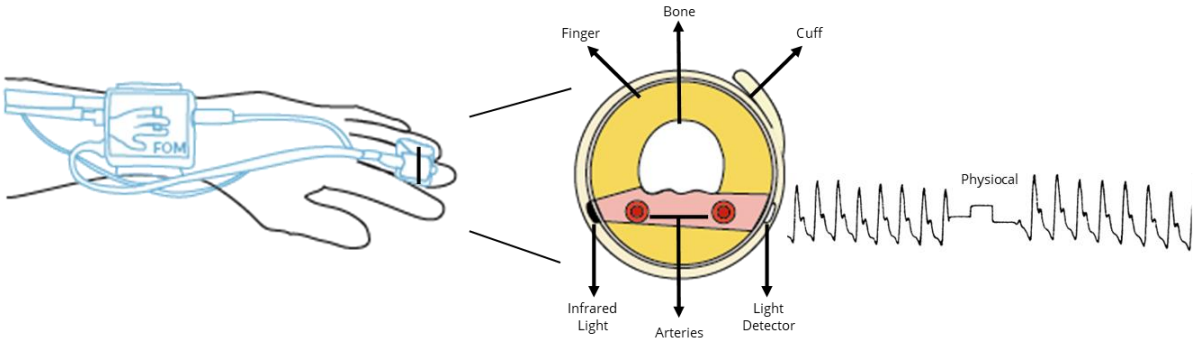

Figure 13 A cross-section of the finger in presenting the process of the Finometer during the procedure.

A criterion for a reliable measure is an interval of 30 or more beats between Physiocal calibrations (Truijen et al., 2012). The finger pressure that is shown by the Finometer is a reconstruction of the brachial artery pressure. A height correction unit is used with the Finometer, to correct for the difference in hydrostatic pressure when the hand is not at heart level. The height correction unit is placed in line with the right atrium of the heart. The hydrostatic difference is measured, and the recordings are continuously corrected to give blood pressure at the heart level. Finger arterial pressures closely resemble non-invasive brachial or radial measurements when the physiological waveform transformation values are reconstructed (Imholz et al., 1998).

Whilst the Finometer is a useful tool for capturing continuous, beat-to-beat blood pressure non-invasively, there are some limitations to consider. The accuracy of reconstructed brachial pressures can be affected by factors such as movement

artefacts or when the hand moves out of alignment with the height correction unit, particularly during dynamic tasks. Although the Finometer corrects for hydrostatic pressure differences, this correction assumes consistent vascular compliance and a stable waveform, which may not be maintained during periods of sympathetic activation or in individuals with altered vascular properties. While previous studies have shown that Finometer-derived blood pressure tracks well with intra-arterial measures at rest, accuracy is reduced during rapid changes in blood pressure or posture (Bogert & Van Lieshout, 2005). Therefore, while suitable for research purposes, especially in controlled settings, caution is warranted when interpreting Finometer data during dynamic conditions or in clinical populations.

4.1.8 Technique of Photoplethysmography

First, a measurement was made around the finger for cuff size selection. The finger cuff was placed on the middle finger at the middle phalanx for all participants as seen in **Figure 14** below. If the blood pressure tracing were unable to be obtained, the participant's hand would be warmed using a water bath and/or, an alternative (index finger) would be used. The cuff would be placed with the infrared light and the light sensor lined up to ensure a good signal (see **Figure 14**). The front unit was secured on the participant's wrist, loosely to not occlude flow. The height correction unit was taped on the ipsilateral side of the participant's arm at the level of the right atrium, after the height nulling procedure. Finometer blood pressure values were checked against an automated sphygmomanometer (Suresigns VM4, Philips Medical Systems, Philips, The Netherlands) periodically during baseline, and following RE.

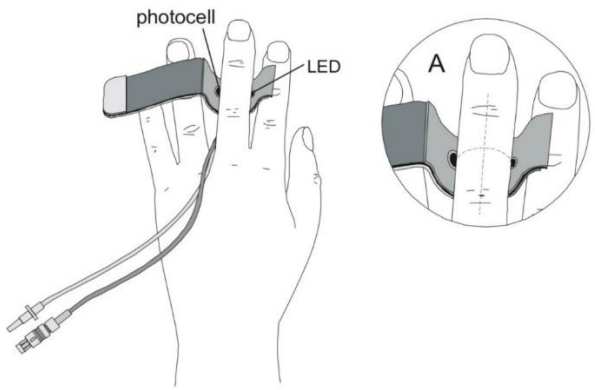

Figure 14 The application method of the finger cuff on the middle finger at the medial phalanx for the continuous measure of ABP (Finapres.com).

4.1.9 Calculation of Mean, Systolic and Diastolic Blood Pressure

The continuous blood pressure recordings during data collection were exported and presented in an interfaced computer via LabChart Software (v8.1.13 ADInstruments, Australia) and stored for offline analysis. Systolic and diastolic pressure was then established as the maximum and minimum pressures during a cardiac cycle. MAP was calculated using the equation 1/3 SBP + 2/3 DBP. MAP was calculated in this manner to allow for the calibration of the finometer-generated blood pressures against the automated sphygmomanometer values. If either SBP or DBP values of the finometer and automated sphygmomanometer were different by ≥5mm Hg, the exported finometer data were corrected in LabChart. Correction of the entire finometer blood pressure waveform is not possible, and thus the MAP cannot be calculated as the true mean of the waveform (e.g. as in the calculation of $MCAv_{mean}$). As mentioned above corrections were only made when necessary and during the resting (baseline) period.

4.1.10 Electrocardiogram

The standard three-lead electrocardiogram (ECG) was used to measure HR in this study. Electrodes were placed below the left and right clavicles, and below the ribs, in the lower left abdominal quadrant. The lead II R-R interval was used to calculate HR. Before applying the ECG electrodes on the participant, the skin was cleaned using an alcohol swab to remove any skin oils and improve the quality of the ECG signal. The raw signal was exported to LabChart.

4.2 General Methods

4.2.1 Ethics and Informed Consent

All participants were informed of the experimental procedures and aware of the purpose of this study, as well as the potential risks associated with participating. All participants provided written informed consent prior to partaking in the research. The study was approved by the Massey University Human Ethics Committee (SOA 21/22, see appendix A for the approval letter) and in agreement with the latest version of the Declaration of Helsinki apart from registration in a database. An information sheet was provided to the participants which outlined the entire experimental trials and instructions for the day of the trials.

4.2.2 Participants

An a priori power analysis (G*Power version 3.1.9.4; Heinrich Heine University Düsseldorf, Düsseldorf, Germany) was conducted using data from Edwards et al. (2002) and Moralez et al. (2012) with similar interventions (dynamic resistance exercise), design and outcome measures (i.e., MCAv and MAP). Based on conventional α (0.05) and β (0.80) values, a minimum of 24 participants (n = 12 per training group) was required. A total of 40 participants were recruited for the study, however, due to loss at follow-up, inability to insonate MCA, and unusable TCD traces (see **Figure 15**), a total of 30 participants (female = 16) were included in the studies (pooled mean ± SD: age, 26 ± 6 years, height 1.75 ± 0.10m, weight 74 ± 15kg, BMI 24 ± 5kg/m^2), with 15 participants in each group (see Table 1 for training group anthropometric data). All participants (n = 30) completed both experimental trials. All participants were healthy and free of any medical conditions, were not taking any form of medication other than oral contraception (RE-trained n = 1, untrained n = 3), or an intrauterine device (untrained = 1), were non-smokers, and had no history or symptoms of cardiovascular, pulmonary, metabolic, or neurological disease. The menstrual cycle phase was self-reported by female participants with all visits occurring during the early follicular phase (low oestrogen and progesterone) and during the placebo phase for those using oral contraceptives. Korad et al. (2022) and Favre and Serrador (2019) have previously reported no differences in functional cerebrovascular responses to acute changes in MAP and CA between menstrual cycle phases. The

participants also self-reported their habitual exercise regimen to be assigned to one of the following training groups:

Resistance-trained individuals: classified as having completed any modality (Olympic, bodybuilding or powerlifting) of RE training for ≥ 30 minutes, ≥ 3 times per week for ≥ 6 months prior to the experiment.

Healthy sedentary: ≤ 1 dedicated exercise session per week for ≥ 6 months prior to the experiment. This does not include regular physical activity e.g., activities that would be classified as low-intensity such as walking, gardening, low-intensity cycling (commuting) and general household chores. If the participants engaged in rowing, they were excluded from the study as rowing produces similar blood pressure fluctuations to RE (Pott et al., 1997).

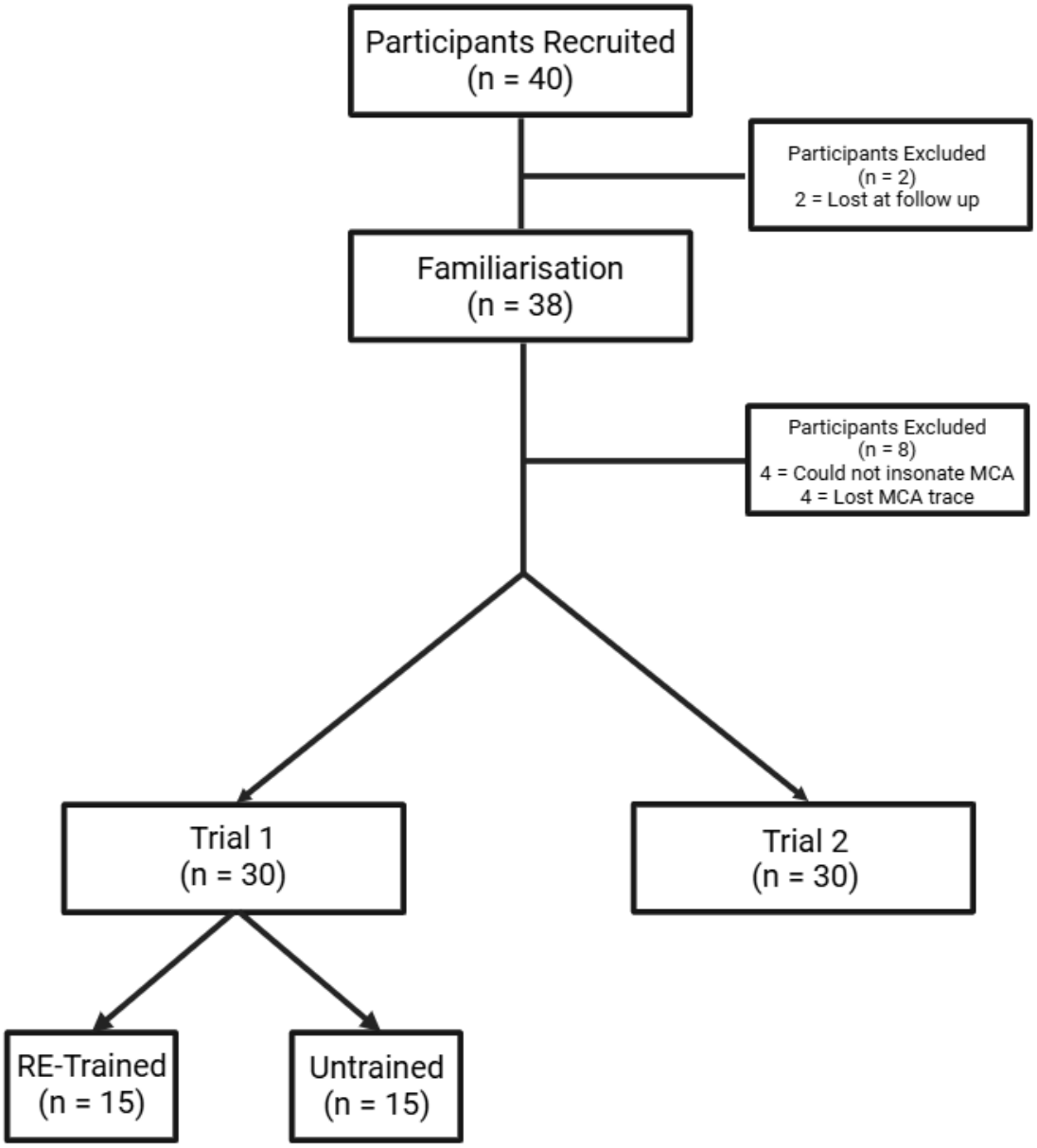

Figure 15 Summary of study design and participant progression, exclusions, and numbers in the analysed data set. For the purpose of this figure, the trials were numbered, however, for the actual experimental trials the order was randomised. Trial 1 refers to experimental **Chapters Five** and **Six**, whilst Trial 2 refers to experimental **Chapter Seven**.

Table 1 Participants Anthropometric and Strength Measurements

Variables	RE-Trained	Untrained	*P value*
Sex (Male: Female)	(11:4)	(3:12)	N/A
Age (years)	26 ± 7	25 ± 6	0.683
Height (metres)	1.77 ± .09	1.72 ± .09	0.167
Weight (kg)	78 ± 15	71 ± 15	0.683
BMI (kg/m^2)	25 ± 4	24 ± 6	0.809
Leg Extension Predicted 1RM (kg)	76 ± 19	52 ± 15	**<0.001**
Leg Extension 60% of 1RM (kg)	44 ± 12	30 ± 8	**<0.001**
RE Experience (months)	49 ± 45	-	-

Data are presented as Mean ± SD; (standard deviation); BMI, body mass index; 1RM, one repetition maximum; RE, Resistance Exercise; RE- Trained; Resistance Exercise Trained. The data included in this table was taken from the group data from Experimental **Chapter Five & Chapter Six**. Statistical significance was set at $P \leq 0.05$. An unpaired t-test was performed to compare training anthropometric, 1RM, and 60%1RM data.

4.2.3 Study design

All participants visited the temperature-controlled laboratory three times, once initially for familiarisation and two subsequent visits for the experimental sessions (see **Figure 16**). A full explanation and demonstration of the risks of participation, and equipment and procedures utilised in the experiment were given during the familiarisation session. Upon providing consent, the MCA contralateral to the exercising limb was insonated for the measurement of MCAv as described in **Section 4.1.2** . The distinction between absolute and relative loading is important when interpreting haemodynamic and cerebrovascular responses to RE. Absolute load refers to the total amount of weight lifted, whereas relative load reflects the weight lifted in relation to an individual's maximal strength (e.g., %1RM) (McCartney, 1999). In RE-trained individuals, higher absolute loads can be lifted at a given relative intensity compared to untrained individuals. This results in a greater pressor response in RE-trained individuals, marked by elevated MAP and sympathetic nervous system activity, due to increased mechanical compression of vessels, higher intrathoracic

pressure, and greater muscular engagement associated with heavier absolute loads (McCartney, 1999). A relative load of 60%1RM was used in this thesis to standardise the exercise stimulus across participants with varying strength levels. Pilot testing confirmed that this moderate-intensity load was sufficient to elicit sinusoidal fluctuations in both blood pressure and MCAv, indicating an appropriate physiological response. This intensity also ensured the protocol remained safe for untrained individuals while still providing an adequate stimulus for the RE-trained individuals. Therefore, the participant's unilateral leg extension and bicep curl one repetition maximum (1RM, dominant side) was estimated using the Brzycki (1993) equation: Weight ÷ (1.0278 - (0.0278 × Number of repetitions)), and the working intensity for the trial, 60% of the 1RM (60%1RM), was calculated. 1RM was predicted rather than directly tested because there are many contributing factors that limit an accurate 1RM. When testing for 1RM multiple reps will be performed, therefore, muscle fatigue may occur, especially if the participants have not trained that muscle before (Niewiadomski et al., 2008). Furthermore, other factors such as starting weight, rest intervals, increment in weights, and criteria for acceptable lifts also restricts for accurate measures (Niewiadomski et al., 2008). Braith et al. (1993) highly recommended that novice lifters do not attempt 1RM testing as maximal lifting from a person with no experience would lead to muscle soreness and possible injury. The results from Dohoney et al. (2002) supported Braith's notion, as 21 participants out of 34 suffered from muscle soreness after 1RM testing. The participant practised executing the leg extension and bicep curl at 60%1RM whilst maintaining the requested pacing and breathing pattern outlined below in **Section 4.2.4** .

4.2.4 Experimental Protocol

The familiarisation occurred > 1 week before the first trial and the participant provided a written informed consent (see Appendix B) to participate in the study and a health screening test, to ensure the participants were able to participate in the study. All visits were separated by > 72 hours. The experimental outline is highlighted in **Figure 16** below.

Participants arrived at the laboratory having refrained from caffeinated beverages for 12 hours, vigorous exercise and alcohol consumption for ≥24 hours prior to testing. The participant was also instructed to consume 500 ml of water the night

before and 500 ml approximately 4 hours before the experiment to ensure euhydration (urine specific gravity, USG < 1.020).

As seen in **Figure 16**, on arrival of the experimental trial day, the participant was asked to provide a urine sample for USG analysis. The participant was then seated on a chair for instrumentation. Once instrumented the participant rested quietly for 20 minutes for initial baseline recordings. Upon completion of baseline measures the participant then completed a pre-exercise sit-to-stand for 1 minute before being transferred to the leg extension machine or bicep curl chair. Baseline values were continued for another 5 minutes, and immediately preceding each exercise set thereafter.

During the exercise trial for experimental **Chapter Five** and **Chapter** Six (a and b in **Figure 16**), the participant performed 10 repetitions (reps) of unilateral leg extensions. For experimental **Chapter Seven** (c in **Figure 16**), each participant performed 10 repetitions of unilateral bicep curl. The intensity for both exercises was 60%1RM, with the repetitions completed to a tempo of 15 repetitions per minute, which equates to a repetition cycle length of 4s (2s per concentric and eccentric phase). Pilot testing revealed that the loading was appropriate for untrained individuals to complete the exercise without fatigue or recruiting the VM given the: 1) number of repetitions and sets 2) length of the rest periods between sets 3) slow controlled contractions and 4) paced breathing. Furthermore, a moderate load decreased the risk of injury in an untrained cohort. The breathing sequence was set to match the tempo of the exercise, with exhalation during the concentric phase (2s), and inhalation during the eccentric phase (2s). As such, all participants avoided the VM during all RE. The participant then rested for five minutes while baseline measures were taken, before repeating the sequence again until a total of four sets of 10 reps were completed for each exercise. Each participant was reminded of the breathing technique prior to each set, with the breathing and repetition timing aided by a metronome. The following criteria were used to ensure that the VM was not performed:

1) No indication of large and acute elevations in blood pressure, beyond what would be expected for the intensity of exercise as gauged by previous repetitions. Previous studies reported that when the VM is recruited during RE MAP (but not necessarily MCAv) is acutely elevated within the repetition (Perry et al., 2020; Perry, Schlader, et al., 2014).

2) Participant produced an expected capnograph that aligned with the paced breathing of the repetitions.
3) Participants were reminded of the exercise and breathing requirements for each set prior to completion.

During the stand section for Experimental **Chapter Six** ((b) in **Figure 16**), immediately following the completion of the 10 reps, the participant was instructed to stand and remain standing for 1 minute. During the stand, the participant was asked to remain standing quietly upright, with both feet parallel and on the floor and with as little movement as possible. If the participant felt dizzy or faint, they were instructed to sit down immediately. Once the 1-minute stand was completed the participant then sat back down on the leg extension machine or bicep curl chair and rested for five minutes while baseline measures were taken, before repeating the sequence again until a total of four sets of 10 reps were completed. A total of 40 reps were completed for **Chapter Five** and **Chapter** Seven, and a total of 5 sit-to-stands were completed for **Chapter Six**, with the first stand being the pre-exercise stand. A total of 5 sit-to-stands were also completed during the biceps curl trial, however, the data for this was not included in the thesis.

