Implications of the Metaboreflex on Cerebral Blood Flow: Physiological Responses and Assessment Strategies

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Abstract

Exercise is responsible for acutely modifying cerebral blood flow (CBF) during an exercise bout, and eliciting chronic increases to resting CBF in trained individuals. Research to date has focussed on the individual mechanisms such as neural metabolism, arterial gas concentration and blood pressure that are responsible for CBF control and are altered by exercise. Altering theses mechanisms at rest, and comparing changes in CBF has been how researchers study the CBF response to exercise. The purpose of this thesis was to provide a scoping review of an important system for the regulation of the CBF exercise response: the exercise pressor reflex (EPR). A total of 30 neurogenic, and 12 cerebrovascular studies were reviewed in a two-part scoping review. The review of cardiovascular responses to varying post exercise muscle ischemia protocols demonstrated a large variance between studies, and a methodological variety of exercise intensities and durations. The scoping review of the CBF research demonstrated a variety of CBF responses to EPR stimulation, where CBF increased, decreased, or remained unchanged. Decreases in arterial carbon dioxide concentration, caused by hyperventilation, were found to disguise the effect EPR stimulation on CBF in several of the investigations. When arterial carbon dioxide was experimentally clamped, increases in CBF appear to correspond with arterial blood pressure (BP) responses. Furthermore, microvascular changes in CBF occurred in some instances while macrovascular flow was unchanged, perhaps indicating a region effect of the EPR on CBF. Overall, it has been shown that the EPR affects CBF by manipulating carbon dixide, BP, and perhaps myogenic factors, depending on region. The influence of these factors requires further experimental research. Future research that manipulates carbon dioxide and BP levels while assessing cerebral artery diameter and blood flow velocity is recommended to address the inconsistencies discovered in the current review.

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Introduction

The regulation of cerebral blood flow (CBF) has been discussed by researchers for well over a century (Roy & Sherrington, 1890). Despite rudimentary measurements, physiological opinions were in agreement that blood flow was coupled to the metabolic demand of most active tissues. For example, there is a history of observing CBF changes resulting from whisker stimulation, that continues to be used presently to understand the mechanism of CBF sensory response (Dirnagl et al. 1994). Contemporary approaches to conceptualizing this important physiological phenomenon has focused on compartmentalizing the vasculatures (i.e. peripheral, central, splanchnic, cerebral) and the specific mechanisms that control blood flow regulation (neural vs hormonal, paracrine vs endocrine) to these tissues (Diaz et al. 1954; Nava and Llorens 2019). The theoretical compartmentalization of individual vasculatures and the mechanisms governing perfusion has largely been determined by the capacity to directly or indirectly measure their circulations. As such, the narratives associated with blood flow regulation and its control become dependent on these techniques and the nuances of measure specific vasculatures at rest and during exercise. It is important to consider the effect of assessment technique on the lens physiological researchers are bound to when disseminating the theories of blood flow regulation. Structures that have limited accessibility, or are difficult to ethically alter may be of underrepresented importance in the physiological literature. Specifically, while CBF regulation in humans has been discussed for nearly 1500 years, it has only been directly measured for 70 years (Kety and Schmidt 1945). The compartmentalization and physiological interpretation that has risen from these experimental perspectives has generated physiological theories explaining how the cerebral circulation is regulated at rest and during exercise.

Due to technological inefficiencies, the brain's involvement in the physiological response to exercise is underrepresented in the current literature. Despite the brain's relative lack of investigation, it has been identified that changes in CBF regulation have effects on cognition and healthy aging, and both the regulation and outcomes are modulated by exercise (Ainslie 2008). Properly quantifying the CBF response to exercise has important implications for neurological disease and healthy aging in normal populations. Thus the following paragraphs will briefly introduce cerebrovascular regulation during exercise, and describe how the scientific instruments and approaches have evolved over time to shape our current interpretations and potentially misinterpretations of the mechanisms associated with cerebrovascular control.