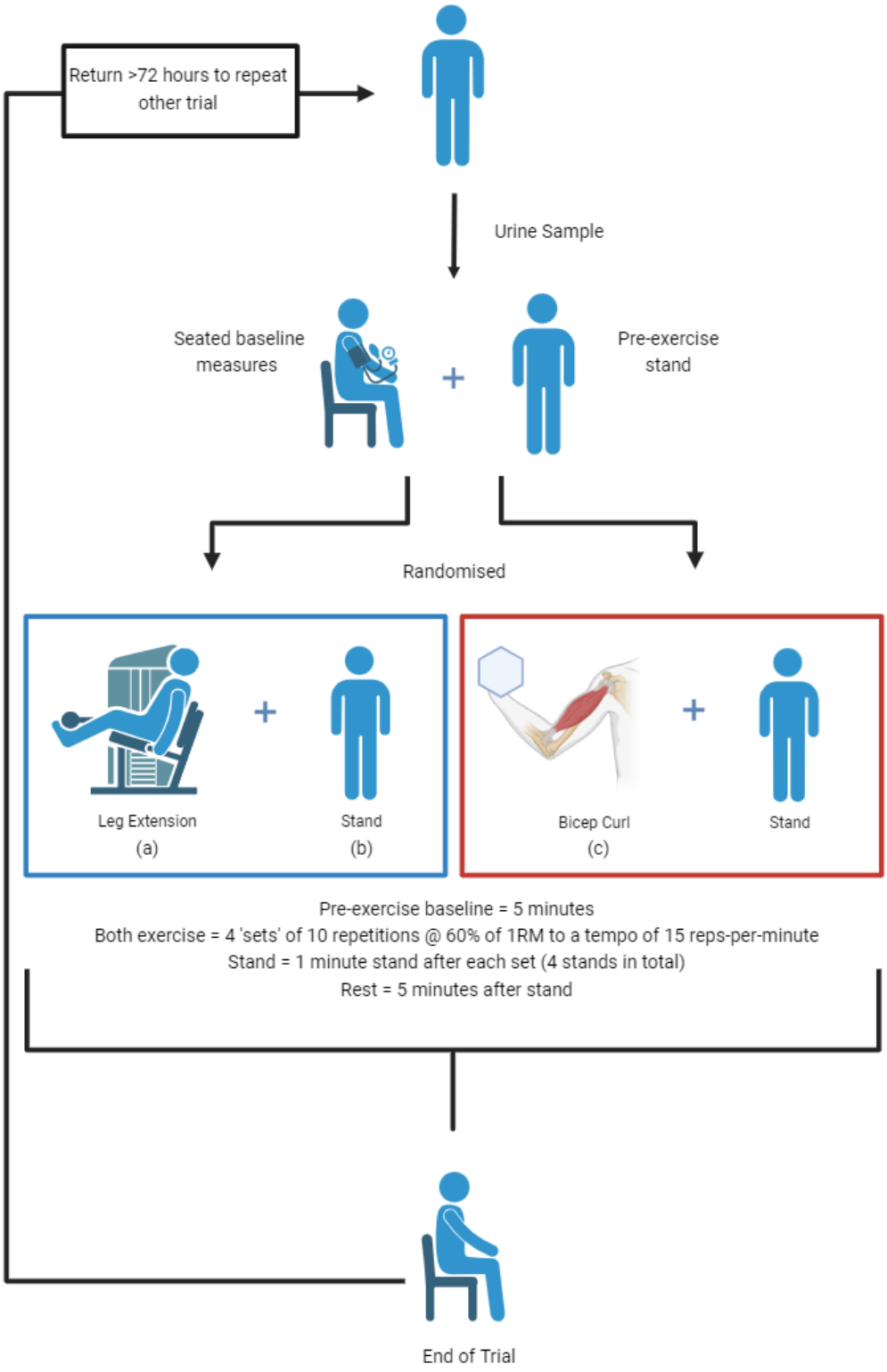

Figure 16 Experimental overview. The blue box highlights the leg extension trial, and the red box highlights the bicep curl trial. (a) denotes the section of the trial being analysed for experimental **Chapter Five**, (b) denotes the section of the trial being analysed for experimental **Chapter Six**, and (c) denotes the section of the trial being analysed for experimental **Chapter Seven.** A total of 5 sit-to-stands were also completed during the biceps curl trial, however, the data for this was not included in the thesis.

4.2.5 Systemic Haemodynamics

Heart rate was measured using a three-lead ECG (ADInstruments, Australia). Non-invasive beat-to-beat ABP was measured by finger photoplethysmography (Finapres Medical Systems, The Netherlands). The cuff was placed on the middle phalanx of either the middle finger or the index finger on the non-dominant hand using techniques described in **Section 4.1.8** above. The cuff was referenced to the level of the heart using the height correction unit as seen in **Figure 17**. During the familiarisation, the participants were instructed on the ways they could hold the leg extension grip without compromising the measurements of the Finometer. The Finometer was placed on the non-dominant hand, and the contralateral hand was used to grip the leg-extension machine or the dumbbell. The non-dominant hand rested on the participant's lap when they performed the exercise to prevent any movement or pressure artefacts in the blood pressure trace. Blood pressure values were checked against an automated sphygmomanometer (Suresigns VM4, Philips Medical Systems, Philips, The Netherlands) during baseline and 2 minutes following each exercise bout and corrected when necessary (see calculation of MAP above **Section 4.1.9** .

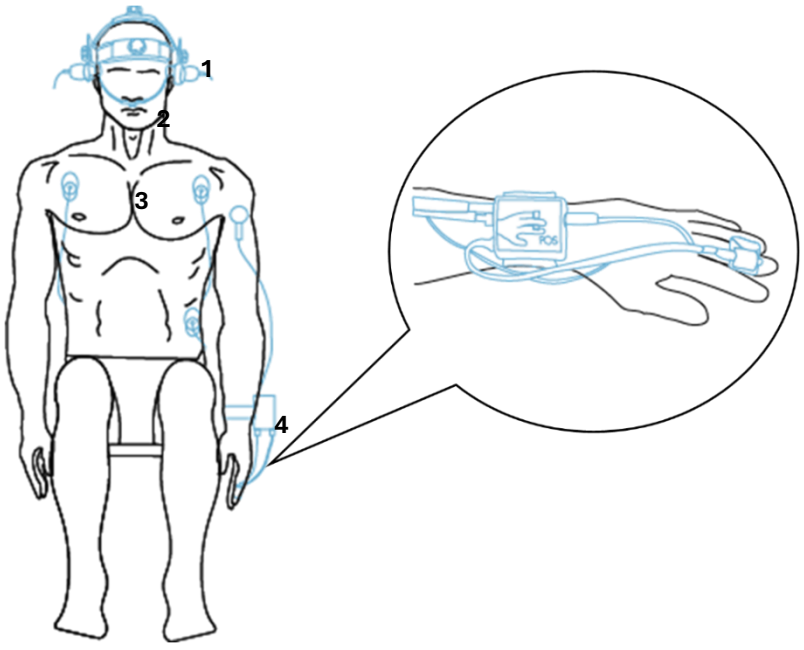

Figure 17 Instrumentation of 1. the Transcranial Doppler (TCD) ultrasound to measure middle cerebral artery blood velocity (MCAv, a proxy for cerebral blood flow), 2. Nasal Canula to measure End-tidal CO_2, 3. ECG electrodes to measure heart rate, and 4. the Finapres to measure beat-to-beat blood pressure.

4.2.6 Middle Cerebral Artery Blood Velocity

Blood velocity in the contralateral MCA to the exercising limb was measured using TCD (Doppler-Box X, DWL, Compumedics, Germany). The contralateral MCA was selected as the motor tracts decussate. Thus, it is possible that NVC, the matching of cerebral perfusion with local neuronal activity, would mediate a larger increase in the contralateral MCAv compared to the ipsilateral side, as seen in static handgrip exercise (Braz et al., 2014). Blood velocity in the M1 segment of the MCA was measured using a 2 MHz probe, fixed in position via an adjustable headband. The probe was fixed over the temporal window using search techniques described in **Section 4.1.2** above. Ultrasound gel (Tensive, Parker Laboratory, Fairfield, NY, USA) was placed between the transducer probe and the skin to ascertain the highest quality image. The average depth of the insonated MCA in the current study was 54 ± 4 mm in alignment with Bathala et al. (2013). Due to the inconsistencies in previous literature regarding the nomenclature describing CBF, CBF velocity, and the proxy measurements, middle cerebral artery blood velocity will be adopted herein as per the recommendation by Skow et al. (2022).

4.2.7 Partial Pressure of End-tidal Carbon Dioxide

$P_{ET}CO_2$ was measured using an online gas analyser (ML206 Gas Analyser, ADInstruments, Australia) and was collected throughout using a nasal cannula. The gas analyser was calibrated to a known gas concentration before each experiment.

4.2.8 Urine Analysis

Hydration status has been reported to influence cerebrovascular regulation (Moralez et al., 2012; Perry et al., 2016), therefore USG was used to confirm hydration status before each experiment using a handheld refractometer (Atago Co., LTD, Tokyo, Japan). All participants were instructed to consume 500 ml of water the night before and 500 ml approximately 4 hours before the experiment. Approximately 30 minutes before the commencement of the experiment USG was measured to confirm euhydration. If the participant did not meet the USG requirement, ~500 ml of water was given to the participant and USG was retaken 30 minutes after the consumption of water, until a value of <1.020 was returned.

4.2.9 Data Acquisition

All data were collected continuously using an analogue to digital converter (PowerLab, ADInstruments, Australia) interfaced with a computer and then analysed using LabChart software (v.8.1.13 ADInstruments, Australia).

Chapter Five: The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study

The work included in this chapter has been published in *Experimental Physiology*. The data, results, and key outcomes of the published work are unchanged within the chapter; however, the layout and formatting have been modified to fit within this thesis.

Korad, S., Mündel, T., & Perry, B. G. (2024). The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study. *Experimental Physiology*, 109, 1478–1491.

5.1 Introduction

There are many benefits of RE as highlighted in **Chapter One**, however, there are potential risks associated with RE, such as post-exercise syncope, however, those instances are rare (Edward & Cornwell, 2022). Case reports have described cerebrovascular events such as subarachnoid haemorrhage occurring during high-intensity RE, often in the context of the Valsalva manoeuvre and underlying vascular abnormalities (Haykowsky et al., 1996). Despite these isolated cases, the overall incidence appears to be extremely low, and large-scale data quantifying risk are lacking. Most evidence suggests that RE is safe for the general population when appropriately prescribed and performed. RE elicits large sinusoidal fluctuations in blood pressure that are reflected in MCAv, however, the brain is equipped with CA to offset these large fluctuations. Whilst CA is a potent regulator of CBF, as with any physiological system there is a delay between stimulus and response, with a ~ 5 s lag between the change in perfusion pressure and subsequent cerebrovascular response (Zhang et al., 1998). The inherent lag in the cerebral autoregulatory process generates a high pass filter, that is, higher frequency oscillations in blood pressure are translated to the cerebral circulation largely unbuffered (Zhang et al., 2002). Such a situation exists during dynamic RE where the rapid sinusoidal fluctuations in ABP are reflected in concurrent changes in middle cerebral artery blood velocity (MCAv) (Edwards et al., 2002; Perry, Schlader, et al., 2014; Romero & Cooke, 2007). Several studies have

suggested that the intermittent ABP extremes during high-intensity RE underpins the reduction in central arterial compliance following a single bout of RE (DeVan et al., 2005), and at rest in RE-trained individuals (Miyachi, 2013; Miyachi et al., 2004), with increased arterial stiffness associated with elevated cardiovascular disease risk (Mattace-Raso et al., 2006; Mitchell et al., 2010).

As the ABP profile during RE is translated to the cerebral circulation, it is unclear if habitual RE training, and the associated repetitive exposure to fluctuating ABP, illicit vasculature adaptations within the brain as occurs in the central arteries. We have previously reported that there was no difference between cerebral autoregulatory capacity between sedentary and RE-trained individuals, with only a trend for lower phase in the RE-trained group at a frequency of 0.05Hz (Perry et al., 2019). Further analysis of our data revealed that RE-trained individuals did not exhibit the hysteresis pattern of cerebral autoregulation, with only sedentary and endurance trained individuals exhibiting greater cerebral autoregulatory capacity during hypertensive challenges (Roy et al., 2022). Thomas et al. (2021), in a randomised and cross over study design, investigated the effects of endurance exercise and RE on cerebrovascular function and reported that RE increases cerebrovascular resistance and decreases pulsatility index (PI) at rest. However, Thomas et al. (2021) did not quantify the effect of habitual exercise on within-exercise RE responses. These findings collectively indicate that habitual exercise may subtly modify cerebrovascular function, yet the impact of habitual RE training on the within RE cerebrovascular responses has yet to be determined. The aim of this chapter as highlighted in **Chapter 3** was to assess the impact of dynamic RE on cerebrovascular responses in RE-trained and untrained individuals. It was hypothesised that RE-trained individuals would exhibit smaller fluctuations in MCAv during exercise compared to their untrained counterparts.

5.2 Methods

This chapter was part (a) of **Figure 16** (see **Section 4.2.4**) which consisted of the participants being assigned to two groups, RE-trained and untrained, depending on their training status. The experimental trial required the participants to complete 4 sets of 10 reps of the leg extension exercise at 60%1RM to a tempo of 15 reps-per-minute. After each set the participant rested for 5 minutes before performing the

exercise again. Baseline data were recorded initially (before exercise) and the immediately preceding each exercise set.

See **Chapter Four Section 4.2** for a detailed description of the techniques and methods used for this experimental chapter.

5.3 Data Analysis

Dependent Measures

The calculations for $MCAv_{mean,}$ MAP, CVCi, and PI was described in **Chapter Four Sections 4.1.3** ($MCAv_{mean}$), **4.1.4** (CVCi), **4.1.5** (PI), **4.1.9** (MAP). Additionally, pulse pressure (PP) was calculated as SBP - DBP. Given the sinusoidal haemodynamic profile during RE, the zenith and nadir $MCAv_{mean}$ and MAP values were identified for each repetition and the average values were calculated for each set. Additionally, zenith-to-nadir $MCAv_{mean}$ and MAP values was calculated as the zenith $MCAv_{mean}$ value – the nadir $MCAv_{mean}$ value and zenith MAP value – the nadir MAP during each repetition, respectively. The average zenith-to-nadir values for $MCAv_{mean}$ and MAP were calculated for each set.

5.4 Statistical Analysis

All data were analysed using SPSS statistical software version 28 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P \leq 0.05$. An unpaired t-test was performed to compare training anthropometric, 1RM, and 60%1RM data. A two-way mixed ANOVA was performed to analyse baseline measures (training x baselines, 2 x 5) and dependent variables of interest during dynamic RE (training x sets 2 x 5 when initial baseline is included as with mean data, and 2 x 4 when within-exercise only data was analysed e.g. Zenith $MCAv_{mean}$). An unpaired T-tests were used for post-hoc comparisons, and a Bonferroni correction factor was used when necessary. Partial eta square (partial $\eta 2$) was reported for the training by set interaction only, with large effect sizes identified as > 0.149, medium 0.059 - 0.138, and small <0.010 (Cohen, 2013). All data were displayed as the mean ± SD.

5.5 Results

Participants' anthropometric and exercise measurements are presented in **Table 1**. There were no significant differences in the anthropometric measurements

between the RE-trained and untrained, however, RE-trained had a greater predicted 1RM and 60% of 1RM versus their untrained counterparts (see

Table *1* in **Chapter Four Section 4.2.2** for *P* values). The RE-trained group trained for 49 ± 45 months, ranging from 6 – 144 months of continuous resistance training.

Baseline measurements

Baseline measures for the initial baseline immediately following instrumentation and baseline prior to each set are shown in **Table 2**. There were no significant main effects of training or training by set interaction for any baseline variables between groups. However, except for HR, there was a main effect of set for all variables, whereby both training groups demonstrated equal ‘drift’ in the baseline variables.

Table 2 Resistance-Trained versus Untrained Baseline Cerebrovascular and Cardiovascular Measures

Variable	Training group	Baseline period					*P* value			Partial η^2
		Initial	Prior to Set 1	Prior to Set 2	Prior to Set 3	Prior to Set 4	Training	Set	Interaction	
$MCAv_{mean}$ (cm s^{-1})	RE-Trained	65 ± 8	68 ± 11	67 ± 10	66 ± 10 [b]	65 ± 10 [b]	0.274	**<0.001**	0.866	0.011
	Untrained	69 ± 11	72 ± 11	71 ± 11	69 ± 11 [b]	69 ± 11 [b]				
MAP (mm Hg)	RE-Trained	82 ± 10	86 ± 12 [a]	87 ± 13 [a]	87 ± 11 [a]	90 ± 12 [a]	0.628	**<0.001**	0.945	0.007
	Untrained	81 ± 6	84 ± 9 [a]	86 ± 8 [a]	85 ± 8 [a]	88 ± 8 [a]				
CVCi (cm s^{-1} mm Hg^{-1})	RE-Trained	.81 ± .15	.80 ± .17	.78 ± .17	.77 ± .18 [a b]	.76 ± .20 [a]	0.366	**<0.001**	0.881	0.010
	Untrained	.86 ± .14	.86 ± .13	.783 ± .14	.81 ± .12 [a b]	.80 ± .14 [a]				
PP (mm Hg)	RE-Trained	55 ± 10	54 ± 10	56 ± 11	54 ± 10 [c]	52 ± 11 [c]	0.501	**0.026**	0.907	0.009
	Untrained	57 ± 13	57 ± 12	58 ± 14	57± 13 [c]	56 ± 14 [c]				
PI	RE-Trained	.84 ± .13	.81 ± .14 [a]	.84 ± .14 [b]	.82 ± .14	.81 ± .15	0.941	**0.006**	0.645	0.022
	Untrained	.83 ± .18	.79 ± .16 [a]	.83 ± .16 [b]	.84 ± .20	.81 ± .16				
$P_{ET}CO_2$ (mm Hg)	RE-Trained	38 ± 5	39 ± 5	38 ± 4	38 ± 4	38 ± 4 [b]	0.162	**0.032**	0.644	0.022
	Untrained	36 ± 4	37 ± 4	36 ± 4	36 ± 4	36 ± 4 [b]				
HR (bpm)	RE-Trained	73 ± 14	73 ± 14	71 ± 14	70 ± 14	72 ± 14	0.821	0.344	0.070	0.074
	Untrained	70 ± 16	70 ± 14	72 ± 15	70 ± 15	72 ± 15				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Middle Cerebral Artery Blood Velocity mean, PI; Pulsatility Index, PV; Pulse Velocity, MAP; Mean Arterial Pressure, HR; Heart Rate, $P_{ET}CO_2$; End-tidal Partial Pressure of Carbon Dioxide. RE-Trained, Resistance-Trained; n = 15, Untrained; n = 15. [a] different to initial. [b] different to set 1. [c] different to set 2.

Averaged Response to Dynamic Resistance Exercise

The typical response to dynamic RE is detailed in **Figure 18** with the averaged cerebrovascular and cardiovascular responses within-exercise presented in **Table 3**. A training by set interaction was seen in MAP (P = 0.010) and SBP (P <0.001). Post-hoc tests revealed higher MAP in the RE-trained group in sets 2, 3 and 4 (all P < 0.012), and in all 4 sets (all P < 0.001) for SBP (see **Table 3** for values). A training by set interaction was demonstrated for DMCAv (P < 0.001), (see **Table 3** for values), although post-hoc tests revealed no differences (all P > 0.113). A set effect was seen for $MCAv_{mean}$, CVCi, PP, and $P_{ET}CO_2$ (all P < 0.001) which reflected values decreasing from set 1 to 4 in both groups, while MAP and HR had set differences of P < 0.001, reflected by increasing values (see **Table 3** for values).

Zenith and Nadir Response to Dynamic Resistance Exercise

Similarly, to the averaged responses during exercise there were set differences for $MCAv_{mean}$, SMCAv, DMCAv, and CVCi at zenith $MCAv_{mean}$ and nadir $MCAv_{mean}$ (all P <0.003, see Table 4 for values). The RE-trained group demonstrated greater SBP at zenith MAP (training effect P = 0.006) and MAP Nadir (training effect P = 0.010, see Table **4** for values), indicating a sustained increase in SBP throughout exercise. Additionally, zenith MAP was greater in the RE-trained group (training effect P = 0.039, see **Figure 19** for values).

Zenith-to-Nadir difference

No significant effect of training was observed in MCA_{vmean} (P = 0.837) however, a difference was apparent for MAP (P = 0.002), with the RE-trained showing a significantly greater zenith-to-nadir difference (see **Table 4**).

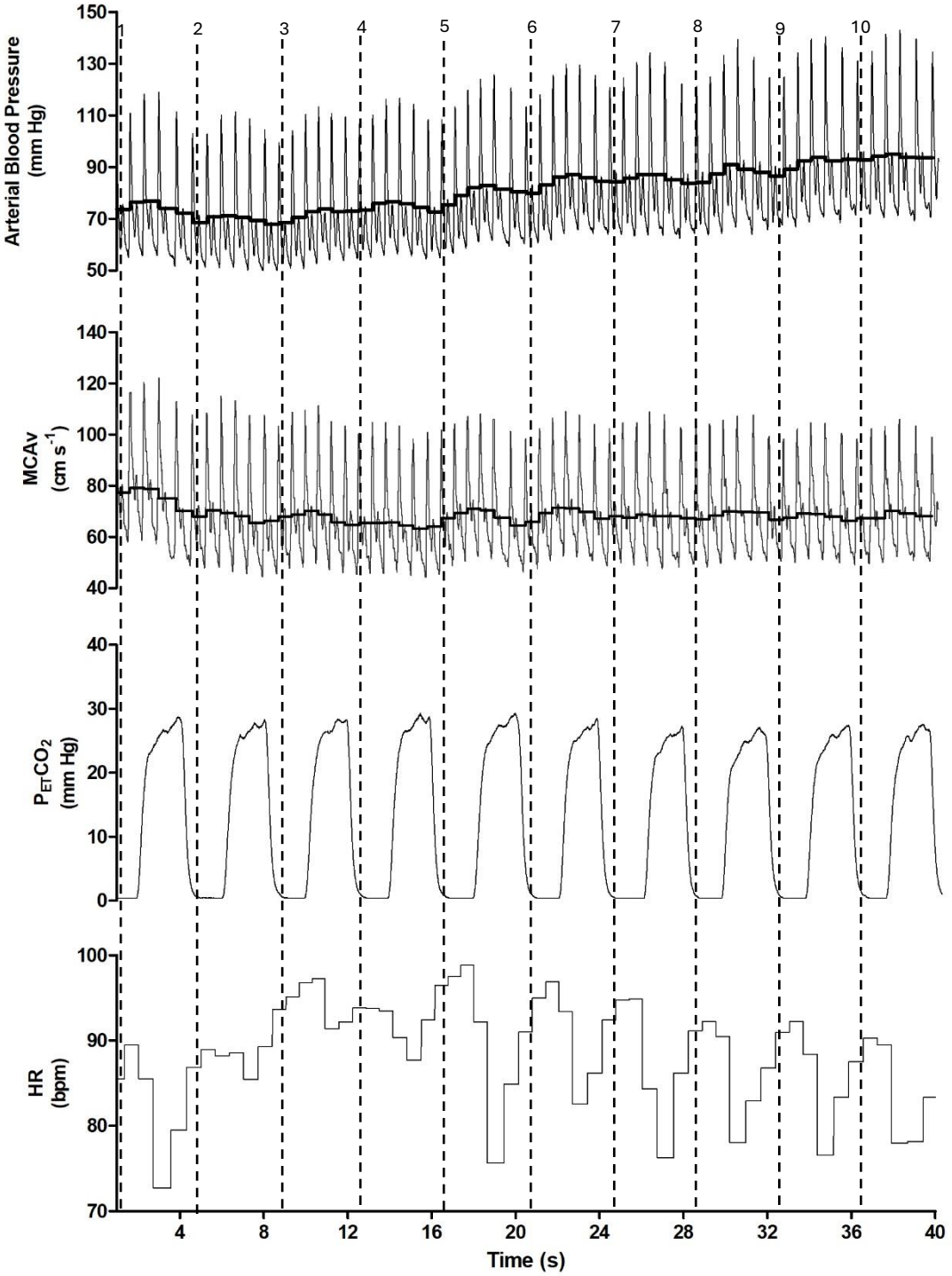

Figure 18 Typical trace of middle cerebral artery blood velocity (MCAv), arterial blood pressure, partial pressure of end tidal carbon dioxide ($P_{ET}CO_2$), and heart rate (HR) during exercise. The thick black line in the MCAv and arterial blood pressure traces represent mean MCAv and mean arterial pressure, respectively. The numbers indicate the rep count with the dotted line denoting the start (concentric phase) of each rep (n = 1, RE-trained).

Table 3 Averaged Cerebrovascular and Cardiovascular Within-Exercise Response during Dynamic Resistance Exercise

Variable	Training group	Sets					*P* value			Partial η^2
		Baseline	Set 1	Set 2	Set 3	Set 4	Training	Set	Interaction	
$MCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	65 ± 8	63 ± 11	63 ± 10	61 ± 9 [a b c]	61 ± 9 [a b c]	0.194	**<0.001**	0.166	0.056
	Untrained	69 ± 11	71 ± 11	67 ± 10	65 ± 8 [a b c]	64 ± 8 [a b c]				
$SMCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	102 ± 12	98 ± 15	96 ± 15	94 ± 14 [a b c]	94 ± 15 [a b c]	0.370	**<0.001**	0.533	0.027
	Untrained	106 ± 18	105 ± 17	102 ± 17	98 ± 15 [a b c]	97 ± 15 [a b c]				
$DMCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	47 ± 6	45 ± 8	50 ± 10	49 ± 10	45 ± 8	0.906	0.293	**<0.001**	0.167
	Untrained	49 ± 9	46 ± 7	45 ± 6	45 ± 6	46 ± 7				
MAP (mm Hg)	RE-Trained	82 ± 10	96 ± 10 [a]	99 ± 11* [a]	100 ± 10* [a]	101 ± 11* [a]	**0.022**	**<0.001**	**0.010**	0.110
	Untrained	81 ± 6	90 ± 10 [a]	89 ± 7 [a]	91 ± 7 [a]	92 ± 7 [a]				
SBP (mm Hg)	RE-Trained	117 ± 14	144 ± 17* [a]	145 ± 19* [a]	148 ± 18* [a]	149 ± 19* [a]	**0.002**	**<0.001**	**<0.001**	0.190
	Untrained	116 ± 11	127 ±15 [a]	126 ± 11 [a]	127 ± 13 [a]	125 ± 12 [a]				
DBP (mm Hg)	RE-Trained	64 ± 8	72 ± 10 [a]	77± 10 [a]	77 ± 10 [a]	78 ± 10 [a c]	0.410	**<0.001**	0.566	0.026
	Untrained	64 ± 6	72 ± 11 [a]	71 ± 10 [a]	73 ± 8 [a]	75 ± 8 [a c]				
CVCi ($cm\ s^{-1}\ mm\ Hg^{-1}$)	RE-Trained	.81 ± .15	.67 ± .13 [a]	.65 ± .14 [a]	.62 ± .13 [a b c]	.62 ± .12 [a b c]	**0.037**	**<0.001**	0.182	0.054
	Untrained	.86 ± .14	.79 ± .13 [a]	.75 ± .11 [a]	.72 ± .10 [a b c]	.60 ± .11 [a b c]				
PP (mm Hg)	RE-Trained	55 ± 10	54 ± 10	51 ± 10	50 ± 10 [a b c]	49 ± 10 [a b c]	0.477	**<0.001**	0.708	0.019
	Untrained	57 ± 13	56 ± 12	56 ± 13	53 ± 13 [a b c]	52 ± 12 [a b c]				
PI	RE-Trained	.84 ± .13	.86 ± .15	.83 ± .15	.83 ± .13	.82 ± .14	0.787	0.676	0.111	0.064
	Untrained	.83 ± .18	.80 ± .16	.84 ± .16	.82 ± .17	.82 ± .15				
$P_{ET}CO_2$ (mm Hg)	RE-Trained	38 ± 5	36 ± 5 [a]	36 ± 5 [a]	35 ± 5 [a b]	35 ± 5 [a b]	0.282	**<0.001**	0.800	0.014
	Untrained	36 ± 4	35 ± 4 [a]	34 ± 4 [a]	33 ± 4 [a b]	33 ± 4 [a b]				
HR (bpm)	RE-Trained	73 ± 14	91 ± 14 [a]	92 ± 16 [a]	93 ± 13 [a]	93± 15 [a]	0.505	**<0.001**	0.567	0.026
	Untrained	70 ± 16	91 ± 13 [a]	88 ± 14 [a]	88 ± 13 [a]	89 ± 12 [a]				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Mean Middle Cerebral Artery Blood Velocity, SMCAv; Systolic Middle Cerebral Artery Blood Velocity, DMCAv; Diastolic Middle Cerebral Artery Blood Velocity, PI; Pulsatility Index, PV; Pulse Velocity, MAP; Mean Arterial Blood Pressure, HR; Heart Rate, $P_{ET}CO_2$; End-tidal Partial Pressure of Carbon Dioxide. RE-Trained, Resistance-Trained; *n* = 15, Untrained; n = 15. Despite a significant training by set interaction post-hoc tests revealed no differences between training groups for DMCAv (*P* >= 0.113), however, post-hoc test revealed significant differences in MAP (all *P* =< 0.012) and SBP (all *P* =< 0.002), differences denoted with *. [a] different to initial baseline. [b] different to set 1. [c] different to set 2.

Table 4 Zenith and Nadir $MCAv_{mean}$, MAP, CVCi, and Zenith-to-Nadir of $MCAv_{mean}$ and MAP during Dynamic Resistance Exercise

Variable	Training group	Sets				*P* value			Partial η^2
		Set 1	Set 2	Set 3	Set 4	Training	Set	Interaction	
Zenith									
SMCAv ($cm\ s^{-1}$)	RE-Trained	102 ± 18	99 ± 17	97 ± 14 [b c]	97 ± 15 [b c]	0.550	**<0.001**	0.165	0.058
	Untrained	105 ± 18	102 ± 17	99 ± 15 [b c]	97 ± 15 [b c]				
DMCAv ($cm\ s^{-1}$)	RE-Trained	48 ± 9	47 ± 8	47 ± 7	47 ± 8 [b]	0.865	**0.003**	0.083	0.076
	Untrained	50 ± 9	48 ± 7	47 ± 6	46 ± 6 [b]				
SBP (mm Hg)	RE-Trained	144 ± 20	146 ± 20	148 ± 21	147 ± 22	**0.006**	0.718	0.119	0.067
	Untrained	129 ± 22	124 ± 18	125 ± 18	126 ± 17				
DBP (mm Hg)	RE-Trained	76 ± 10	79 ± 11	80 ± 10	80 ± 12 [b]	0.318	**0.017**	0.082	0.076
	Untrained	75 ± 11	73 ± 9	76 ± 10	77 ± 9 [b]				
CVCi ($cm\ s^{-1}\ mm\ Hg^{-1}$)	RE-Trained	.69 ± .15	.66 ± .17	.64 ± .15 [b c]	.64 ± .16 [b c]	0.225	**<0.001**	0.489	0.028
	Untrained	.76 ± .14	.74 ± 14	.70 ± .10 [b c]	.68 ± .12 [b c]				
Nadir									
SMCAv ($cm\ s^{-1}$)	RE-Trained	97 ± 17	94 ± 14	92 ± 14 [b c]	91 ± 15 [b c]	0.690	**<0.001**	0.585	0.023
	Untrained	100 ± 18	97 ± 15	94 ± 15 [b c]	92 ± 15 [b c]				
DMCAv ($cm\ s^{-1}$)	RE-Trained	43 ± 9	42 ± 8	42 ± 8 [b]	42 ± 7 [b]	0.784	**<0.001**	*0.053*	0.087
	Untrained	46 ± 9	43 ± 6	42 ± 5 [b]	41 ± 5 [b]				
SBP (mm Hg)	RE-Trained	136 ± 18	138 ± 19	140 ± 20	141 ± 20	**0.010**	0.651	0.063	0.083
	Untrained	125 ± 19	119 ± 17	120 ± 17	120 ± 16				
DBP (mm Hg)	RE-Trained	70 ± 10	72 ± 11	74 ± 10	74 ± 12	0.610	*0.052*	0.204	0.053
	Untrained	71 ± 10	69 ± 9	71 ± 9	72 ± 8				
CVCi ($cm\ s^{-1}\ mm\ Hg^{-1}$)	RE-Trained	.67 ± .15	.64 ± .17	.62 ± .15 [b c]	.62 ± .16 [b c]	0.268	**<0.001**	0.446	0.031
	Untrained	.73 ± .13	.72 ± 14	.67 ± .11 [b c]	.66 ± .14 [b c]				
Zenith-to-Nadir Difference									
$MCAv_{mean}$	RE-Trained	8 ± 3	8 ± 3	7 ± 3	8 ± 2	0.837	0.894	0.459	0.030
	Untrained	8 ± 2	8 ± 2	8 ± 2	8 ± 2				
MAP	RE-Trained	7 ± 2	7 ± 2	7 ± 2	7 ± 2	**0.002**	0.476	0.422	0.033
	Untrained	4 ± 2	4 ± 2	5 ± 2	5 ± 2				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Mean Middle Cerebral Artery Blood Velocity, SMCAv; Systolic Middle Cerebral Artery Blood Velocity, DMCAv; Diastolic Middle Cerebral Artery Blood Velocity, MAP; Mean Arterial Blood Pressure, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure. RE-trained, Resistance-Trained; n = 15, Untrained; n = 15. [b] different to set 1. [c] different to set 2.

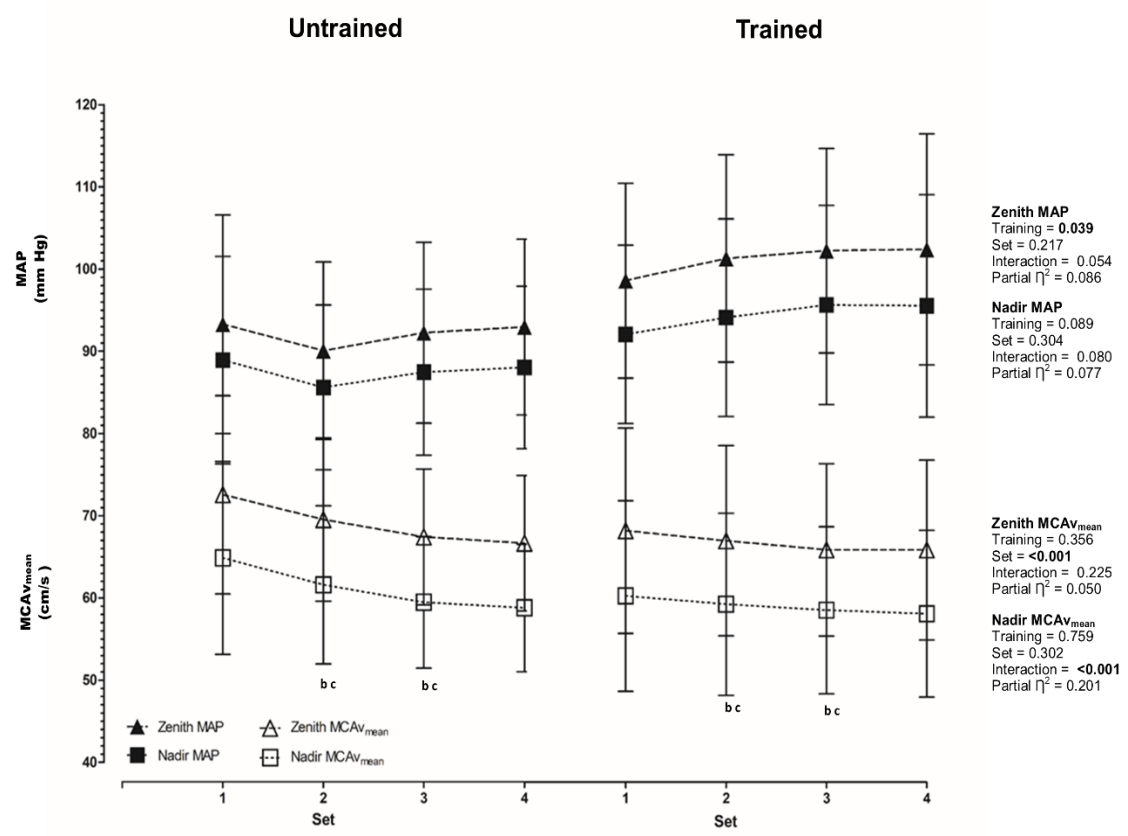

Figure 19 Zenith and nadir mean arterial blood pressure (MAP) and mean middle cerebral artery blood velocity ($MCAv_{mean}$) during dynamic resistance exercise. Data are means ± SD. b different to set 1. c different to set 2. Despite a significant training by set interaction post-hoc tests revealed no differences between training groups for Nadir MCAv (P>=0.293).

5.6 Discussion

The purpose of this chapter was to investigate the effect of habitual RE training on the cerebrovascular response to dynamic RE. No difference in average $MCAv_{mean}$ or zenith-to-nadir difference during RE between groups was observed. However, this occurred despite higher average MAP and SBP, and zenith-to-nadir MAP difference during RE in the RE-trained group. Collectively, these data indicate that despite higher within-exercise average blood pressures, and greater fluctuations in blood pressure, in the RE-trained group, $MCAv_{mean}$ responses were not different. These findings align with our hypothesis and suggest that RE-trained individuals can maintain a more stable MCAv despite more profound changes in MAP.

In the current chapter we have found no group differences in cardiovascular or cerebrovascular measures at the initial baseline period (pre-exercise) or between sets. Notably, there was similar 'drift' between groups in the baseline periods between sets,

for example, MAP was similarly elevated in both groups between sets compared to the initial baseline period prior to exercise (see **Figure 19** and **Table 2**). However, $MCAv_{mean,}$ was reduced from the initial baseline period prior to each subsequent exercise bout in both groups. Repetitive exposure to extreme ABP perturbations during high-intensity dynamic RE (e.g. ~80% of 1RM) has been reported to produce unfavourable adaptations within the circulatory system, evidenced by a reduction in central arterial compliance (DeVan et al., 2005; Miyachi, 2013; Miyachi et al., 2004; Okamoto et al., 2009; Palmiere et al., 2018) and increased CVR at rest compared to sedentary controls (Nakamura & Muraoka, 2018; Thomas et al., 2021), although the latter is not a consistent finding (Corkery et al., 2021). Koch et al. (2005) reported that CA is temporarily impaired immediately (<90s) following RE in RE-trained individuals. In a mixed cohort of RE-trained and untrained individuals Smail et al. (2023) reported that transfer function derived gain at 0.10Hz was increased from baseline 10 minutes post-RE but recovered at 45 minutes. Anterograde shear rate and blood flow can increase in inactive limbs following dynamic RE (Thomas et al., 2020) with an increase in blood flow turbulence and intensity dependent increase in endothelial shear stress in the common carotid artery during dynamic RE (Montalvo et al., 2022). These data indicate that dynamic RE produces profound increases in shear rate and endothelial shear stress, accompanied with sinusoidal changes in CBF and perfusion pressure that may acutely alter cerebrovascular function. Whilst we report no change in baseline $MCAv_{mean}$ values between groups, repeated exposure to such conditions induced by habitual RE may alter the within RE cerebrovascular responses.

To more accurately categorise the nature of the within RE haemodynamic profile we analysed the averaged data, the zenith and nadir, and zenith-to-nadir difference for both MAP and $MCAv_{mean}$. We demonstrate that despite more profound increases in average MAP during exercise, and greater perturbations in blood pressure (e.g., zenith-to-nadir difference for MAP) for the RE-trained group, average and zenith-to-nadir difference for $MCAv_{mean}$ was not different (see **Table 4**). Although we did not directly assess CA in the current chapter, we have previously compared CA between RE-trained, endurance trained and healthy sedentary, with the RE-trained group demonstrating a trend towards a lower transfer function phase during forced oscillations in blood pressure (Perry et al. (2019). Hysteresis refers to the asymmetric cerebral autoregulatory response, with more effective cerebral autoregulatory

buffering capacity during hypertensive challenges compared to hypotensive insults (Brassard, Ferland-Dutil, et al., 2017). (Roy et al., 2022) reported that RE-trained individuals did not exhibit hysteresis during 0.10Hz repeated squat–stands, but the asymmetric autoregulatory responses persisted in sedentary and endurance trained individuals at this frequency. As cerebral autoregulation was not assessed in the current chapter, and the frequency of blood pressure fluctuations produced were faster (0.25Hz) than those analysed by Roy et al. (2022), these data cannot be used to indicate the modification or absence of hysteresis. Additionally, rhythmic handgrip exercise has been postulated to produce a sympathetically mediated vasoconstriction of the MCA (Verbree et al., 2017). Following ganglionic blockade, a substantially greater rise in MCAv was observed during the rapid increase in MAP during phase IV of the VM, indicating the presence of autonomic vasoconstriction during rapid increases in perfusion pressure (Zhang et al., 2004), like those experienced during RE. Thus, more widespread cerebral vasoconstriction cannot be excluded, which may act to prevent hyperperfusion when cerebral perfusion pressure is elevated during RE. Further research is required to assess the effect of RE on hysteresis and regulation of CBF by the sympathetic nervous system.

Thomas et al. (2021) assessed the effects of 12 weeks of RE and endurance training on cerebrovascular haemodynamics using a randomised cross over design. Whilst the cerebrovascular responses to RE were not recorded, the authors report that following 12 weeks of RE training larger increases in MAP were apparent during incremental cycling exercise with a concomitant lower MCAv response compared to before the exercise intervention. Additionally, indices of cerebrovascular resistance in the MCA, posterior cerebral artery, and internal carotid artery (ICA) were all increased following 12 weeks of RE training, whilst CA during spontaneous oscillations in blood pressure was unchanged. Our findings largely corroborate those of Thomas et al. (2021) as the current chapter indicates that compared to the untrained group (healthy sedentary) the RE-trained group demonstrated a similar within MCAv during RE despite greater average and magnitude of change in MAP Collectively, these data indicate that CA may be altered by habitual RE with the adaptations only elucidated during exercise, where blood pressure oscillations are rapid and forced as previously suggested (Perry & Lucas, 2021).

Few studies have investigated the cerebrovascular response to dynamic RE. Studies investigating the acute cerebrovascular response to RE have produced equivocal results. When considering the average $MCAv_{mean}$ during RE, an increase (Moralez et al., 2012; Romero & Cooke, 2007), decrease (Dickerman et al. 2000) and no change (Edwards et al. (2002) has been reported. Furthermore, the average peak MCAv values, (the Zenith $MCAv_{mean}$ in the current chapter) was reported to increase from baseline, with the increase independent of exercise intensity, although this is likely due to recruitment of the Valsalva manoeuvre (Perry et al. 2014). Interestingly, the study of Dickerman, that reports a reduction in MCAv during RE, did not report the partial pressure of arterial carbon dioxide or an appropriate proxy (e.g., $P_{ET}CO_2$). The reporting of such data is critical for interpretation as the carbon dioxide content of the arterial blood is the most potent regulator of CBF at rest and during exercise as evidenced by a reduction in within RE MCAv when lifters hyperventilate prior to exercise onset (Romero & Cooke, 2007). In the current chapter the gradual reduction in averaged $MCAv_{mean}$ across the sets in both groups (see **Table 3**) appears to be driven by a declining $P_{ET}CO_2$. Whilst there were no differences between groups, similar reductions in $P_{ET}CO_2$ for both groups across the exercise sets were observed (e.g., set effect), with $P_{ET}CO_2$ lowest in set 3 and 4 (see **Table 3**). Even small reductions in $P_{ET}CO_2$ could underpin the observed decrease with a 2 – 3 % reduction in MCAv observed for every mm Hg decrease in $P_{ET}CO_2$ at rest (Brugniaux et al., 2007). Furthermore, although CO_2 reactivity was not measured, cerebrovascular reactivity to CO_2 appears to not be altered by habitual RE training when compared to healthy sedentary individuals and aerobically trained individuals (Corkery et al., 2021). The limited research on cerebrovascular responses to dynamic RE has yielded conflicting results, which highlights the importance of accounting for a potent regulator like CO_2.