Oxygen delivery, metabolism and CBF increase during submaximal exercise (Jarvis et al. 2007; Smith and Ainslie 2017), primarily in response to neural excitation (Roy and Sherrington 1890) and hypercapnia (Moraine et al. 1993). Increases in arterial blood pressure (BP) and cardiac output also provide support to the CBF response during exercise (Lucas et al. 2015; Pott et al. 1997; Smith and Ainslie 2017). Because of the complexity of cerebrovascular control, the mechanistic contributions to the CBF changes during exercise are confounded. Thus, current understandings were typically identified during investigations attempting to elucidate the impact a single factor has on CBF during exercise, while attempting to control for other confounding factors. While mechanistically important, this method establishes a simplistic understanding of CBF regulation during exercise. Quantifying the cerebrovascular response during exercise requires the observation of multiple mechanisms that act together to maintain perfusion and nutrient delivery to match metabolic demand centrally and peripherally. However, the consequence of observing these mechanisms during exercise is that the systemic responses to

exercise confounds the central cerebrovascular response during exercise. Thus a more holistic understanding of the interplay between the cerebrovascular and systemic responses to exercise is needed. The development of a theoretical schemata that includes the brain as an active player in governing its own (and systemic) vascular responses to exercise will provide a comprehensive, integrative understanding of central and peripheral regulation during exercise. For instance, the neurogenic governance of the systemic responses to exercise are controlled through two physiological mechanisms: 1) central command; and 2) the exercise pressor response (EPR). Central command is facilitated by the descending cortical neurons responsible for pre-emptive cardiovascular preparation, and coincides with the planned motor neuronal output of the cortex (Goodwin, McCloskey, and Mitchell 1972). In contrast, the EPR is the reflexive stimulation of systemic sympathetic activity triggered by afferent neurons originating in active skeletal muscles ascending to the autonomic centers in the brain stem (Alam and Smirk 1937). Both central command and the EPR provoke localized excitations in neurons in the brainstem (nucleus tractus sulitatii; ventrolateral medulla), and other cortical regions (ie., motor, premotor cortex). In concert, these two systems elevate BP, heart rate (HR) and cardiac output, and interact to influence perceptual awareness of effort. Because the feedforward nature of Central Command originates from the brain and descends outward to the systemic systems, the theoretical study of how central command activation influences CBF is more simple than the EPR. The cerebrovascular cascade activated by the EPR on the other hand, which originates in the periphery, is more difficult to evaluate. Largely because of its original definition, the majority of studies solely focus on the peripheral efferent responses, versus the afferent sensory inputs. As a result, research studying the EPR has mostly ignored any cerebrovascular effects, instead focusing on cardiorespiratory responses, and peripheral vascular changes in response to EPR

stimulation. Distorted EPR responses occur in subjects with hypertension, (Delaney et al. 2010) Down Syndrome, (Fernhall and Otterstetter 2003; Heffernan et al. 2005) metabolic syndrome (Doneddu et al. 2020; Guicciardi et al. 2019) and Parkinson's Disease (Sabino-Carvalho et al. 2018) and improved EPR sensitivity is observed in athletes, (Figueroa et al. 2009a) concurrent with decreased resting CBF (Ainslie et al. 2008). By failing to investigate the central integration of the EPR and the effect on CBF control, our understanding of certain disease states and athletic performance is severely limited.

Considering that the EPR primary end-point is a sympathetic mediated change in BP and total peripheral resistance, the relationship between BP and CBF needs to be considered. For instance, systemic changes in BP can have downstream effects on the cerebral vasculature, either altering perfusion, or causing a compensatory change in vascular resistance. Traditionally, CBF regulation through BP mediation was believed to be autoregulated, and thus early EPR research was largely unconcerned with the brain. Recently, the brain has been observed to be more pressure passive than autoregulated (Numan et al. 2014), suggesting the hemodynamic changes induced by central command and the EPR may have direct CBF benefits. Systemic haemodynamic changes aside, the exact process by which CBF is directly influenced by central command and the EPR remains elusive. Considering that central command and the EPR are directly involved in preparing and stabilizing the cardiovascular exercise response, understanding how these mechanisms interact with the other primary mechanisms that determine the cerebrovascular responses to exercise is crucial. Determining this, historically, has been limited by instruments with poor temporal and spatial resolution, and simple technological approaches that do not comprehensively measure CBF regulation. Furthermore, the approach to

assessing the influencing factors for CBF has been confined to the smallest and most proximal factors, having a direct effect, and the more distant factors, whose pathways of influence is less clear (Figure 1.1). The link that could facilitate the interpretation of CBF and EPR is the mechanisms that respond to the 'external' stimuli and influence the factors of direct influence. Thus, making it difficult to discern, with any sort of precision how the EPR impact cerebrovascular regulation.