This is the first research to our knowledge that assessed the zenith and nadir of MCAv and MAP measures during RE. Dynamic RE causes sinusoidal fluctuations in MAP which are mirrored by MCAv. Previous studies reporting average MCAv, and MAP likely oversimplify the within RE haemodynamic responses. As the magnitude and rate of change in MAP determines the MCAv response to acute perturbation in blood pressure (Tzeng et al., 2011), the current findings suggest that repetitive RE may subtly modify cerebrovascular function as RE-trained individuals exhibit similar fluctuations in MCAv to untrained individuals during dynamic RE despite larger

fluctuations in blood pressure. We have previously reported (Perry, Schlader, et al., 2014) that following RE there is a selective decrease in DMCAv. Though there was a training by set interaction for within-exercise DMCAv in the current chapter, post-hoc tests revealed no differences. Future studies that investigate the haemodynamic responses to RE should consider measuring zenith and nadir $MCAv_{mean}$ and MAP to gain further understanding of the sinusoidal pattern and its influence on the cerebrovascular response.

Limitations

The limitations included in this experimental chapter are specific to this chapter, more general limitations will be discussed in **Chapter Eight Section 8.2**

Blood flow in the ICA or the external carotid artery (ECA) was not measured in this thesis. Hirasawa et al. (2016) reported increases in ECA blood flow during low-intensity (30% of maximum voluntary contraction) static RE. However, the current study used dynamic RE and a higher intensity (60% of 1RM). The dynamic nature of RE raises methodological challenges when measuring blood flow, namely movement of the participant during exercise and the sinusoidal fluctuations in blood pressure and flow. These considerations precluded the measurement of ICA or ECA blood flow in the thesis, but does not mean that we can exclude the occurrence of an extracranial shunt during RE. However, as the VM was not utilised at any time during RE in this thesis, and the within RE increases in MAP were modest, shunting of blood to the ECA may have been limited.

5.7 Conclusion

The current findings indicate that despite RE-trained individuals demonstrating greater fluctuations in blood pressure during dynamic lower body RE, $MCAv_{mean}$ was not different versus their untrained counterparts. Therefore, it is possible that engaging in habitual resistance training may produce functional vascular adaptations that maintain CBF during RE despite greater blood pressure. Future studies should consider the sinusoidal nature of blood pressure during RE to better characterise the cerebrovascular response during dynamic RE. Furthermore, exploring whether these adaptations are present following RE is important as hypotension and syncope are the main risks associated with engaging in RE. Identifying if these results translate into

post-RE response could add to the list of benefits linked with RE, in that RE-trained individuals are less likely to experience cerebral hypoperfusion and syncope following RE.

Chapter Six: Larger reductions in blood pressure during post-exercise standing, but not middle cerebral artery blood velocity, in resistance-trained versus untrained

The work included in this chapter has been accepted by Experimental Physiology but has not yet been published. The data, results, and key outcomes of the published work are unchanged within the chapter; however, the layout and formatting have been modified to fit within this thesis.

Korad, S., Mündel, T., & Perry, B. G. (2025). Larger reductions in blood pressure during post-exercise standing, but not middle cerebral artery blood velocity, in resistance-trained versus untrained individuals. *Experimental Physiology*, 110, 424–437.

6.1 Introduction

The results of the previous chapter indicate that during dynamic RE at the same exercise intensity, RE-trained individuals exhibited greater ABP during leg extension exercise versus their untrained counterparts. However, despite having significantly higher blood pressures, there was no difference in the within-exercise $MCAv_{mean}$, which suggests that the RE-trained individuals may have gained some functional adaptation to the repetitive exposure to the high blood pressures associated with RE training. Whether these adaptations extend to the post-exercise period when blood pressure is declining is not understood and is this focus of this chapter.

Previous studies investigating the effects of dynamic RE on the cerebrovascular response to post-exercise standing predominately used a leg press machine (Moralez et al., 2012; Romero & Cooke, 2007) or upright squat (Perry, Schlader, et al., 2014). The consensus of these studies was that a reduction in $MCAv_{mean}$ was seen immediately during standing alongside an acute reduction in MAP, with the reduction in $MCAv_{mean}$ being exacerbated by pre-exercise hyperventilation (Romero & Cooke, 2007) and dehydration (Moralez et al., 2012). Furthermore, Perry, Schlader, et al. (2014) emphasized that higher relative loads produced larger post-exercise hypotension that resulted in a proportionate reduction in $MCAv_{mean}$. Transient hypertension is said to be buffered more effectively by CA than hypotensive

challenges – a concept termed hysteresis (Brassard, Ferland-Dutil, et al., 2017; Roy et al., 2022; Tzeng et al., 2011). Roy et al. (2022) reported that RE-trained individuals did not exhibit signs of hysteresis during forced oscillations in ABP induced by repeated squat-stands at a frequency of 0.10Hz, but those in the healthy sedentary and endurance trained groups did. Whether cerebrovascular function is modified in RE-trained individuals during acute post-exercise hypotension remains unknown. As highlighted in **Chapter Three**, the purpose of this chapter was to examine the cerebrovascular response to orthostasis induced post-RE hypotension in RE-trained and untrained individuals. We hypothesised that although RE-trained individuals would display a greater blood pressure response during RE there would be no difference in recovery indicating that RE-trained individuals had better CA than the untrained.

6.2 Methods

This chapter was part (b) **Figure 16** (see **Section 4.2.4**), which was a continuation from part (a) in chapter 5. Once the participants completed the leg extension exercise (results described in Chapter 5), the participants immediately stood up for 1 minute. The participant completed 5 stands in total, once before the exercise trial, then once after each exercise set.

See **Chapter Four Section 4.2** for a detailed description of the techniques and methods used for this experimental chapter.

6.3 Data Analysis

30 participants were recruited for this experiment, however, only 28 participants had usable traces that could be analysed in this chapter, one participant did not have acceptable traces for the post-exercise stand data due to multiple premature ventricular contractions and the MCAv traces were substandard during the post-exercise stand for another participant. Therefore, the data presented herein will be for 28 participants, 14 participants in the RE-trained group and the 14 in the untrained group.

Dependent Measures

The calculations for $MCAv_{mean,}$ MAP, CVCi, and PI are described in **Chapter Four** Sections **4.1.3** ($MCAv_{mean}$), **4.1.4** (CVCi), **4.1.5** (PI), **4.1.9** (MAP). Additional calculations that are specific to this chapter are described below.

Baseline data were averaged during the last minute of rest before each set. In total, 5 stands were completed, with stand 1 occurring before exercise after the recording of baseline measures and stands 2 through 5 occurring immediately after each of the exercise sets. Pre-stand measures were averaged for 4 seconds immediately before the stand, as such for stands 2 through 5 (following sets 1 through 4) these data represent the haemodynamic status during the last repetition of exercise. The $MCAv_{mean}$ and MAP nadir were defined as the lowest values in a single cardiac cycle observed following the stand for each variable after which both began to recover (increase) toward baseline values. $MCAv_{mean}$, SMCAv, DMCAv, MAP, SBP, DBP, CVCi, HR, and $P_{ET}CO_2$, were measured at the MCAv and MAP nadir points. Furthermore, these values were used to calculate absolute changes from baseline (rest) and pre-stand values (immediately prior to the stand).

The area under the curve (AUC) was calculated from a method previously described by Pruessner et al. (2003) and the AUC was calculated with respect to the baseline values. That is, the AUC calculation began when the variable of interest decreased below the baseline value and ended when the value then returned to the baseline value. The baseline value refers to the measurement taken during the resting period before each set. The time to recovery data was taken after the stand and was defined as the time it took for MCAv or MAP values to fall below baseline to when MCAv or MAP returned to baseline was used to analyse time to recovery.

Rate of Regulation

The Rate of Regulation (RoR) was used to evaluate the relationship between MAP and $MCAv_{mean}$ during the acute hypotension induced by the stand immediately following RE. RoR was calculated using the method outlined by Labrecque et al. (2019), utilising the equation:

$$RoR = \frac{(\Delta \mathrm{CVCi} \,/\, \Delta \mathrm{t})}{\Delta \mathrm{MAP}}$$

where (ΔCVCi/Δt) represents the linear regression slope of the change in CVCi over time (t) during the initial regulatory response to standing (Aaslid et al., 1989; Ogoh et al., 2008). The time interval (Δt) is a 2.5-second period following the onset of the regulatory response, characterized by a continuous rise in CVCi upon standing (Labrecque et al., 2019). The change in MAP (ΔMAP) is calculated as the difference between 4 seconds immediately preceding the stand (Aaslid et al., 1989), and the average MAP during the initial haemodynamic response to standing, where changes in $MCAv_{mean}$ occur independently of baroreflex control (van Beek et al., 2008).

The equation:

(%MCAv / %MAP)

was used to calculate the contribution of the MAP response to the MCAv reduction during each stand. The percentage change was calculated from the 4 seconds immediately prior to the stand to the MCA nadir following the stand.

Time to nadir was determined as the time taken to achieve the nadir values for both MAP and $MCAv_{mean}$ at the onset of the stand. The time lag of these responses was also calculated as: time to $MCAv_{mean}$ nadir - time to MAP nadir, as MCAv nadir is reached prior to MAP nadir following RE (Perry, Schlader, et al., 2014).

6.4 Statistical Analysis

All data were analysed using SPSS statistical software version 28 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P \leq 0.05$. An unpaired t-test was performed to compare anthropometric, 1RM, and 60%1RM data. A two-way mixed ANOVA was performed to analyse baseline measures (training x baselines, 2 x 5) and dependent variables of interest during post-dynamic RE stand (training x sets 2 x 5). Unpaired T-tests were used for post-hoc comparisons, and a Bonferroni correction factor was used when necessary. Partial eta square (partial $\eta 2$) was reported for the training by set interaction only, with large effect sizes identified as > 0.134, medium 0.059 - 0.134, and small <0.010 (Cohen, 2013). All data were displayed as the mean ± SD.

6.5 Results

Participants' anthropometric and exercise measurements are presented in Table 1. There were no significant differences in the anthropometric measurements between the RE-trained and untrained, however, RE-trained had a greater predicted 1RM and 60% of 1RM versus their untrained counterparts (see **Table 1** in **Chapter Four Section 4.2.2** for *P* values). The RE-trained group trained for 49 ± 45 months, ranging from 6 – 144 months of continuous RE training.

Baseline measurements

Baseline measures for the initial baseline immediately following instrumentation and baseline prior to each set were analysed. There were no significant main effects of training (all $P > 0.240$) or training by set interaction (all $P > 0.111$) for any baseline variables between groups. However, with the exception of heart rate and $P_{ET}CO_2$, there was a set effect for all variables, whereby both training groups demonstrated equal 'drift' in the baseline variables (all $P < 0.009$). Whereby blood pressure variables (SBP, DBP, and MAP) increased (e.g. MAP pre-exercise 82 ± 10mm Hg for RE-trained and 81 ± 6mm Hg for untrained, versus immediately prior to set 4: 90 ± 13mm Hg and 87 ± 8mm Hg, $P < 0.001$ for both post-hoc tests).

Pre-Stand Values measurements

There was no significant main effect of training for $MCAv_{mean}$, SMCAv, DMCAv, CVCi, $P_{ET}CO_2$ or HR (All $P > 0.181$ see **Table 5** for values). However, a training by set interaction effect was observed for MAP ($P = 0.002$), SBP ($P < 0.001$), and DBP ($P = 0.020$). Post-hoc tests revealed that the RE-trained group had higher MAP in sets 2, 3, and 4 (all $P < 0.006$, Bonferroni corrected) and higher SBP in sets 3 and 4 (all $P < 0.008$, Bonferroni corrected). However, there were no post-hoc difference for DBP (all $P > 0.016$, Bonferroni corrected) observed (see **Table 5** for values). A set effect ($P < 0.003$) was seen for all variables, with $MCAv_{mean}$, SMCAv, DMCAv, and CVCi and $P_{ET}CO_2$ decreasing across sets, while MAP, SBP, DBP, and HR increased across sets (see **Table 5** for values).

Table 5 Resistance-Trained versus Untrained Pre-Stand Values for Cerebrovascular and Cardiovascular Measures

Variable	Condition	Sets					*P* values			Partial η^2
		Pre-Exercise	Set 1	Set 2	Set 3	Set 4	Training	Set	Interaction	
$MCAv_{mean}$ (cm s^{-1})	RE-Trained	69 ± 11	64 ± 12[a]	64 ± 14[a]	64 ± 13	65 ± 13	0.766	0.001	0.074	0.078
	Untrained	70 ± 13	69 ± 13[a]	67 ± 12[a]	65 ± 10[b]	62 ± 11 [abcd]				
$SMCAv_{mean}$ (cm s^{-1})	RE-Trained	103 ± 16	98 ± 18[a]	94 ± 18[a]	94 ± 17[a]	96 ± 17[a]	0.630	<0.001	0.167	0.060
	Untrained	106 ±20	102 ± 18[a]	100 ± 19[a]	98 ± 16[ab]	93 ± 16 [abcd]				
$DMCAv_{mean}$ (cm s^{-1})	RE-Trained	50 ± 8	46 ± 10[a]	46 ± 10[a]	46 ± 10	48 ± 10[c]	0.940	0.003	0.058	0.083
	Untrained	50 ± 9	49 ± 10[a]	47 ± 9[a]	46 ± 8[a]	44 ± 8[abcd]				
CVCi (cm s^{-1} mm Hg^{-1})	RE-Trained	.80 ± .18	.63 ± .14[a]	.61 ± .18[a]	.60 ± .18[a]	.60 ± .17[ab]	0.242	<0.001	0.534	0.029
	Untrained	.85 ± .16	.70 ± .14[a]	.69 ± .13[a]	.68 ± .11[a]	.64 ± .12[abcd]				
MAP (mm Hg)	RE-Trained	87 ± 10	104 ± 11[ab]	108 ± 12*[ab]	110 ± 14*[ab]	112 ± 14*[abc]	0.012	<0.001	0.002	0.312
	Untrained	83 ± 7	100 ± 11[a]	97 ± 8[a]	96 ± 9 [a]	98 ± 8 [a]				
SBP (mm Hg)	RE-Trained	127 ± 16	149 ± 22[a]	154 ± 23[a]	156 ± 28*[a]	159 ± 29*[ab]	0.020	<0.001	<0.001	0.175
	Untrained	120 ± 12	138 ± 21[a]	134 ± 16[a]	132 ± 16[a]	133 ± 16 [a]				
DBP (mm Hg)	RE-Trained	68 ± 9	81 ± 8[a]	85 ± 8[ab]	87 ± 10[ab]	88 ± 9[ab]	0.050	<0.001	0.030	0.097
	Untrained	65 ± 7	80 ± 9[a]	78 ± 8[a]	78 ± 10[a]	80 ± 7 [a]				
$P_{ET}CO_2$ (mm Hg)	RE-Trained	38 ± 5	37 ± 4[a]	35 ± 4[a]	36 ± 4[a]	36 ± 4[a]	0.181	<0.001	0.640	0.024
	Untrained	37 ± 5	34 ± 4[a]	34 ± 4[a]	33 ± 3[a]	33 ± 4[a]				
HR (bpm)	RE-Trained	73 ± 18	86 ± 27[a]	89 ± 16[a]	90 ± 14[a]	95 ± 21[a]	0.602	<0.001	0.498	0.032
	Untrained	71 ± 15	93 ± 13[a]	94 ± 14[a]	95 ± 13[a]	94 ± 13 [a]				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Mean Middle Cerebral Artery Blood Velocity, SMCAv; Systolic Middle Cerebral Artery Blood Velocity, DMCAv; Diastolic Middle Cerebral Artery Blood Velocity, MAP; Mean Arterial Blood Pressure, HR; Heart Rate, $P_{ET}CO_2$; End-tidal Partial Pressure of Carbon Dioxide. RE-Trained, Resistance-Trained; n=14, Untrained; n=14. Despite a significant training by set interaction for DBP, post-hoc tests revealed no differences between training groups (*P* >= 0.016, Bonferroni corrected), however, post-hoc test revealed significant differences for MAP (all *P* =< 0.006, Bonferroni corrected) and SBP (all *P* =< 0.008, Bonferroni corrected), differences between groups within a set denoted with *. [a] different to initial baseline. [b] different to set 1. [c] different to set 2. [d] different to set 3.

Reduction from Baseline to $MCAv_{mean}$ nadir

The baseline to $MCAv_{mean}$ nadir cerebrovascular variables reported set differences for all variables barring SMCAv (P = 0.213) and $P_{ET}CO_2$ (P = 0.616). The set differences seen in $MCAv_{mean}$, DMCAv, CVCi, and HR were observed to increase in magnitude from baseline from pre-exercise measures to set 4 (set effect; all P < 0.042). Whilst, MAP, SBP and DBP were observed to have decreased across the sets (all P < 0.001).

Absolute Reduction from Pre-stand values to $MCAv_{mean}$ Nadir

A training effect was observed for MAP (P = 0.036), DBP (P = 0.016), and HR (P = 0.048), with the RE-trained group exhibiting greater reductions for all three variables (see Table 3 for values). Set differences were observed for SMCAv, MAP, DBP, $P_{ET}CO_2$ and HR (P =< 0.011) for the pre-stand values to $MCAv_{mean}$ nadir (see **Table 6** for values). HR difference across the sets was the only variable that decreased in magnitude across the sets (all P < 0.001), while the rest of the variables increased in difference from pre-exercise to set 4 (all P < 0.005).

Table 6 Resistance-Trained versus Untrained Absolute Change from Pre-Stand Values to $MCAv_{mean}$ Nadir

Variable	Condition	Sets					*P* values			Partial η^2
		Pre-Exercise	Set 1	Set 2	Set 3	Set 4	Training	Set	Interaction	
$MCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	-20 ± 8	-16 ± 6[a]	-18 ± 5[a]	-19 ± 7	-20 ± 7	0.752	0.647	0.478	0.033
	Untrained	-19 ± 8	-18 ± 7[a]	-18 ± 6[a]	-18 ± 7	-17 ± 6				
$SMCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	-4 ± 10	15 ± 20[a]	11 ± 6[a]	11 ± 10[a]	9 ± 11[a]	0.225	<0.001	0.229	0.052
	Untrained	-4 ± 9	3 ± 13[a]	7 ± 11[a]	10 ± 18[a]	6 ± 9[a]				
$DMCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	-23 ± 12	-22 ± 9[a]	-25 ± 8[a]	-25 ± 9	-28 ± 8[b]	0.127	0.195	0.908	0.010
	Untrained	-21 ± 11	-19 ± 7[a]	-21 ± 9[a]	-22 ± 10	-22 ± 8				
CVCi ($cm\ s^{-1}\ mm\ Hg^{-1}$)	RE-Trained	-.07 ± .15	-.07 ± .11[a]	-.06 ± .07[a]	-.05 ± .11	-.05 ± .08	0.717	0.938	0.967	0.005
	Untrained	-.05 ± .10	-.06 ± .12[a]	-.07 ± .12[a]	.04 ± .09	.05 ± .08				
MAP (mm Hg)	RE-Trained	-30 ± 12	-33 ± 6[a]	-36 ± 7[a]	-38 ± 10	-39 ± 10[ab]	0.036	0.011	0.569	0.028
	Untrained	-26 ± 10	-31 ± 10[a]	-31 ± 7[a]	-30 ± 10	-31 ± 9				
SBP (mm Hg)	RE-Trained	-33 ± 21	-31 ± 10[a]	-34 ± 12[a]	-37 ± 16	-39 ± 19	0.133	0.884	0.567	0.028
	Untrained	-28 ± 14	-30 ± 17[a]	-29 ± 11[a]	-28 ± 14	-28 ± 14				
DBP (mm Hg)	RE-Trained	-29 ± 9	-34 ± 5[a]	-36 ± 5[a]	-38 ± 8[a]	-39 ± 7[ab]	0.016	<0.001	0.657	0.023
	Untrained	-24 ± 10	-32 ± 8[a]	-33 ± 5[a]	-31 ± 9	-32 ± 7[a]				
$P_{ET}CO_2$ (mm Hg)	RE-Trained	-1 ± 2	3 ± 2[a]	3 ± 3[a]	3 ± 3[a]	1 ± 8	0.755	0.005	0.328	0.043
	Untrained	-0 ± 2	2 ± 3[a]	3 ± 3[a]	2 ± 2[a]	2 ± 2[a]				
HR (bpm)	RE-Trained	25 ± 15	15 ± 24[a]	12 ± 21[a]	4 ± 30[a]	6 ± 22[a]	0.048	<0.001	0.627	0.024
	Untrained	16 ± 10	1 ± 7[a]	-1 ± 5[a]	1 ± 5[a]	-1 ± 6[a]				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Mean Middle Cerebral Artery Blood Velocity, SMCAv; Systolic Middle Cerebral Artery Blood Velocity, DMCAv; Diastolic Middle Cerebral Artery Blood Velocity, MAP; Mean Arterial Blood Pressure, HR; Heart Rate, $P_{ET}CO_2$; End-tidal Partial Pressure of Carbon Dioxide. RE-Trained, Resistance-Trained; n=14, Untrained; n=14. [a] different to initial baseline. [b] different to set 1.

Reduction from Baseline to MAP nadir

Set differences were observed for SMCAv, MAP, and DBP for baseline to MAP nadir data. SMCAv differences increased from pre-exercise to set 4 ($P < 0.001$, SMCAv pre-exercise: -4 ± 19mm Hg RE-trained, pre-exercise: -4 ± 8mm Hg untrained, versus set 4: 4 ± 22mm Hg RE-trained, -1 ± 9mm Hg untrained). MAP and DBP differences decreased across the sets (all $P =< 0.024$, SBP pre-exercise: -29 ± 17mm Hg RE-trained, pre-exercise: -27 ± 14mm Hg untrained, versus set 4: -19 ± 23mm Hg RE-trained, -25 ± 17mm Hg untrained).

Reduction from Pre-stand to MAP nadir

Training effects were observed for MAP *(*$P = 0.026$) and DBP ($P = 0.010$), with the RE-trained group having higher differential values for both variables (see **Table 7** for values). All variables except for DMCAv and SBP demonstrated set differences with decreases across sets being seen for $MCAv_{mean}$, SMCAv, CVCi, and HR (all $P =< 0.004$, see **Table 7** for values). MAP, DBP, and $P_{ET}CO_2$ showed increases across sets (all $P < 0.001$).

Table 7 Resistance-Trained versus Untrained Absolute Change from Pre-Stand Values to MAP Nadir

Variable	Condition	Sets					*P* values			Partial η^2
		Pre-Exercise	Set 1	Set 2	Set 3	Set 4	Training	Set	Interaction	
$MCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	-18 ± 7	-9 ± 7[a]	-11 ± 8[a]	-13 ± 9	-13 ± 11	0.630	0.001	0.321	0.044
	Untrained	-17 ± 7	-13 ± 9[a]	-14 ± 8[a]	-14 ± 9	-12 ± 5[a]				
$SMCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	-4 ± 10	16 ± 14[a]	18 ± 8[a]	17 ± 13[a]	14 ± 12[a]	0.235	<0.001	0.184	0.057
	Untrained	-4 ± 9	9 ± 13[a]	15 ± 16[a]	8 ± 10[a]	12 ± 9[a]				
$DMCAv_{mean}$ ($cm\ s^{-1}$)	RE-Trained	-23 ± 12	-16 ± 9[a]	-19 ± 8[a]	-22 ± 9	-19 ± 10	0.598	0.318	0.493	0.032
	Untrained	-18 ± 9	-18 ± 8[a]	-19 ± 10[a]	-19 ± 10	-19 ± 9				
CVCi ($cm\ s^{-1}\ mm\ Hg^{-1}$)	RE-Trained	-.14 ± .12	-.23 ± .13[a]	-.22 ± .11[a]	-.19 ± .10	-.20 ± .11	0.652	0.004	0.878	0.011
	Untrained	-.12 ± .08	-.21 ± .12[a]	-.19 ± .11[a]	.19 ± .17	.21 ± .16				
MAP (mm Hg)	RE-Trained	-33 ± 11	-38 ± 7[ab]	-43 ± 8[ab]	-44 ± 9[ab]	-45 ± 11[ab]	0.026	<0.001	0.092	0.073
	Untrained	-28 ± 9	-38 ± 10[a]	-36 ± 6[a]	-35 ± 10[a]	-36 ± 8[a]				
SBP (mm Hg)	RE-Trained	-38 ± 20	-40 ± 11[a]	-45 ± 13[a]	-46 ± 16[b]	-49 ± 22[b]	0.101	0.058	0.097	0.072
	Untrained	-32 ± 12	-41 ± 14[a]	-35 ± 10[a]	-35 ± 16	-36 ± 14				
DBP (mm Hg)	RE-Trained	-30 ± 8	-37 ± 5[ab]	-42 ± 5[ab]	-43 ± 7[ab]	-43 ± 7[ab]	0.010	<0.001	0.180	0.058
	Untrained	-26 ± 8	-36 ± 7[a]	-35 ± 9[a]	-35 ± 9[a]	-36 ± 6[a]				
$P_{ET}CO_2$ (mm Hg)	RE-Trained	-1 ± 3	3 ± 2[a]	4 ± 2[a]	4 ± 3[a]	3 ± 2[a]	0.359	<0.001	0.416	0.037
	Untrained	-0 ± 2	3 ± 3[a]	4 ± 3[a]	3 ± 3[a]	2 ± 2[a]				
HR (bpm)	RE-Trained	21 ± 26	11 ± 20[a]	-8 ± 37[a]	13 ± 20[c]	-6 ± 9[a]	0.729	<0.001	0.219	0.053
	Untrained	19 ± 11	2 ± 7[a]	1 ± 7[a]	2 ± 7[a]	2 ± 9[a]				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Mean Middle Cerebral Artery Blood Velocity, SMCAv; Systolic Middle Cerebral Artery Blood Velocity, DMCAv; Diastolic Middle Cerebral Artery Blood Velocity, MAP; Mean Arterial Blood Pressure, HR; Heart Rate, $P_{ET}CO_2$; End-tidal Partial Pressure of Carbon Dioxide. RE-Trained, Resistance-Trained; n=14, Untrained; n=14. [a] different to initial baseline. [b] different to set 1.

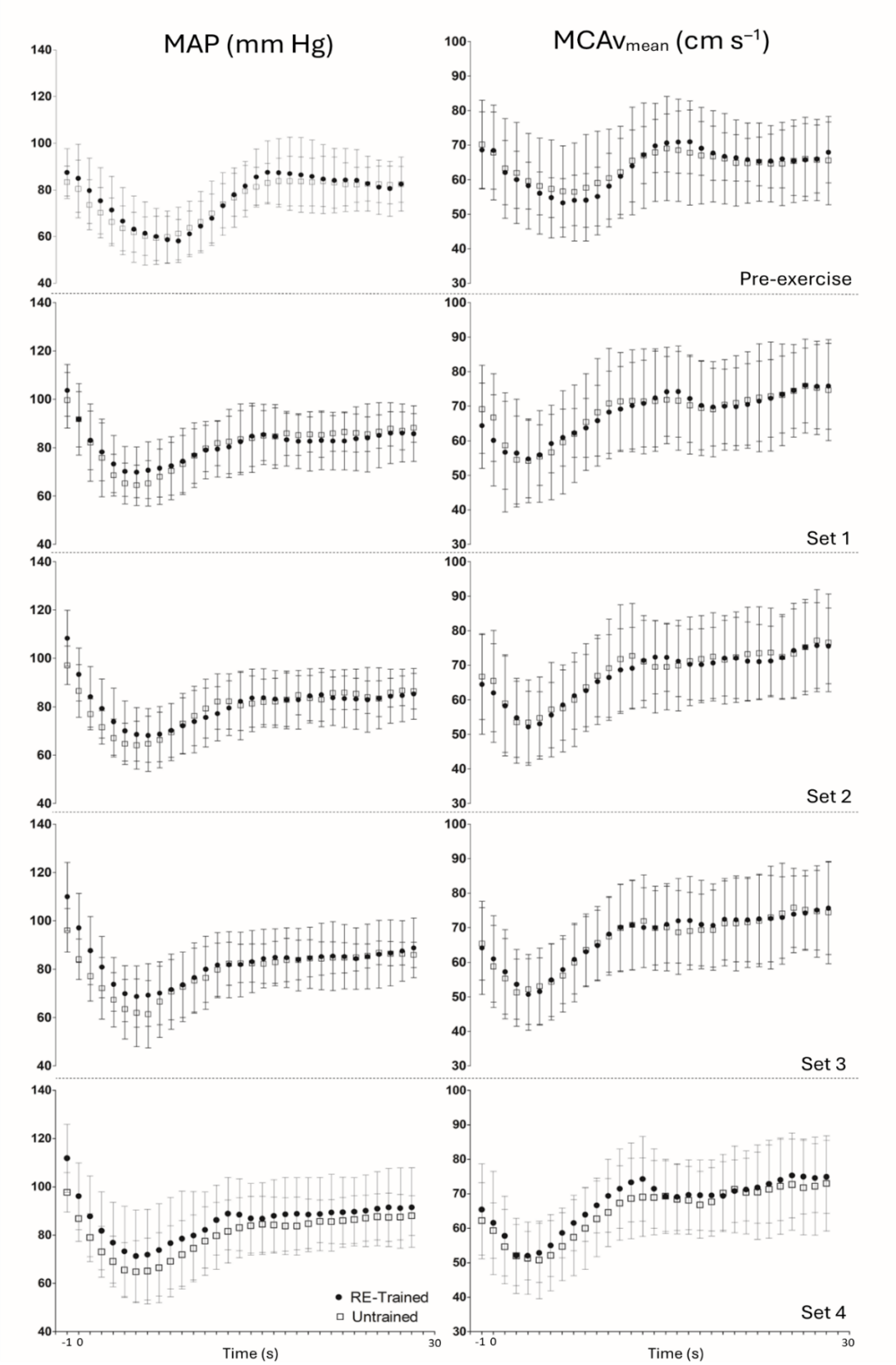

Figure 20 Temporal changes in mean arterial pressure (MAP) and mean middle cerebral artery blood velocity ($MCAv_{mean}$) during recovery from standing. On the x axes, -1 indicates the mean values for the 4s prior to standing which includes the last repetition of RE (i.e. pre-stand values) and standing occurred at time point 0. RE-trained (resistance exercise-trained) n = 14 and untrained n = 14.

Haemodynamic recovery during stand

There were no significant differences between the RE-trained and untrained groups for $MCAv_{mean}$ (interaction effect P = 0.657, RE-trained pre-exercise; 14 ± 7s, set 1;13 ± 9s, set 2; 12 ± 6s, set 3; 12 ± 7s, set 4; 11 ± 6s versus untrained group means;17 ± 18s,13 ± 7s, 12 ± 6s, 13 ± 12s, 15 ± 9s) and MAP (interaction effect P = 0.810; 17 ± 8s, set 1;17 ± 10s, set 2; 21 ± 12s, set 3; 17 ± 9s, set 4; 19 ± 11s versus 16 ± 9s, 17 ± 11s, 21 ± 19s, 19 ± 19s, 22 ± 19s) time to recovery after the stand. As illustrated in **Figure 20**, no significant differences were seen between the RE-trained and untrained group during recovery. Similarly, the AUC analysis for $MCAv_{mean}$ and MAP were also not different between groups; $MCAv_{mean}$ (interaction effect P = 0.428; -139 ± 66, set 1; -147 ± 138, set 2; -129 ± 68, set 3; -123 ± 70, set 4; -115 ± 65 versus -172 ± 253, -149 ± 109, -139 ± 80, -154 ± 133, -220 ± 251) and MAP (interaction effect P = 0.982; -236 ± 86, set 1; -203 ± 143, set 2; -265 ± 237, set 3; -203 ± 155, set 4; -252 ± 198 versus -242 ± 131, -204 ± 156, -259 ± 268, -227 ± 200, -281 ± 196).

Time to nadir

RE-trained and untrained individuals showed no significant differences in time to $MCAv_{mean}$ nadir (interaction P = 0.452) and MAP time to nadir (P = 0.818). Furthermore, there were no significant differences observed in the time-lag difference for $MCAv_{mean}$ and MAP nadir between the groups (P = 0.592).

Cerebral Autoregulation

A significant effect of training only was observed in RoR (P = 0.023), with the RE-trained group having a greater RoR (pre-exercise; 0.215 ± 0.12, set 1; 0.301 ± 0.17, set 2; 0.312 ± 0.10, set 3; 0.280 ± 0.12, set 4; 0.278 ± 0.15) versus the untrained group (0.172 ± 0.14; 0 .167 ± 0.09; 0.223 ± 0.13; 0 .240 ± 0.10; 0.229 ± 0.08). However, there were no significant training (P = 0.973), set (P = 0.384), or training by set (P = 0.959) effects between groups for the ratio of percentage change in MCAv versus percentage change in MAP at MCAv nadir.

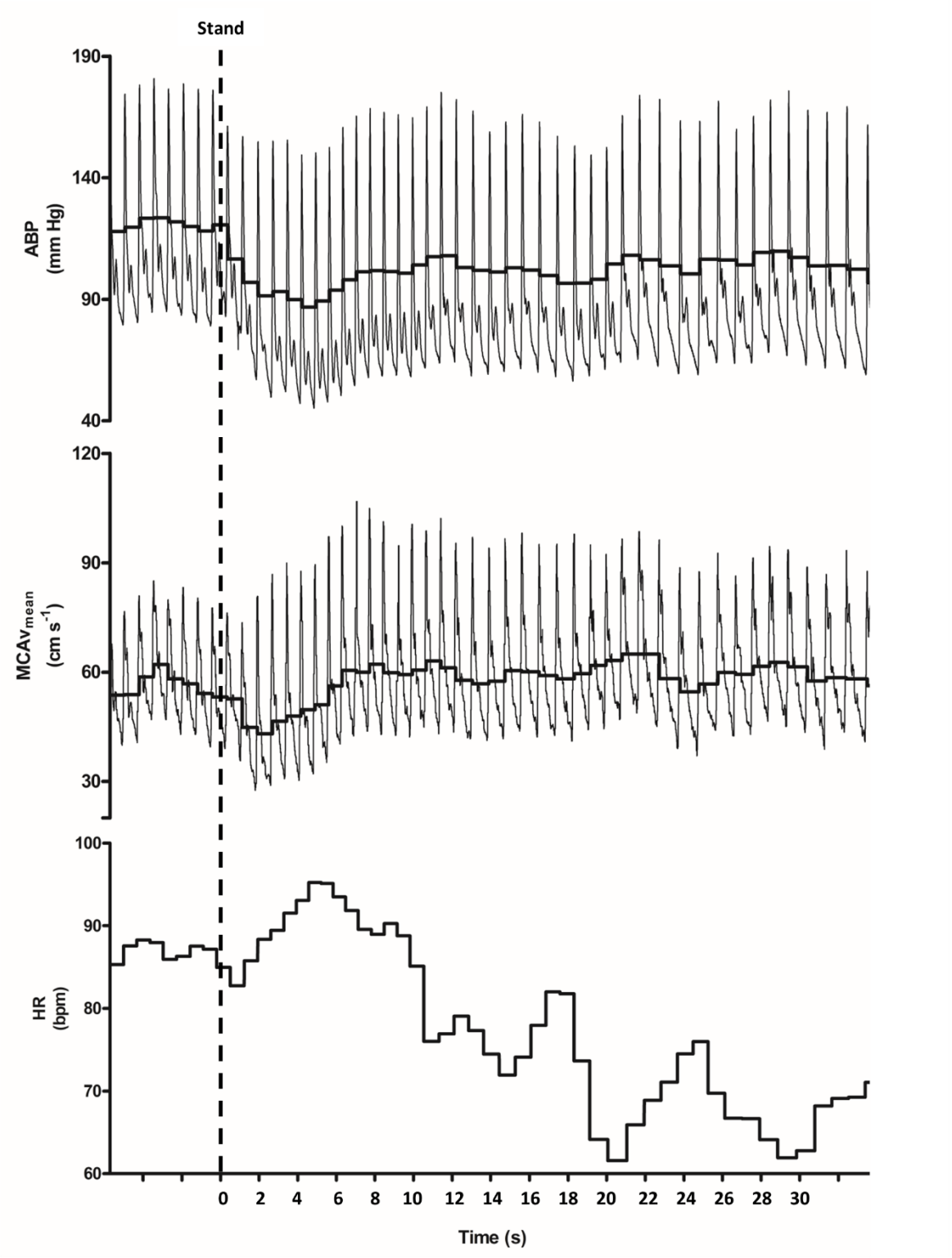

Figure 21 Typical trace of the arterial blood pressure (ABP), middle cerebral artery blood velocity (MCAv), and heart rate (HR) during post-exercise stand and 30s after the stand. The thick black line in the ABP and MCAv traces represent mean arterial blood pressure and mean MCAv. The dotted line labelled 'stand' (at time point 0) denotes the initiation of standing following RE (n = 1, RE-trained).

6.6 Discussion

The purpose of this chapter was to investigate the effects of training status on the cerebrovascular response to post-RE hypotension. The main findings from this chapter are as follows: 1) The RE-trained group had greater MAP pre-stand values than their untrained counterparts – indicating higher MAP in the last repetitions of RE 2) the RE-trained individuals demonstrated a larger decrease in MAP upon standing post-dynamic RE compared to the untrained individuals. However, 3) despite the greater reduction of MAP following RE in the RE-trained group, there was no group difference in the $MCAv_{mean}$ response. Furthermore, this was supported by 4) the recovery time and AUC which were not different between the groups and 5) the RE-trained individuals displayed significantly greater RoR values suggesting a more effective CA in the RE-trained group. These results are in agreement with **Chapter Five**, which highlighted that during RE, compared to their untrained counterparts RE-trained individuals were better at counteracting blood pressure changes during RE such that MCAv was similar despite greater MAP. The results in this chapter indicate that RE-trained individuals are more effective in countering the orthostasis-induced post-exercise hypotension as there was no difference in $MCAv_{mean}$ despite a greater reduction in post-exercise blood pressure upon standing. These data indicate more efficient CA in the RE-trained group following exercise, which is in accordance with our hypothesis. The cerebral adaptations that were evident in the RE-trained group during RE in **Chapter Five** persist in the post-exercise period, revealing the increased effectiveness of dCA in RE-trained individuals during and post-RE compared to healthy untrained.

Despite larger absolute decreases in MAP for RE-trained individuals, both groups experienced a smaller reduction in MAP post-stand than reported by others. Previous studies, using bilateral leg press exercises at higher intensities (>65% of 1RM) (Moralez et al., 2012; Romero & Cooke, 2007), reported greater MAP reductions (>70mm Hg), likely due to larger engaged muscle mass and higher exercise intensity. As within-exercise MAP responses are muscle mass and intensity-dependent, therefore the within-exercise MAP begins at a greater value (MacDougall et al., 1992) and has further to “fall” to achieve the MAP nadir value and return to baseline. Due to the use of unilateral leg extension at the moderate intensity of 60% 1RM in the current chapter, smaller post-RE MAP decreases are reported herein, aligning with Perry,

Schlader, et al. (2014), who noted that higher exercise intensities produce a greater rise in MAP during exercise and increases the magnitude of post-exercise hypotension.

Although a greater decrease in MAP in the RE-trained group was observed during the stand-following dynamic RE, the reduction in $MCAv_{mean}$ did not differ between training groups. This aligns with our previous chapter of the current data, indicating that despite greater within-exercise MAP perturbations in the RE-trained compared to the untrained, the $MCAv_{mean}$ response was similar between groups. It is therefore possible that the RE-trained group have improved autoregulation. Indeed, RoR was greater in the RE-trained group versus the untrained in all stands. Additionally, analysis of the AUC and time to recovery data revealed no group differences, indicating that the magnitude (extent of the decrease and duration) of the post-RE hypotension and cerebral hypoperfusion were similar in the context of this experiment. Despite RE-trained individuals experiencing a larger initial drop in MAP, their CA effectively compensated, allowing them to return to baseline MAP values just as quickly as the untrained group. This is noteworthy, as greater reductions in MAP are associated with increased symptoms of orthostatic instability (Romero & Cooke, 2007). Although Perry et al. (2019) found no difference in CA between RE-trained, aerobic-trained, and untrained individuals, further analysis of this data by Roy et al. (2022) indicated that the directional sensitivity of CA is present in sedentary, but not RE-trained individuals. That is, when comparing CA effectiveness during bidirectional ABP perturbations untrained individuals demonstrated a greater ability to defend against increases in ABP during repeated squat-stands at both 0.10Hz and 0.05Hz frequencies. Collectively, these data indicate that habitual RE may produce subtle differences in CA, although comparing studies is difficult due to the different methods used to measure CA (Brassard et al., 2024).

P_aCO_2 is a potent regulator of CBF, with elevations in P_aCO_2 increasing CBF, whilst a reduction has the opposite response (Ainslie & Duffin, 2009). Whilst MAP rapidly fluctuates during RE, the overriding influence of P_aCO_2 persists, with pre-RE hyperventilation reducing $MCAv_{mean}$ during leg press exercise (Romero & Cooke, 2007). Furthermore, increases in $MCAv_{mean}$, are seen during fatiguing isometric handgrip exercise only when $P_{ET}CO_2$ (as a proxy for arterial CO_2 content) is clamped at near baseline levels (Braz et al., 2014). Importantly for the current chapter, there was no observed difference in $P_{ET}CO_2$ between groups at pre-stand values (i.e. end

of exercise) and at $MCAv_{mean}$ or MAP nadir, which suggests that the $MCAv_{mean}$ responses were unlikely to be influenced by $P_{ET}CO_2$. However, although there are no statistical differences during or following RE in the current chapter, given the potency of CBF regulation by P_aCO_2 even small reductions in P_aCO_2 induced by the paced breathing during RE in the current experiment should be considered when interpreting the data.

The repetitive exposure to high-intensity (~80% of 1RM) sinusoidal fluctuations in ABP has been observed to elicit adverse adaptations within the cardiorespiratory system, with a reduction in central arterial compliance (DeVan et al., 2005; Miyachi, 2013; Miyachi et al., 2004; Okamoto et al., 2009; Palmiere et al., 2018) and increased CVR at rest when compared to sedentary controls (Nakamura & Muraoka, 2018; Thomas et al., 2021), although the last point is not a consistent finding (Corkery et al., 2021). Koch et al. (2005) reported that immediately after (<90 s) RE CA was temporarily impaired in RE-trained individuals. Furthermore, dynamic RE elicits an intensity-dependent rise in blood flow turbulence and endothelial shear stress in the brain and the common carotid artery (Montalvo et al., 2022) and increased anterograde shear rate and blood flow in inactive limbs (Thomas et al., 2020). These findings suggest that dynamic RE significantly elevates shear rate and endothelial shear stress, which are accompanied by sinusoidal fluctuations in CBF and perfusion pressure, potentially leading to acute changes in cerebrovascular function (Dawson et al., 2021).