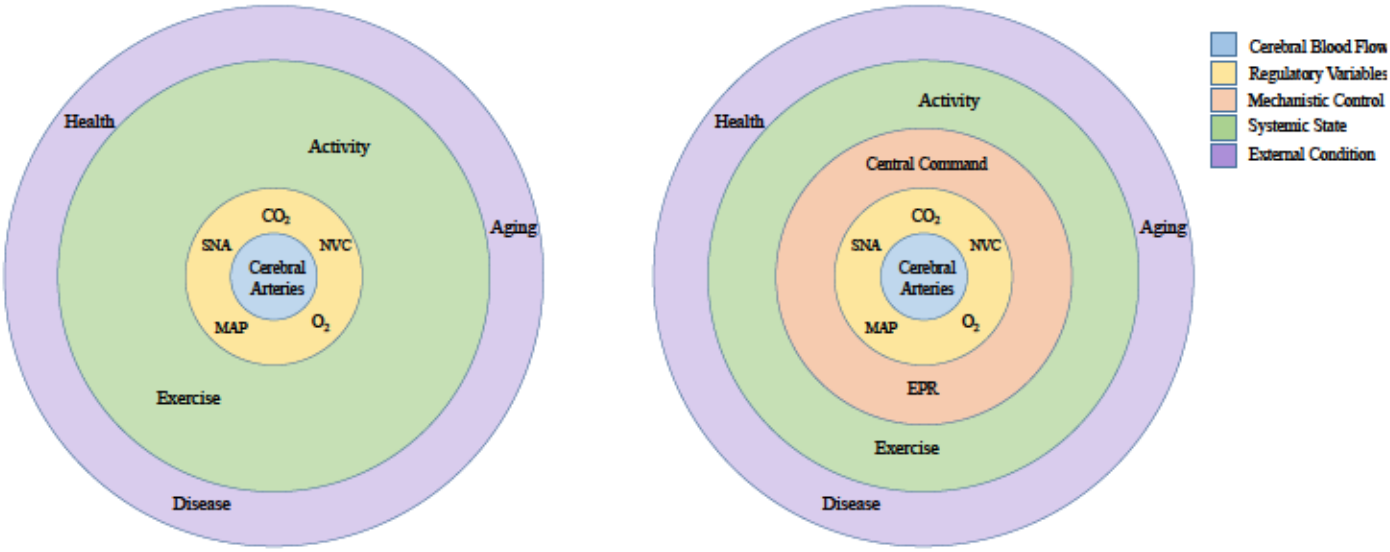

Figure 0. 1. Conceptual model of the "Spheres of Cerebrovascular Influence'. Extending outward, the traditional model posits that the direct functional influencers - arterial oxygen (O_2) and carbon dioxide (CO_2) tension, metabolic NVC (NVC) and sympathetic nerve activity (SNA) - regulate cerebral blood flow (CBF) independently during exercise, which have direct impacts on healthy and diseased cerebrovascular aging. The novel model posits that an additional influencer ring is required to accurately illustrate CBF regulation at rest and during exercise in healthy and diseased aging. The addition of the neural-mechanistic influencer ring suggests that mechano- and metaboreflexes as well as central command are directly involved in integrating the synergistic redundancy of the functional influencers, to preserve CBF despite profound systemic changes during exercise in healthy and diseased cerebrovascular aging. In each model, the outer spheres impact the inner spheres and vice versa, that exists centrally to them. Thus, the addition of the neural-mechanistic integration ring provides a crucial layer that involves synergistic integration of the functional influencers which can be used to enhance the evaluation of cerebral vascular control during exercise in health and disease.

Purpose

The purpose of the following thesis is to address the absence of a scoping approach to the understanding of the exercise pressor influence on CBF. There are an adequate number of systematic reviews that summarize the research in each specific area of the mechanistic control of CBF, or of the general conditions that modify CBF, such as the CBF response to exercise. For specific in depth reviews of the various systems, read (Ainslie and Duffin 2009; Ainslie and Ogoh 2009; Hoiland et al. 2016; Numan et al. 2014; Smith and Ainslie 2017; Willie et al. 2014). What is currently lacking is a scoping review which addresses the quantity and quality of research focused on the exercise pressor component of cerebrovascular research. Thus, the purpose of this thesis is to specifically discuss the assessment strategies, experimental conditions, and research outcomes of studies stimulating the EPR (chapter 3). Furthermore, the intention of the thesis is also to provide an in-depth discussion of the research pertaining to EPR and CBF during exercise (chapter 4). The thesis will then address future research suggestions, including recommendations for assessing CBF (chapter 5) to provide a more holistic interpretation of the CBF response to EPR stimulation.