Limitations

The limitations included in this experimental chapter are specific to this chapter, more general limitations will be discussed in **Chapter Eight Section 8.2**

The mechanisms underpinning CA are not yet fully understood, however, it may be that large sinusoidal fluctuations in MAP are needed to engage the functional adaptations of RE as challenges at lower frequencies are effectively buffered by CA as previously elucidated by Perry and Lucas (2021). The current chapter shows that standing after moderate intensity dynamic RE induces large absolute decreases in ABP in RE-trained individuals, however, the dynamic RE was unilateral, engaging a modest muscle mass and therefore inducing moderate increases in blood pressures.

Confirmation of these data at higher intensities, or RE recruiting a greater muscle mass is required.

Though this study included both RE-trained and untrained groups, a higher proportion of females participated in the untrained group compared to the RE-trained group. Whilst this imbalance was not intentional, given the limited research in this area with female participants these data were included. There is some evidence to indicate that there are sex differences in cerebral autoregulation and haemodynamic responses to forced perturbations in blood pressure. However, the results of these studies indicate superior CA in females. During a supine-sit-stand protocol, Abidi et al. (2017) reported lower $MCAv_{mean}$ in males. In the same study, Abidi reported that during the recovery of blood pressure during late phase II of the VM $MCAv_{mean}$ was greater in eumenorrheic females during the high hormone phase of the menstrual cycle (luteal phase) compared to males. Similarly, during the same phase of the VM, females using oral contraceptives (during both placebo and hormone phase) exhibited significantly greater diastolic MCAv compared to males. Moreover, Favre and Serrador (2019) reported significantly improved cerebral autoregulation in females (transfer function analysis during repeated squat stands) and had a smaller decrease in $MCAv_{mean}$ during sit-to-stand manoeuvres. When considering the regulation of blood pressure, females demonstrate greater baroreflex sensitivity compared to males during acute reductions in blood pressure (Fu et al., 2009). Collectively, these data indicate superior haemodynamic counter-regulation during acute perturbations in blood pressure in females compared to males. Given the greater number of females in the untrained group, it would therefore be expected that the untrained group would have superior CA and blood pressure regulation during the acute reduction in blood pressure induced by the experimental conditions of the current study. However, this was not evident, thus supporting our findings that the difference between groups is due to habitual exercise.

6.7 Conclusion

The results of the current chapter indicate that despite the RE-trained group demonstrating a greater absolute decrease in post-RE blood pressure compared to the untrained group, the $MCAv_{mean}$ response was similar between groups This

indicates that the RE-trained group has a more efficient cerebral autoregulation, and it may be possible that habitual RE could induce functional vascular adaptations that assists with maintaining CBF during more pronounced blood pressure reductions. The results of this chapter complement the findings of **Chapter Five**, as both chapters observed more effective dCA in the RE-trained group compared to the untrained group. CA is not the only regulator that is involved in CBF regulation during dynamic RE, as regulators such as $PaCO_2$ and NVC are also involved. The regulators of CBF interact with one another, with $PaCO_2$ and CA exhibiting an overwhelming influence on CBF regulation. However, exploring whether the contribution of NVC is present during dynamic RE would provide valuable insight into the hierarchy of CBF regulators.

Chapter Seven: Neurovascular coupling during dynamic upper body resistance exercise in healthy individuals

The work included in this chapter has been published in *Experimental Physiology*. The data, results, and key outcomes of the published work are unchanged within the chapter; however, the layout and formatting have been modified to fit within this thesis.

Korad, S., Mündel, T., & Perry, B. G. (2024). Neurovascular coupling during dynamic upper body resistance exercise in healthy individuals. *Experimental Physiology,* 109, 2017 – 2025.

7.1 Introduction

As mentioned in **Chapter Two Section 2.1.5** NVC is one of the regulators of CBF and refers to the matching of perfusion to tissue activity, whereby increased neuronal activity mediates a rise in local CBF. During unilateral static handgrip exercise at low-intensities (30 – 40 % of maximal voluntary contraction), NVC mediates an increase in blood velocity in the middle cerebral artery (MCAv, as a proxy for CBF) contralateral to the exercising limb by 14 – 18% (Braz et al., 2014; Imms et al., 1998), and contralateral internal carotid artery (ICA) blood flow by 14 – 22% (Fernandes et al., 2016; Hirasawa et al., 2016). Similarly, during unilateral rhythmic handgrip exercise (30 contractions per minute for 5 minutes) Jorgensen et al. (1993) reported an increase in MCAv contralateral to the exercising limb only, whilst others have reported a bilateral increase in MCAv, with slightly greater increases in contralateral MCAv (Giller et al., 2000; Ide et al., 1998). Collectively, these data indicate that low-intensity static RE increases CBF, primarily in the contralateral hemisphere to the exercising limb.

Dynamic RE generates sinusoidal fluctuations in blood pressure that are transmitted to the cerebral circulation (Perry & Lucas, 2021). Whilst rare, the dynamic RE-induced rapid changes in blood pressure and cerebral perfusion pressure has the potential to cause cerebrovascular injury (Edwards et al., 2002), however, any risk associated with dynamic RE is usually post-exercise hypoperfusion or syncope. However, this is greatly influenced by the magnitude of reduction in MAP and MCAv

and the intensity (load lifted %1RM) (Perry, Schlader, et al., 2014). Given the wide range of benefits RE confers (e.g. increased muscle mass and strength) dynamic RE is recommended during the recovery from stroke and can improve quality of life (Ali et al., 2021). Consideration is required when prescribing RE following stroke as CA is globally impaired (Aries et al., 2010). Thus, the correct prescription of RE in this population is critical in limiting exposure to extreme blood pressures to avoid further cerebrovascular injury yet still be sufficiently stimulating to permit the advantageous adaptations that RE confers.

The plethora of CBF regulators still exert individual control during RE despite the background of rapidly fluctuating perfusion pressure (Perry & Lucas, 2021). However, the contribution of NVC to the within dynamic RE MCAv profile is yet to be determined. We have seen in the previous two chapters these dynamic fluctuations in blood pressure even during very low-intensity unilateral exercise. Therefore, the results of the current chapter could inform the safe prescription of dynamic RE, particularly for individuals who have experienced cerebrovascular injury. This current chapter aimed to investigate the cerebral haemodynamic response to unilateral dynamic upper body RE in healthy individuals. As alluded to in the previous chapter, $PaCO_2$ and CA have an overwhelming influence on CBF, however, NVC is an important regulator of CBF, particularly during static/isometric RE. The magnitude of the contribution of NVC to the MCAv response is the focus of this chapter. It was hypothesised that during unilateral dynamic RE, there will be no differences between contralateral and ipsilateral MCAv as MAP and $PaCO_2$ will override NVC.

7.2 Methods

A total of 30 participants (female = 16) were recruited for this study (mean ± SD: age, 26 ± 6 years, height 1.75 ± 0.1m, weight 74 ± 15 kg, BMI 24 ± 5 kg/m^2). All the participants were pooled together for this chapter, as the focus was investigating the effects of NVC on the cerebral haemodynamic response to unilateral upper body RE. This chapter was part (c) of **Figure 16** (see **Section 4.2.4**) in which the participants completed 4 sets of 10 reps of the bicep curl exercise at 60%1RM to a tempo of 15 reps-per-minute. The working intensity for the trial was 60% of the predicted 1RM (60%1RM, mean ± SD: bicep curl predicted 1RM 12 ± 5 kg, 60% of 1RM 7 ± 3 kg). Modifications to **Chapter Four Section 4.2.6** were made as this chapter required the insonation of both the contralateral and ipsilateral MCA to the exercising limb. To

accurately measure NVC, MCAv needed to be measured bilaterally so that the MCAv responses between the contralateral and ipsilateral sides could be compared during upper body dynamic RE.

After each set the participant rested for 5 minutes before performing the exercise again. A total of 40 reps were performed.

See **Chapter Four Section 4.2** for a detailed description of the techniques and methods used for this experimental chapter.

7.3 Data Analysis

Dependent Measures

The calculations for $MCAv_{mean,}$ MAP, CVCi, and PI were described in **Chapter Four Sections** 4.1.3 ($MCAv_{mean}$), **4.1.4** (CVCi), **4.1.5** (PI), **4.1.9** (MAP). Given the sinusoidal haemodynamic profile during RE, the zenith and nadir $MCAv_{mean}$ values for both the ipsilateral and contralateral sides were identified for each repetition and the average values were calculated for each set. Additionally, zenith-to-nadir $MCAv_{mean}$ differences for both sides were calculated as the zenith $MCAv_{mean}$ value – the nadir $MCAv_{mean}$ value during each repetition, respectively. The average zenith-to-nadir values for $MCAv_{mean}$ were calculated for each set.

7.4 Statistical Analysis

Data were analysed using SPSS statistical software version 28 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P \leq 0.05$. The Shapiro-Wilk test confirmed all data was normal ($P > 0.081$). To check for drift in physiological variables of interest before exercise a two-way ANOVA was performed to analyse cerebrovascular variables in the baseline period immediately prior to each set of exercise (side x baselines, 2 x 5), and a one-way ANOVA was performed to analyse cardiovascular baseline data. Cerebrovascular dependent variables of interest at initial baseline (following instrumentation at the beginning of the trial) and during dynamic RE (average data across all performed repetitions) were analysed using a two-way ANOVA (side x sets (including initial baseline), 2 x 5), whilst cardiovascular data was analysed using a one-way ANOVA. Partial eta square (partial $\eta 2$) is reported for the training by set interaction only, with large effect sizes identified as > 0.138, medium 0.059 - 0.134, and small <0.010 (Cohen, 2013). All data were displayed as the mean

± SD. A linear mixed model analysis was also performed to investigate the effects of $P_{ET}CO_2$ and MAP on MCAv. The analysis included a random effect for participants to control for within-subject correlations. Fixed effect included $P_{ET}CO_2$, MAP, sets, and MCAv side. Four models were analysed: a baseline model, $P_{ET}CO_2$-only, MAP-only, and a combined $P_{ET}CO_2$ and MAP model. Type III test of fixed effect and estimates of fixed effects were examined.

7.5 Results

Baseline measurements

Baseline measures across the trial are shown in **Table 8** for cardiovascular measures and **Table 9** for cerebrovascular measures. There were no significant differences in baseline data for cerebrovascular measures, however, MAP was increased from initial baseline prior to set 4 (see **Table 8** for values).

Table 8 Mean cardiovascular measures during baseline and within-exercise

Variable	Sets					*P* value
	Initial	Set 1	Set 2	Set 3	Set 4	
Baseline (pre-exercise)						
$P_{ET}CO_2$ (mm Hg)	37 ± 5	37 ± 5	36 ± 5	36 ± 5	35 ± 5	0.706
HR (bpm)	70 ± 13	72 ± 13	70 ± 14	70 ± 13	71 ± 13	0.928
MAP (mm Hg)	82 ± 8	87 ± 9	88 ± 9	88 ± 9	91 ± 10 [a]	**0.011**
Exercise						
$P_{ET}CO_2$ (mm Hg)	37 ± 5	35 ± 5	34 ± 5	33 ± 5 [a b]	33 ± 5 [a b]	**0.005**
HR (bpm)	70 ± 13	88 ± 15 [a]	87 ± 14 [a]	88 ± 14 [a]	88 ± 15 [a]	**<0.001**
MAP (mm Hg)	82 ± 8	95 ± 13 [a]	96 ± 13 [a]	98 ± 14 [a]	100 ± 14 [a]	**<0.001**

Data are presented Mean ± SD, $P_{ET}CO_2$; End Tidal Carbon Dioxide, HR; heart rate, MAP; Mean Arterial Pressure, mm Hg; millimetres of mercury, bpm; beats per minute. *n = 30*. [a] different to initial baseline (*P* =< 0.024). [b] different to set 1 (*P* =< 0.002).

Table 9 Mean cerebrovascular measures during baseline and within-exercise

Variable	Condition	Sets					*P* value			Partial η^2
		Initial	Set 1	Set 2	Set 3	Set 4	Side	Set	Interaction	
Baseline (pre-exercise)										
$MCAv_{mean}$ (cm s^{-1})	Contralateral	66 ± 11	67 ± 10	66 ± 10	65 ± 10 [b]	64 ± 10 [a b]	0.753	**<0.001**	0.677	0.010
	Ipsilateral	66 ± 11	65 ± 10	64 ± 11	64 ± 10 [b]	63 ± 11 [a b]				
CVCi (cm s^{-1} mm Hg^{-1})	Contralateral	.81 ± .14	.77 ± .14 [a]	.76 ± .15 [a b]	.75 ± .14 [a b]	.71 ± .14 [a b c d]	0.771	**<0.001**	0.902	0.004
	Ipsilateral	.80 ± .15	.76 ± .14 [a]	.74 ± .14 [a b]	.74 ± .14 [a b]	.71 ± .14 [a b c d]				
PI	Contralateral	.82 ±.12	.81 ± .13	.83 ± .15	.82 ± .16	.82 ± .16	0.781	0.496	0.997	0.001
	Ipsilateral	.83 ± .13	.83 ± .13	.84 ± .15	.83 ± .15	.83 ± .15				
Exercise										
$MCAv_{mean}$ (cm s^{-1})	Contralateral	66 ± 11	64 ± 9	61 ± 9 [a b]	60 ± 8 [a b]	59 ± 8 [a b c]	0.633	**<0.001**	0.894	0.005
	Ipsilateral	66 ± 11	62 ± 10	60 ± 9 [a b]	59 ± 9 [a b]	59 ± 10 [a b c]				
CVCi (cm s^{-1} mm Hg^{-1})	Contralateral	.81 ± .14	.69 ± .13 [a]	.65 ± .13 [a b]	.63 ± .13 [a b c]	.61 ± .13 [a b c d]	0.716	**<0.001**	0.959	0.003
	Ipsilateral	.80 ± .15	.67 ± .13 [a]	.64 ± .13 [a b]	.62 ± .13 [a b c]	.60 ± .13 [a b c d]				
PI	Contralateral	.82 ±.12	.81 ± .14	.80 ± .14	.80 ± .13	.80 ± .13	0.884	0.259	0.996	0.001
	Ipsilateral	.83 ± .13	.81 ± .13	.80 ± .13	.81 ± .13	.80 ± .12				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Mean Middle Cerebral Artery Blood Velocity, PI; Pulsatility Index, cm s^{-1}, centimetres per second, cm s^{-1} mm Hg^{-1}; centimetres per second per millimetre of mercury, mm Hg; millimetres of mercury. *n = 30*. [a] different to initial baseline (*P* =<0.020). [b] different to set 1(*P* =<0.007). [c] different to set 2 (*P* =<0.050). [d] different to set 3 (*P* =<0.006).

Response to Dynamic Resistance Exercise

The typical cerebrovascular and cardiovascular responses to exercise are detailed in **Error! Reference source not found.**. Mean group within-exercise cardiovascular responses across the 10 bicep curls are shown in **Table 8**, with the cerebrovascular responses during the same period shown in **Table 9**. When examining the cerebrovascular responses to exercise, there were no significant differences between the ipsilateral or contralateral MCAv, CVCi, or PI (all $P > 0.633$). However, there was a significant decrease in $P_{ET}CO_2$ in sets 3 and 4 relative to initial baseline and set 1, and MAP and HR increased compared to initial baseline across all exercise sets (all $P < 0.005$). An effect of set (all $P < 0.001$) indicates that both ipsilateral and contralateral $MCAv_{mean}$ and CVCi values decreased across the sets during exercise (see **Table 2**).

Linear Mixed Model Analysis

The results of the linear model analysis reflected that seen by the ANOVA. The baseline model revealed the significant effect of sets ($F = 14.652$, $P < 0.001$) but non-significant effects of MCAv side ($F = 2.407$, $P = 0.122$). The $P_{ET}CO_2$-only model showed a strong positive effect of $P_{ET}CO_2$ on MCAv (Estimate = 1.027, t = 8.537, $P < 0.001$), with a high F-value (72.874), indicating a strong relationship. The MAP-only model also showed a positive effect of MAP on MCAv (Estimate = 0.127, t = 2.388, $P = 0.018$). The combined model revealed that both $P_{ET}CO_2$ (Estimate = 1.019, t = 8.490, $P < .001$) and MAP (Estimate = 0.107, t = 2.243, $P = 0.026$) were significant predictors, with $P_{ET}CO_2$ having a greater influence. The influence of set remained significant ($F = 2.996$, $P = 0.019$), suggesting changes in MCAv over sets.

Table 10 Main cerebrovascular measures during zenith, nadir, and zenith-to-nadir difference

Variable	Condition	Sets				*P* value			Partial η^2
		Set 1	Set 2	Set 3	Set 4	Side	Set	Interaction	
MCAv Zenith									
MCAv (cm s^{-1})	Contralateral	69 ± 11	66 ± 10	65 ± 9	64 ± 9	0.557	**<0.001**	0.912	0.003
	Ipsilateral	67 ± 11	65 ± 11	63 ± 10	63 ± 10				
CVCi (cm s^{-1} mm Hg^{-1})	Contralateral	.74 ± .16	.71 ± .16	.68 ± .15	.66 ± .15	0.659	**<0.001**	0.953	0.002
	Ipsilateral	.72 ± .16	.69 ± .16	.67 ± .14	.64 ± .15				
MCAv Nadir									
MCAv (cm s^{-1})	Contralateral	61 ± 11	59 ± 9	58 ± 9	57 ± 9	0.598	**<0.001**	0.970	0.001
	Ipsilateral	59 ± 11	58 ± 10	57 ± 10	56 ± 10				
CVCi (cm s^{-1} mm Hg^{-1})	Contralateral	.68 ± .16	.65 ± .16	.63 ± .15	.61 ± .14	0.715	**<0.001**	0.973	0.001
	Ipsilateral	.67 ± .16	.64 ± .16	.62 ± 15	.59 ± .14				
Zenith-to-Nadir Difference									
$MCAv_{mean}$	Contralateral	8 ± 2	7 ± 2	7 ± 3	7 ± 3	0.645	0.067	0.956	0.002
	Ipsilateral	8 ± 2	7 ± 2	7 ± 3	7 ± 3				
CVCi	Contralateral	.06 ± .02	.05 ± .02	.05 ± .03	.05 ± .02	0.558	0.085	0.892	0.004
	Ipsilateral	.05 ± .02	.05 ± .02	.05 ± .02	.05 ± .02				

Data are presented Mean ± SD, CVCi; Cerebrovascular Conductance Index, $MCAv_{mean}$; Mean Middle Cerebral Artery Blood Velocity, cm s^{-1}, centimetres per second, cm s^{-1} mm Hg^{-1}; centimetres per second per millimetre of mercury, mm Hg; millimetres of mercury. *n = 30*.

Zenith and Nadir Response to Dynamic Resistance Exercise

Similarly, to the averaged responses during exercise only set differences were seen for contralateral and ipsilateral $MCAv_{mean}$ and CVCi, at zenith $MCAv_{mean}$ and nadir $MCAv_{mean}$ (all $P < 0.001$, see Table 3 for values).

Zenith-to-Nadir difference

No significant effect of side ($P = 0.645$) and interaction ($P = 0.956$) was observed in MCA_{vmean} Furthermore, there were no side ($P = 0.558$) or interaction ($P = 0.892$) effect was seen for CVCi zenith-to-nadir difference (see **Table 10**).

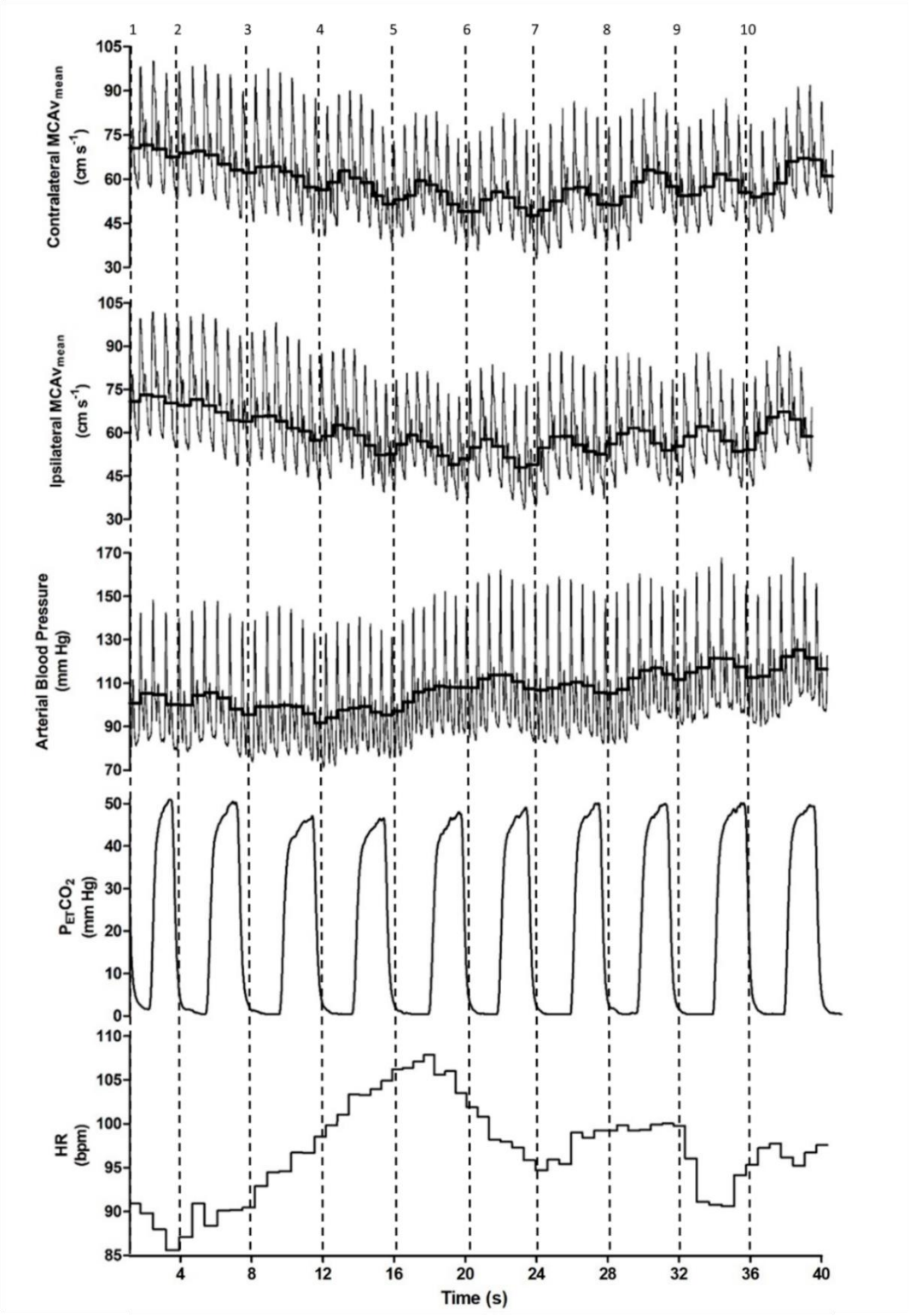

Figure 22 Typical trace of the contralateral and ipsilateral middle cerebral artery blood velocity (MCAv), arterial blood pressure (ABP), partial pressure of end tidal carbon dioxide ($P_{ET}CO_2$), and heart rate (HR) during exercise. The thick black line in the MCAv and ABP traces represents mean MCAv and mean arterial pressure, respectively. The number indicate the repetition count with the dotted line denoting the start (concentric phase) of each repetition (n = 1).

7.6 Discussion

The purpose of this chapter was to investigate the effects of the cerebral haemodynamic response to unilateral dynamic upper body RE in healthy individuals. In agreement with our initial hypothesis, the data revealed no significant differences in $MCAv_{mean}$, or any cerebrovascular variables, between the contralateral and ipsilateral sides to the exercising limb. The findings of this chapter indicate that the effects of NVC were not discernible in the MCAv data.

Previous studies report NVC as the primary mechanism for increasing contralateral MCAv during static (Braz et al., 2014; Imms et al., 1998) and rhythmic (Giller et al., 2000; Ide et al., 1998; Jorgensen et al., 1993) handgrip exercise. During static RE NVC is responsible for mediating an increase in CBF during modest increases in MAP (Braz et al., 2014). The increase in MAP during handgrip exercise is gradual and plateaus after ~90s (Hirasawa et al., 2016). The slow gradual increase in blood pressure allows for CA to counteract the prevailing blood pressure, thereby facilitating observable NVC-mediated increases in MCAv contralateral to the exercising limb. However, the current chapter implemented dynamic upper body RE to assess the contribution of NVC to CBF and observed no difference in contralateral and ipsilateral $MCAv_{mean}$ with respect to the exercising limb. The current chapter measured blood velocity in a large feed artery (the middle cerebral artery) to estimate the blood flow response to each hemisphere. Indeed, the posterior cerebral artery blood velocity response to a visual stimulus is a common method of assessing NVC in the occipital lobe, indicating NVC responses can be readily detected in the large arteries of the circle of Willis. However, in the context of the current experiment, the sinusoidal perturbations in blood pressure generates constantly changing cerebral autoregulatory stimuli, and the adjustments in vessel tone and radius will lag the changes in perfusion pressure (Zhang et al., 1998). It appears from the current data that the changing blood pressure may obfuscate any NVC-mediated response that is otherwise apparent when MAP is more stable or changing slowly (e.g. during static RE). Furthermore, hypocapnia, as induced by pre-exercise hyperventilation, reduces within-exercise MCAv (Romero & Cooke, 2007), indicating the potency of arterial CO_2 content in regulating CBF (vasoconstriction in this instance) even during rapid changes in perfusion pressure. In the current experiment, the modest within RE decrease (2mm

Hg) in $P_{ET}CO_2$ likely underpins the reduction in $MCAv_{mean}$ across exercise sets. Although a variety of vessels are involved in regulating CBF (Tzeng et al., 2014), as the NVC vascular responses are occurring downstream of the middle cerebral artery in the smaller arteries and arterioles supplying the active brain areas, other methods with greater spatial resolution may be required to identify potential changes in local blood flow between the cerebral hemispheres during dynamic RE.

Even though no differences between the contralateral and ipsilateral $MCAv_{mean}$ were apparent, dynamic RE recruiting a small muscle mass generated modest fluctuations in blood pressure that were sufficient to generate bilateral fluctuations in $MCAv_{mean}$. The observed bilateral changes in $MCAv_{mean}$ occurred with much smaller perturbations in blood pressure (and presumably cerebral perfusion pressure) than previously reported (Edwards et al., 2002; Perry, Schlader, et al., 2014). Thus, the contraction of a small muscle mass dynamically could still confer beneficial vascular adaptations in both cerebral hemispheres and unilateral RE could be used therapeutically to acutely increase bilateral shear stress in individuals with hemiplegia or hemiparesis. However, further testing in a clinical setting is required to confirm this.

Limitations

The limitations included in this experimental chapter are specific to this chapter, more general limitations will be discussed in **Chapter Eight Section 8.2**

The use of TCD limits the measurement of blood velocity (as a proxy for blood flow) to the large intracranial arteries. Using near-infrared spectroscopy (NIRS) could further explore localised NVC responses (e.g. in the primary motor cortex). However, concurrent blood volume measurements using NIRS would be difficult in the context of the current experiment as the TCD probes are fixed in position using a headband that limits space on the scalp for the placement of additional technologies.

7.7 Conclusion

The current findings indicate that during dynamic upper body RE, there were no differences between contralateral and ipsilateral $MCAv_{mean}$. The effects of NVC were not discernible in the MCAv data and this may be due to the overriding influence

of $P_{ET}CO_2$ and MAP. Further research is required to investigate how NVC and the regulators of CBF interact during dynamic RE.

Chapter Eight: General Discussion

This thesis sought to investigate the effects of dynamic RE on the within and post-RE cerebrovascular responses in healthy individuals. The sinusoidal blood pressure fluctuations elicited during dynamic RE provides the cerebral circulation with a unique challenge to overcome and ensure that the brain receives adequate blood flow. Whether repeated exposure to dynamic RE elicits functional vascular adaptations that mitigate the sinusoidal blood pressure fluctuations in the cerebral circulation during RE were not recognised in previous literature. Furthermore, if functional vascular adaptations do occur, it is also unclear how this affects cerebral autoregulation. The effects of habitual RE during dynamic RE and post-RE were the focus of **Chapter Five** and **Chapter Six**. Previous studies have used static RE to investigate the effect of exercise on NVC, however, dynamic RE is more functional and readily performed than static RE, therefore it is important to investigate NVC using dynamic RE. Subsequently, **Chapter Seven** investigated the contribution of NVC to the CBF response during dynamic upper body RE.

8.1 Discussion

Chapter Five of this thesis investigated the effect of habitual RE training on the cerebrovascular response to dynamic RE induced sinusoidal fluctuations in blood pressure between RE-trained and untrained individuals. **Chapter Six** then investigated the effect of habitual RE training on the cerebrovascular response to orthostasis induced post-RE hypotension. The results presented in **Chapter Five** showed that during dynamic RE, RE-trained individuals achieved higher blood pressures during exercise, however, there were no differences in $MCAv_{mean}$ between the two groups. Unlike previous studies (Dickerman et al., 2000; Edwards et al., 2002; Moralez et al., 2012; Perry, Schlader, et al., 2014; Romero & Cooke, 2007) that only analysed the mean of $MCAv_{mean}$ across all repetitions in a set, in **Chapter Five** and **Chapter Seven** the zenith and nadir measures, and zenith-to-nadir difference, were analysed to represent the blood pressure more accurately and $MCAv_{mean}$ profiles. To my knowledge, this is the first study to use the zenith and nadir measures during dynamic RE. The MAP zenith and nadir measures revealed that it was the SBP values that were significantly elevated and therefore driving the increased MAP in the RE-trained group during RE. Furthermore, the RE-trained group exhibited greater within-

RE zenith-to-nadir difference in MAP. Thus, in RE-trained individuals not only were zenith and nadir MAP values greater, the magnitude of the fluctuations (the zenith-to-nadir difference) were also greater than the untrained group. Despite these greater perturbations in MAP, $MCAv_{mean}$ did not follow a similar pattern and was similar between groups during RE. The results from **Chapter Five** suggest that habitual exposure to the sinusoidal fluctuations in blood pressure may have provided RE-trained individuals with functional adaptations which enabled more robust cerebrovascular response during the familiar stressor to limit the rise in MCAv and potential hyperperfusion.

The results of **Chapter Six** complement the findings of **Chapter Five**, as the results from **Chapter Six** highlighted that RE-trained had a greater reduction in MAP during the post-exercise stand compared to the untrained group. However, despite the larger reduction in MAP, $MCAv_{mean}$ was not different between groups during post-exercise stand. Thus, the findings of the within-RE data (**Chapter Five**) persist post-RE (**Chapter Six**) in that larger perturbations in MAP in the RE-trained group are not translated to greater differences in $MCAv_{mean}$. This is supported by the RoR data, which was greater in the RE-trained group, indicating more effective dCA during the recovery from the post-RE hypotension induced by standing. Unlike **Chapter Five** that observed that the increase in MAP was driven by the prevailing systolic blood pressure, during the post-RE stand it was the decrease in diastolic blood pressure that was driving the reductions in MAP. Collectively, these findings suggest that engaging in habitual RE does elicit some adaptations that allow individuals that regularly experience fluctuating blood pressures during dynamic RE to maintain a more stable $MCAv_{mean}$ during and following RE. Whilst the effects of habitual RE on dCA are unclear in an experimental setting (Perry et al., 2019; Roy et al., 2022), the effects of habitual RE on dCA are revealed during and immediately following RE.

The findings confirmed the hypothesis for **Chapter Five**, that RE-trained did have smaller fluctuations in $MCAv_{mean}$ despite having greater fluctuations in blood pressure during RE compared to the untrained group. Similarly, these data also confirm the hypothesis for **Chapter Six**, that although RE-trained individuals would display a greater blood pressure response during RE there was no difference in recovery time for MCAv indicating that RE-trained individuals had better CA than the untrained. RE is beneficial in many ways as described in **Chapter One**, and the

findings of **Chapter Five** and **Chapter** Six reveal that particularly with RE, there is some type of adaptation that occurs, so despite moderate changes in blood pressure, there are smaller variations in MCAv. Whether that is a benefit long term is uncertain because it is the swings in blood pressure and shear stress that are important for vascular health (Lu & Kassab, 2011). Previous studies have shown that even after an acute bout of RE, an increase in arterial stiffness was observed (Kawano et al., 2006; Miyachi, 2013). Furthermore, cross-sectional studies have reported greater arterial stiffness in RE-trained compared to untrained individuals (DeVan et al., 2005; Miyachi et al., 2004). This increase in stiffness could exacerbate blood pressure fluctuations and transmit them to the cerebral circulation as the damping effect of the central arteries is reduced. However, although central arterial compliance (e.g. aorta) was not measured in this thesis, in this thesis RE-trained individuals did not demonstrate elevated PI before and following RE, and $MCAv_{mean}$ during RE was similar between groups. Therefore, it is possible that some reciprocal adaptation occurs between central arterial compliance and the regulation of CBF as governed by dCA. In endurance trained individuals a similar adaptation is seen, as the heart becomes more powerful as a result of habitual endurance exercise stroke volume increases, but the central arteries become more compliant to accommodate this increase such that pulsatility in intracranial arteries is unchanged (Hellsten & Nyberg, 2011). Whereas in RE even though there is a reduction in central arterial compliance, dCA is maintained (Perry et al., 2019) or even improved (Roy et al., 2022). Therefore, improved dCA may be a way of offsetting the potential reduction in central arterial compliance to defend against the large sinusoidal fluctuations in blood pressure experienced during RE.

These findings suggest that post-RE, RE-trained individuals may be less likely to experience fainting or syncope, given their better cerebral autoregulatory response despite the moderate blood pressure fluctuations experienced during RE. The current thesis used moderate-intensity unilateral RE (60% 1RM) in a seated position, and future studies should investigate the effects of higher-intensity bilateral RE, which would induce greater blood pressure fluctuations and provide a stronger challenge to CA. Additionally, exploring the compounded effect of upright RE on CA during both the exercise and recovery phases would offer further insights into how posture and intensity interact with CA regulation. Such studies would not only build upon the findings of this thesis but also complement research like that of Perry, Schlader, et al.

(2014). Future work in this area could inform exercise prescription and safety guidelines for a broad range of populations, including those with varying cardiovascular profiles and clinical conditions.

The results of **Chapter Five** and **Chapter Six** highlight the cerebrovascular benefits of engaging in habitual RE, which should be considered for future exercise prescription. Moreover, it uncovers the potential for future studies to examine CA during and following RE at higher intensities and in an upright position.

Chapter Seven of this thesis investigated the cerebral haemodynamic response to unilateral dynamic upper body RE in healthy individuals. Previous studies investigating the contribution of NVC to CBF during exercise, predominantly used static RE, which produces slow small to moderate increases in blood pressure that can be buffered by CA (Braz et al., 2014; Fernandes et al., 2016; Imms et al., 1998; Jorgensen et al., 1993; Ogoh, Sato, et al., 2010). However, **Chapter Seven** implemented dynamic RE, which caused sinusoidal fluctuations in MAP. The results of this chapter revealed that during dynamic upper body RE, MCAv was homogenous, as no differences between the ipsilateral and contralateral sides were observed. This highlighted that unilateral dynamic RE elicits similar $MCAv_{mean}$ in both sides of the brain, which could be beneficial for those who suffer from hemiparesis and hemiplegia. We observed fluctuations in MCAv, bilaterally, with a small muscle mass RE. This suggests that engaging in small muscle mass exercises, which generally involve moderate fluctuations in blood pressure, may offer a relatively safe and beneficial form of exercise for individuals with hemiparesis and hemiplegia as a result of stroke. Undertaking RE with the unimpaired limb in clinical cohorts may enable participants/patients to receive vascular adaptations on the ipsilateral side because of the increase in shear stress which is driven by the changes in blood pressure (Lu & Kassab, 2011). The blood pressure fluctuations observed during small muscle mass exercise still elicits swings in $MCAv_{mean}$, which could be beneficial for the clinical population, however, further studies are needed to examine this in the clinical cohort to confirm these findings. The findings of these future studies can be used to encourage participating in RE in the clinical population, as the benefits of RE exercise would not be confined to the physical benefits such as muscular strength, power, and endurance, but may also extend to the cerebral vasculature.

Chapter Seven highlights the hierarchy of CBF regulation and also confirms the hypothesis that NVC is likely masked by the modest, yet sinusoidal, changes in MAP. Furthermore, it reveals that MCAv is homogenous during unilateral bicep curl, which could be beneficial for the clinical population, however, more studies are needed.

8.2 Limitations

Some limitations must be discussed to contextualise the findings herein. Firstly, TCD was used to measure MCAv as a non-invasive proxy for CBF (As described in **Section 4.1.1**). Whilst the TCD provides dynamic and continuous measurements, the use of MCAv as a proxy for CBF is dependent on a constant diameter of the MCA (Ainslie & Hoiland, 2014). Verbree et al. (2014) observed that a reduction in $P_{ET}CO_2$ of 7.5mm Hg (hypocapnia) did not elicit any significant change in MCA diameter. However, Coverdale et al. (2014) found that the relative decrease in CBF during hypocapnia was 7% ± 4% greater than the TCD measured change in MCAv, although the mean $P_{ET}CO_2$ during hypocapnia was ~23 torr which is a considerably larger hypocapnic stimulus than any change reported in this thesis. In each of the experimental chapters breathing was paced during RE which produced a small decrease (~1 – 2mm Hg) in $P_{ET}CO_2$. Thus, it is unlikely that the mild hypocapnia alone produced a change in MCA diameter. However, using high-resolution MRI Verbree et al. (2017) reported that simple handgrip exercise produces a 2% decrease in MCA cross-section which was suggested to reflect sympathetic vasoconstriction. It is therefore possible that the RE utilised in the current study produced a constriction of the MCA. As such, the within-exercise findings of the current thesis must be interpreted with caution.

The studies comprising this thesis included males and a substantial number of females. Previous literature (Dickerman et al., 2000; Moralez et al., 2012; Perry, Schlader, et al., 2014) investigating the effects of RE on cerebrovascular response predominantly included only males. Ovarian hormone fluctuations, particularly oestrogen, may influence variations in vascular function and blood pressure in females (Krejza et al., 2004; Krejza et al., 2003). Krejza et al. (2004) revealed that 17-beta-estradiol influences cerebrovascular tone and vascular resistance. The authors demonstrated that cerebrovascular impedance, which reflects vascular resistance, changes throughout the menstrual cycle, with distinct variations in response to

different phases of the cycle. Oestrogen levels peak during the late follicular phase and are thought to contribute to a decrease in resistance in the ICA, whilst during the luteal phase, progesterone levels are the highest which could increase vascular resistance in the ICA and CCA (Krejza et al., 2003). Previous literature examining blood pressure changes across the menstrual cycle has shown inconsistent findings. One study observed a decrease in MAP during the luteal phase (Chapman et al., 1997), while two other studies reported higher blood pressure during the luteal phase compared to the follicular phase (Haneda et al., 2022; Lutsenko & Kovalenko, 2017). In contrast, some studies have found the lowest blood pressure to occur in the follicular phase (Adkisson et al., 2010), and others reported no significant changes in blood pressure across the menstrual cycle (Hartwich et al., 2013; Kwissa et al., 2022). The studies in this thesis attempted to control for those fluctuations by conducting experimental trials during the same self-reported menstrual phase and accounting for any form of contraception. While blood tests were not conducted to confirm hormonal phases, the study used self-reported menstrual cycle phase and contraception use to minimise hormonal variability.

Cardiovascular differences between females and males have been identified during static handgrip exercise, with male participants showing a greater exercise pressor response and increase in blood pressure (Ettinger et al., 1996; Matthews & Stoney, 1988; Simoes et al., 2013). However, recent studies investigating sex differences in haemodynamic responses to dynamic exercise have found that when body surface area and composition (Bassareo & Crisafulli, 2020), as well as maximal voluntary contraction (Notay et al., 2018), body size and strength measurements, are similar (no statistical differences), the differences in exercise pressor reflex are small or absent (Tharpe et al., 2023). The anthropometric measures of the participants in both groups (**Chapter Five** and **Chapter Six**) in this thesis were not different, furthermore, there were no baseline differences in cardiovascular measures. A systematic review and meta-analysis examining cerebrovascular function across the menstrual cycle found that during the high hormone phase, females exhibited higher PI and resistance and lower CBF and CA compared to the low hormone phase (Skinner et al., 2021). However, some studies included in the meta-analysis investigating the changes in PI and resistance measured ICA blood flow instead of MCAv. Abidi et al. (2017) found that MAP was greater during the high hormone phase

versus the lower hormone phase during the VM. However, the authors did not provide baseline cerebrovascular measures for males or females, nor were baseline measures recorded and analysed between the menstrual phases, only the cerebrovascular measures in response to a stressor were reported. Therefore, it was difficult to distinguish if there were sex differences at baseline at the different stages of the menstrual cycle. Favre and Serrador (2019) found that CA was lower during squat-to-stand manoeuvres compared to men in the early follicular phase, however, the authors used saliva to measure their oestradiol concentrations and did not report any significant difference in salivary oestradiol across the menstrual cycle, and thus the exact phase of the menstrual cycle was not confirmed. Favre and Serrador (2019) did provide baseline measures for cerebrovascular measures across the menstrual cycle, and between males and females, with no differences apparent. The authors also found that there was no difference in cerebral autoregulation during both repeated squat-to-stand and sit-to-stand manoeuvres between males and females. Previous literature highlighted the importance of measuring CBF during the same phase of the menstrual cycle for consistency as the high hormone phase exhibits greater blood pressures and HR (Abidi et al., 2017) and lower CBF and CA (Skinner et al., 2021) compared to the low hormone phase. However, Korad et al. (2022) found that the menstrual cycle phase does not alter cerebrovascular responses during stressors that acutely manipulate MAP. Korad et al. (2022) examined CA across three phases of the menstrual cycle (early follicular, late follicular, and mid-luteal) using TFA during spontaneous blood pressure oscillations, RoR during sit-to-stand manoeuvres, and Tieck's autoregulatory index during VM phases II and IV. The menstrual cycle phases were confirmed with a blood sample, which was collected 60 minutes after each trial. There were no differences in CA observed for spontaneous oscillations in blood pressure, following sit-to-stand, and VM during the three phases of the menstrual cycle. The authors concluded that dCA during acute blood pressure fluctuations remains consistent across all phases of the menstrual cycle.