Chapter 1: Review of Cerebrovascular and Systemic Responses to Rest and Exercise (Literature Review)

The following section is comprised of the themes highlighted above, and includes specific discussions that defines the complex regulation of CBF during exercise, the techniques used to determine this, and the involvement of how the EPR impacts the systemic exercise response, and how changing systemic factors impact CBF regulation.

Assessment techniques have varied widely since the first studies on CBF and the EPR performed by Jorgenson and colleagues (1992). Assessment has become less invasive and enhanced standardization of imaging techniques. Though the necessity to continually discuss the importance of accounting for revisions to previous dogmatic theories (Tzeng and Ainslie 2014) and controlling for physiological confounds remain. For instance, controlling for confounding changes in diameter continues to be met with resistance or is outright ignored by researchers, despite the recent studies documenting intracranial vasodilation and constriction observed during dynamic CBF measurement (Verbree et al. 2014). Considering the above, and the fact that no review has yet extensively reviewed the EPR's influence in CBF during exercise, the following sections will provide in detail how the EPR influences mechanistic cerebrovascular regulation and ultimately influences cerebrovascular control during exercise.

1.1 Neural control of the systemic and cerebral exercise response

The following sections outline the neural mechanisms stimulated by exercise and which regulate the human exercise response.

1.1.1 Neurogenic Response to Exercise

In direct relation to this thesis, the condition that elicits provocation of these elaborate neurogenic responses is exercise. During exercise, cardiovascular and respiratory function is increased to meet systemic metabolic demands; HR increases, as does ventricular contractility and stroke volume to facilitate the required increase in cardiac output. Sympathetic nerve activity, the nerve stimulus responsible for the systemic response to external stimuli, such as exercise and temperature, causes vasoconstriction in the non-active viscera, which is lysed in the active musculature by vasodilatory metabolites (Fisher 2015). There are two neurogenic mechanisms understood to induce the systemic response to exercise. Afferent (ascending) and efferent (descending) neurons are responsible for the neurogenic maintenance of nutrient delivery during exercise. Reflexive control of the cortical cardiovascular and adrenal centers originates from afferent feedback neurons in skeletal muscle (Kaufman and Hayes 2002). The reflexive component of an afferent feedback loop provides homeostatic responses to stimuli without cerebral input (Amann et al. 2011; Fadel 2015; Mitchell, Kaufman, and Iwamoto 1983; Taylor et al. 2016). Central command is defined as the neural signalling feed forward mechanism from the motor cortex and subthalamus to cardiac and respiratory neurons (Fadel 2013). Thus, central command and reflexive exercise pressor responses are theorized to work in isolation as separate, redundant systems. Yet, considering the parallels in the systemic responses, it is highly likely that their integration is required to maintain functional systemic conditions during periods

of internal or environmental stimulation. Furthermore, as the severity of each systems stimulation increases, the likelihood that integration will be required to maintain appropriate blood flow dispersion increases. The systemic (cardiorespiratory) changes that occur in response to exercise are methodologically simple to directly assess. The difficulty in assessing the cerebral effects of exercise are likely why there is currently an under-represented role for CBF as a response to the EPR and central command, which will make up the principle topic of this MSc thesis and is introduced in section 1.2.