A further limitation of the present study is the study only measured the MCA. Although the MCA supplies most of the cerebral cortex and is commonly used to study cerebral haemodynamics, it does not represent global cerebral perfusion. As highlighted in the literature review, the posterior circulation, supplied primarily by the vertebral arteries, which merge to form the basilar artery and give rise to the PCAs,

plays an important role in perfusing the occipital lobe, cerebellum, and brainstem. There is growing evidence that PCAv may be regulated differently from MCAv under certain physiological conditions (Hirasawa et al., 2016; Labrecque et al., 2020; Sato et al., 2011; Smirl et al., 2014; Smith et al., 2012; Washio et al., 2020). Furthermore, this study did not include extracranial measurements of the ICA, which limits the ability to assess changes in upstream inflow to the anterior circulation. Including measures of PCAv, VA and ICA blood flow would provide a more complete assessment of cerebrovascular responses across multiple vascular territories during dynamic RE. Furthermore, it could clarify what happens to cerebral circulation during high-intensity exercise that requires the recruitment of the VM.

8.3 Future Directions

Additional research is required to corroborate the current findings. **Section 8.1** discusses some future directions, while this section describes additional future studies not yet discussed.

Building on what was observed in **Chapter Six**, investigating whether the reductions seen during post lower body dynamic RE stand will also be observed during post upper body dynamic RE would provide useful information about how these different exercise modalities might influence CA during post-exercise orthostatic stress. Lower body exercises may induce different and greater hemodynamic responses compared to upper body exercises due to the larger muscle mass and gravitational effects, potentially leading to varying degrees of orthostatic challenge when standing. Understanding these differences could provide crucial insights into post-exercise cardiovascular recovery strategies and help identify potential risks for orthostatic intolerance following different types of RE.

Future research should also explore sex differences in orthostatic intolerance during post-exercise standing, particularly following dynamic RE. Females are known to experience more orthostatic intolerance compared to males (Ali et al., 2000; Cheng et al., 2011), which may be influenced by hormonal fluctuations across different phases of the menstrual cycle, with an increase in light-headedness reported in the luteal phase (Peggs et al., 2012). However, Claydon et al. (2006) reported that orthostatic tolerance, orthostatic vasoconstriction, and the effectiveness of cerebrovascular autoregulation were the same throughout the menstrual cycle. Regardless, it is

important to investigate how these phases affect blood pressure and CBF during dynamic RE and subsequent standing as it could provide valuable information about how hormones affect within dynamic RE cerebral haemodynamics and the consequences. This could assist with exercise prescription and also exercise performance in healthy females.

Given the potent effect of $PaCO_2$ on CBF, future studies should consider implementing $P_{ET}CO_2$ clamping techniques to minimise the confounding influence of respiratory-induced CO_2 fluctuations during RE. Clamping CO_2 would help isolate the contributions of blood pressure and neural mechanisms to CBF by eliminating fluctuations in $P_{ET}CO_2$, as observed during RE in this thesis. $P_{ET}CO_2$ can be clamped using a method described by Robbins et al. (1982), which employs a dynamic end-tidal forcing system that adjusts the inspired gas mixture on a breath-by-breath basis using a prediction–correction approach to maintain $P_{ET}CO_2$ at a constant target level. $PETCO_2$ clamping has been used effectively in both aerobic and RE studies (Braz et al., 2014), and may be particularly helpful for understanding cerebrovascular responses during high-intensity RE, where ventilation and $PaCO_2$ levels can vary significantly (Ogoh, Fadel, et al., 2005).

To further assess the impact of the pressor response on CBF response, the absolute load could be clamped. While relative load is a valid approach for inter-individual comparisons, it does not account for difference in absolute loading and the resultant pressor response. Standardising absolute load across participants, when comparing trained and untrained individuals, could help identify the role of total muscular force production on the magnitude of blood pressure elevation and cerebrovascular responses. Furthermore, studying responses using a fixed absolute load, and therefore different relative intensities, would allow researchers to understand whether cerebrovascular outcomes (e.g., MCAv responses, CA indices) are more tied to total load or individual effort.

The influence of RE training history on cerebrovascular regulation remains relatively unexplored. It is plausible that longer durations of resistance training may induce chronic adaptations in cerebrovascular tone, CA function, or cerebrovascular reactivity to CO_2. Future work should stratify participants based on training age to assess whether the duration of exposure to RE is associated with different

cerebrovascular profiles, especially during manoeuvres that elevate MAP and/or ICP. This could help inform whether cerebrovascular adaptations are time-dependent or stabilise after a certain training threshold and also further identify the influence of different training intensities long-term, which can be useful information for future exercise prescriptions.

As discussed in the limitations, the current study was restricted to MCAv measurements, which reflect blood flow within the anterior cerebral circulation. While MCAv provides valuable insight into cerebrovascular responses within a large vascular territory, potential regional differences in blood flow regulation across the brain cannot be excluded. Future research should incorporate extracranial duplex ultrasonography to directly measure blood flow in the ICA and VA, which are the major conduits supplying the anterior and posterior cerebral circulations, respectively. These extracranial measurements would allow for a more comprehensive evaluation of CBF, particularly during dynamic RE where haemodynamic stressors may affect regions of the brain differently. Additionally, assessing PCAv would enhance our understanding of posterior circulation dynamics. This is particularly relevant, as emerging evidence suggests that PCAv may respond differently to fluctuations in MAP and $PaCO_2$ compared to MCAv as Sato et al. (2011) demonstrated that cerebrovascular reactivity to CO_2 varies between cerebral regions. Furthermore, Hirasawa et al. (2016) reported that during low-intensity RE, PCAv exhibited a blunted response to exercise-induced increases in MAP compared to MCAv, suggesting a lower sensitivity of the posterior circulation to pressor stimuli during RE. These findings emphasise the need to assess multiple vascular territories to fully understand the potential heterogeneity of cerebrovascular control during exercise. Expanding future investigations to include both anterior and posterior circulation measurements will provide more insight into regional cerebrovascular adaptations and potential clinical implications, especially in populations with cerebrovascular vulnerabilities.

8.4 Conclusion

The purpose of this thesis was to investigate the effects of dynamic RE on cerebrovascular response in healthy individuals, as well as investigate the

cerebrovascular haemodynamics response to unilateral dynamic upper body exercise. Corresponding to the aims and objective of Chapter 3, it can be concluded that:

1) When performing dynamic RE at the same relative load, RE-trained individuals had greater blood pressures. Zenith and nadir measures for MAP showed that it was the systolic blood pressure that was driving the changes in blood pressure.
2) Despite the greater blood pressure fluctuations seen in RE-trained individuals during RE, $MCAv_{mean}$ remained similar to untrained individuals.
3) During post-exercise stand, RE-trained had a larger reduction in blood pressure, yet there were no differences in recovery time, rate of regulation (as a metric of dCA), and $MCAv_{mean}$.
4) Cerebral autoregulation appears to be improved by habitual RE with both hypertensive and hypotensive challenges being effectively buffered.
5) There is no difference between the ipsilateral and contralateral sides during moderate intensity unilateral dynamic upper body RE.
6) The contribution of NVC is masked by sinusoidal fluctuations and moderate increases in blood pressure during dynamic RE.

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Appendices

Appendix A: Ethics Approval

Date: 09 June 2021

Dear Stephanie Korad

Re: Ethics Notification - **SOA 21/22 - Cerebrovascular responses to resistance exercise in healthy individuals**

Thank you for the above application that was considered by the Massey University Human Ethics Committee: **Human Ethics Southern A Committee** at their meeting held on **Wednesday, 9 June,**

Approval is for three years. If this project has not been completed within three years from the date of this letter, reapproval must be requested.

If the nature, content, location, procedures or personnel of your approved application change, please advise the Secretary of the Committee.

Yours sincerely

Professor Craig Johnson
Chair, Human Ethics Chairs' Committee and Director (Research Ethics)

Research Ethics Office, Research and Enterprise
Massey University, Private Bag 11 222, Palmerston North, 4442, New Zealand T 06 350 5573; 06 350 5575 F 06 355 7973
E humanethics@massey.ac.nz W http://humanethics.massey.ac.nz

Appendix B: Consent Form

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

PARTICIPANT CONSENT FORM

Cerebrovascular responses to resistance exercise in healthy individuals

I have read the participant information sheet for the above experiment and had the procedures, and potential risks explained to me by the researchers. I am satisfied that my concerns and questions have been addressed fully.

I understand that I have the right to withdraw my consent for being a participant at any time without giving reasons and without penalty.

I have read the information sheet describing this project, and I have no known medical or other condition which would exclude me from being a participant in this experiment.

I have been given one week to consider my involvement in the project.

☐ **I agree to participate as an experimental participant.**

☐ **I understand that I can withdraw at any time without reason and without penalty.**

☐ **I would like the bodily fluid not used for measurement in this study returned to me**

Declaration by Participant:

I _____ hereby consent to take part in this study.

Signature: _____ Date: _____

Te Kunenga ki Pūrehuroa
Massey University – School of Health Sciences College of Health
PO Box 756, Wellington 6140, New Zealand T 0800 MASSEY www.massey.ac.nz

Appendix C: Statement of Contribution

DRC 16

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Stephanie Korad
Name/title of Primary Supervisor:	Dr Blake G. Perry
Name of Research Output and full reference:	
Korad, S., Mündel, T., & Perry, B. G. (2024). The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study. Experimental Physiology, 109, 1479–1491. https://doi.org	
In which Chapter is the Manuscript /Published work:	Chapter Five
Please indicate:	
• The percentage of the manuscript/Published Work that was contributed by the candidate:	85%
and	
• Describe the contribution that the candidate has made to the Manuscript/Published Work:	
Conception and design of study. Recruitment of participants. Acquisition, analysis, and interpretation of data for the manuscript. Writing and submitting manuscript.	
For manuscripts intended for publication please indicate target journal:	
Candidate's Signature:	Stephanie Korad Digitally signed by Stephanie Korad Date: 2024.11.01 12:05:59 +13'00'
Date:	01/11/2024
Primary Supervisor's Signature:	Blake Perry Digitally signed by Blake Perry DN: cn=Blake Perry, c=NZ, o=Massey University, ou=School of Health Sciences, email=B.G.Perry@Massey.ac.nz Date: 2024.11.01 16:00:44 +13'00'
Date:	01/11/2024

(This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis)

GRS Version 4– January 2019

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Stephanie Korad
Name/title of Primary Supervisor:	Dr Blake G. Perry
Name of Research Output and full reference:	
Korad, S., Mündel, T., & Perry, B. G. Cerebrovascular and Haemodynamic Response to Standing Following Dynamic Resistance Exercise: A Cross-Sectional Study	
In which Chapter is the Manuscript /Published work:	Chapter Six
Please indicate:	
• The percentage of the manuscript/Published Work that was contributed by the candidate:	85%
and	
• Describe the contribution that the candidate has made to the Manuscript/Published Work:	
Conception and design of study. Recruitment of participants. Acquisition, analysis, and interpretation of data for the manuscript. Writing and submitting manuscript.	
For manuscripts intended for publication please indicate target journal:	
Experimental Physiology	
Candidate's Signature:	Stephanie Korad Digitally signed by Stephanie Korad Date: 2024.11.01 12:08:56 +13'00'
Date:	01/11/2024
Primary Supervisor's Signature:	Blake Perry Digitally signed by Blake Perry DN: cn=Blake Perry, c=NZ, o=Massey University, ou=School of Health Sciences, email=B.G.Perry@Massey.ac.nz Date: 2024.11.01 16:01:29 +13'00'
Date:	01/11/2024

(This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis)

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Stephanie Korad
Name/title of Primary Supervisor:	Dr Blake G. Perry
Name of Research Output and full reference:	
Korad, S., Mündel, T., & Perry, B. G. (2024). Neurovascular coupling during dynamic upper body resistance exercise in healthy individuals. Experimental Physiology, 1–9. https://doi.org/10.1113/EP091970	
In which Chapter is the Manuscript /Published work:	Chapter Seven
Please indicate:	
• The percentage of the manuscript/Published Work that was contributed by the candidate:	85%
and	
• Describe the contribution that the candidate has made to the Manuscript/Published Work:	
Conception and design of study. Recruitment of participants. Acquisition, analysis, and interpretation of data for the manuscript. Writing and submitting manuscript.	
For manuscripts intended for publication please indicate target journal:	
Candidate's Signature:	Stephanie Korad Digitally signed by Stephanie Korad Date: 2024.11.01 12:10:15 +13'00'
Date:	01/11/2024
Primary Supervisor's Signature:	Blake Perry Digitally signed by Blake Perry DN: cn=Blake Perry , c=NZ, o=Massey University , ou=School of Health Sciences , email=B.G.Perry@Massey.ac.nz Date: 2024.11.01 16:01:48 +13'00'
Date:	01/11/24

(This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis)

Appendix D: Published Papers

The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study

Received: 3 December 2023 | Accepted: 4 June 2024

DOI: 10.1113/EP091707

RESEARCH ARTICLE

The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study

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Funding information
Massey University School of Health Sciences Postgraduate Fund

Handling Editor: Damian Bailey

Abstract

Dynamic resistance exercise (RE) produces sinusoidal fluctuations in blood pressure with simultaneous fluctuations in middle cerebral artery blood velocity (MCAv). Some evidence indicates that RE may alter cerebrovascular function. This study aimed to examine the effects of habitual RE training on the within-RE cerebrovascular responses. RE-trained (n = 15, Female = 4) and healthy untrained individuals (n = 15, Female = 12) completed four sets of 10 paced repetitions (15 repetitions per minute) of unilateral leg extension exercise at 60% of predicted 1 repetition maximum. Beat-to-beat blood pressure, MCAv and end-tidal carbon dioxide were measured throughout. Zenith, nadir and zenith-to-nadir difference in mean arterial blood pressure (MAP) and mean MCAv ($MCAv_{mean}$) for each repetition were averaged across each set. Two-way ANOVA was used to analyse dependent variables (training × sets), Bonferroni corrected t-tests were used for *post hoc* pairwise comparisons. Group age (26 ± 7 trained vs. 25 ± 6 years untrained, P = 0.683) and weight (78 ± 15 vs. 71 ± 15 kg, P = 0.683) were not different. During exercise average MAP was greater for the RE-trained group in sets 2, 3 and 4 (e.g., set 4: 101 ± 11 vs. 92 ± 7 mmHg for RE trained and untrained, respectively, *post hoc* tests all P = < 0.012). Zenith MAP and zenith-to-nadir MAP difference demonstrated a training effect (P < 0.039). Average $MCAv_{mean}$ and $MCAv_{mean}$ zenith-to-nadir difference was not different between groups (interaction effect P = 0.166 and P = 0.459, respectively). Despite RE-trained individuals demonstrating greater fluctuations in MAP during RE compared to untrained, there were no differences in $MCAv_{mean}$. Regular RE may lead to vascular adaptations that stabilise MCAv during RE.

KEYWORDS
blood pressure, middle cerebral artery blood velocity, resistance exercise

Larger reductions in blood pressure during post-exercise standing, but not middle cerebral artery blood velocity, in resistance-trained versus untrained

Received: 25 September 2024 | Accepted: 3 December 2024

DOI: 10.1113/EP092327

Experimental Physiology WILEY

RESEARCH ARTICLE

Larger reductions in blood pressure during post-exercise standing, but not middle cerebral artery blood velocity, in resistance-trained versus untrained individuals

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Funding information
This study was funded by Massey University School of Health Sciences Postgraduate Fund.

Handling Editor: Shigehiko Ogoh

Abstract

Dynamic resistance exercise (RE) produces sinusoidal fluctuations in blood pressure, with hypotension and cerebral hypoperfusion commonly observed immediately following RE. Whether the cerebral vasculature adapts to these regular blood pressure challenges is unclear. This study examined the cerebrovascular response to post-dynamic RE orthostasis. RE-trained (n = 15, female = 4) and healthy untrained individuals (n = 15, female = 12) completed five stands: one after seated rest, with each of the subsequent four stands occurring immediately following a set of 10 repetitions of unilateral leg extension exercise at 60% of their one repetition maximum. Beat-to-beat blood pressure, mean middle cerebral artery blood velocity ($MCAv_{mean}$) and end-tidal carbon dioxide were measured throughout. During standing the mean arterial blood pressure (MAP) and $MCAv_{mean}$ nadirs were identified. There was no difference between groups for age (mean ± SD, 26 ± 7 RE-trained vs. 25 ± 6 years untrained, P = 0.683) or weight (78 ± 15 vs. 71 ± 15 kg, P = 0.683). At MAP nadir during the post-exercise stand, a greater reduction in MAP was observed in the RE-trained group (e.g., set 4, −45 ± 11 vs. −36 ± 6 mmHg, training effect P = 0.026). However, post-exercise stand $MCAv_{mean}$ at $MCAv_{mean}$ nadir was not different (e.g., set 4, −20 ± 7 vs. −17 ± 6 cm/s, interaction effect P = 0.478). Rate of regulation was higher in the RE-trained group (set 1, 0.301 ± 0.170 vs. 0.167 ± 0.009, training effect P = 0.023). Despite RE-trained individuals demonstrating greater absolute reductions in MAP during orthostasis following RE, there were no differences in $MCAv_{mean}$, suggesting that habitual RE may mitigate post-exercise cerebral hypoperfusion.

KEYWORDS
blood pressure, middle cerebral artery blood velocity, resistance exercise

1 | INTRODUCTION

The benefits of resistance exercise (RE) have been well documented, with RE increasing muscle strength and muscle mass (Deschenes & Kraemer, 2002), improving mental health (O'Connor et al., 2010), decreasing fat mass (Lopez et al., 2022) and having a neuroprotective effect (Yarrow et al., 2010). However, despite the plethora of benefits associated with RE, RE can produce severe hypertension (MacDougall

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DOI: 10.1113/EP091970

Experimental Physiology WILEY

SHORT COMMUNICATION

Neurovascular coupling during dynamic upper body resistance exercise in healthy individuals

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Funding information
Massey University School of Health Sciences Postgraduate Fund

Handling Editor: Shigehiko Ogoh

Abstract

During unilateral static and rhythmic handgrip exercise, middle cerebral artery blood velocity (MCAv) increases in the contralateral side to the exercising limb. However, whether this neurovascular coupling-mediated increase in contralateral MCAv is apparent against a background of fluctuating perfusion pressure produced by dynamic resistance exercise (RE) is unclear. We examined the cerebral haemodynamic response to unilateral dynamic RE in 30 healthy individuals (female = 16, mean ± SD: age, 26 ± 6 years; height, 175 ± 10 cm; weight, 74 ± 15 kg; body mass index, 24 ± 5 kg m^{-2}). Participants completed four sets of 10 paced repetitions (15 repetitions min^{-1}) of unilateral bicep curl exercise at 60% of the predicted one-repetition maximum (7 ± 3 kg). Beat-to-beat blood pressure, bilateral MCAv and end-tidal carbon dioxide were measured throughout. One-way ANOVA was used to analyse cardiovascular variables and two-way ANOVA to analyse dependent cerebrovascular variables (side × sets, 2 × 5). A linear mixed model analysis was also performed to investigate the effects of end-tidal carbon dioxide and mean arterial blood pressure on MCAv. In comparison to baseline, within-exercise mean arterial blood pressure increased ($P < 0.001$) across the sets, whereas bilateral MCAv decreased ($P < 0.001$). However, no significant interaction effect was observed for any dependent variables (all $P > 0.787$). The linear mixed model revealed that end-tidal carbon dioxide had the greatest effect on MCAv (estimate = 1.019, t = 8.490, P < 0.001). No differences were seen in contralateral and ipsilateral MCAv during dynamic RE, suggesting that neurovascular coupling contributions during dynamic RE might be masked by other regulators, such as blood pressure.

KEYWORDS
middle cerebral artery blood velocity, neurovascular coupling, resistance exercise

1 | INTRODUCTION

Cerebral haemodynamics during dynamic exercise are complicated because the many regulators of cerebral blood flow (CBF) are perturbed concomitantly. These regulators include neurovascular coupling (NVC), arterial carbon dioxide content, arterial blood pressure, sympathetic nerve activity and cerebral autoregulation (CA) (Willie et al., 2014). Neurovascular coupling refers to the matching

Appendix E: Copyright

The effects of habitual resistance exercise training on cerebrovascular responses to lower body dynamic resistance exercise: A cross-sectional study

Author: Blake G. Perry, Toby Mündel, Stephanie Korad

Publication: Experimental Physiology

Publisher: John Wiley and Sons

Date: Jun 18, 2024

Larger reductions in blood pressure during post-exercise standing, but not middle cerebral artery blood velocity, in resistance-trained versus untrained individuals

Author: Blake G. Perry, Toby Mündel, Stephanie Korad

Publication: Experimental Physiology

Publisher: John Wiley and Sons

Date: Dec 25, 2024

Neurovascular coupling during dynamic upper body resistance exercise in healthy individuals

Author: Stephanie Korad, Blake G. Perry, Toby Mündel

Publication: Experimental Physiology

Publisher: John Wiley and Sons

Date: Sep 25, 2024