1.1.2 Central Command

Central command represents the descending drive from the cerebrum, responsible in part for the systemic cardiovascular response to the onset of exercise and the activation of corticomotor centers (Goodwin et al. 1972; Williamson 2010). Studies using imagined exercise and hypnosis have determined that central command is responsible for the anticipatory cardiovascular response that precedes the onset of an exercise session (Williamson et al. 2002). Other studies demonstrated that when central command input was reduced by using muscle vibration to increase afferent stimulus during exercise, the systemic exercise response was smaller (Goodwin et al. 1972). Unlike the EPR, research pertaining to central command differences with disease is limited to animal studies (Koba et al. 2006) and indirect assessments in humans (Carrington et al. 2001) that suggest increased central command mediated sympathoexcitation in participants with heart failure. Whereas central command was once understood to respond primarily to corticomotor fatigue, it is now understood that central command responds to signals of muscular fatigue (McNeil et al. 2009) and cardiovascular fatigue, as well as cognitive anticipation of exercise (Williamson, Fadel, and Mitchell 2006). The traditional simplification of a feed forward

central command influence on the cerebral exercise response may be misleading, given the complex, and incompletely understood nuance of sensorimotor function. Research has demonstrated the abolition of motor cortical stimuli by an intracortical mechanism in the spine. Central fatigue, for example, as a result of fatiguing exercise appears to be the result of a decline in motor unit output, but *also* an increase in motor inhibition originating from the spine, further blurring the lines between the EPR and central command (McNeil et al. 2009). These findings suggest that central command is not 'all-cortical' just as this thesis will argue that the EPR is not 'all-reflexive'. To this point, studies isolating the EPR should be weary of the possibility for central command confounding, and studies translating knowledge about the EPR to the systemic or CBF response to exercise should consider the interaction between the EPR and central command (discussed in more detail below).

1.1.3 Exercise Pressor Reflex

The EPR is the reflexive projection of active skeletal muscle tissue through group III and IV afferent nerve fibres to the brainstem cardiovascular centers. The EPR responds to two main stimuli, mechanical stretch and metabolic milieu of active skeletal muscle. While efferent signals from the brain control skeletal muscle precisely to elicit force outputs, afferent signals from skeletal muscle generate a systemic response, required to maintain an optimal physiological state of the active musculature. Without this system, the metabolic demand of the active skeletal muscle would not be met with an increase in metabolic delivery. The EPR is known to vary with age (Markel et al. 2003) and training level (Saito, Iwase, and Hachiya 2009) and is often modified in disease (Smith, Mitchell, and Garry 2006) but the link between EPR and long-term health is yet to be identified. In terms of performance, periods of high afferent stimulation

impede motor unit recruitment, decreasing force output to spare the skeletal muscle from dangerous intramuscular conditions. In a recent study, the pharmacological blockade of afferent feedback during a cycling time trial improved short term performance, likely as a result of greater motor neuronal outflow from the cerebrum, but impaired long term performance, likely due to both a lack of fuel delivery for metabolism and a decreased efficiency in metabolic consumption (Hureau et al. 2019). Therefore, in conditions where the EPR is impaired, ability to exercise is also likely impaired. Despite obvious cerebral implications associated with afferent blockade (changes in motor unit output from the cortex) no study has yet to study CBF during afferent blockade, to indicate the cerebral effects of EPR impairment. The role of the various muscle afferents is described below.

1.1.4 Reflexivity

The EPR response to exercise has long been defined as reflexive in relation to the cardiovascular response (Coote, Hilton, and Perez-Gonzalez 1971). In a reflexive system, neural projection to brainstem areas elicits an efferent neural response. Simple (monosynaptic) reflexes involve single neurons with a predictable stimulus and response. Multisynaptic reflexes can generate more elaborate responses, such as the reciprocal innervation of contracting flexor muscles, and relaxing extensors, but crucially do not require cognitive input to generate the response. If the EPR response involves the integration of central command, punctuated by communication between the brainstem and cerebrum that alters the response, then EPR is likely more nuanced than purely reflexive (Figure 1.1). The reflexivity of the EPR is important for understanding how organs and systems compete for the limited supply of nutrients during exercise. During periods of high metabolic demand, exacerbated by the metabolic work of skeletal muscles, the systemic

requirement for nutrients may outweigh the cardiovascular capacity for delivery. Despite the skeletal muscles increasing metabolic demand, the brain and respiratory system are also in competition for blood flow and nutrient delivery. The 'selfish brain hypothesis' states that in such a condition, the cerebrum is able to maintain energy delivery at the detriment of all other metabolically active tissue (Peters 2011). The management of metabolic competition between systems is counter to the idea of a reflexive response to exercise, since the integration of the different metabolic requirements between tissues would require more complex processing than a reflexive system permits. As a minimum, the neurogenic control of systemic blood flow would have some overriding mechanism that could interfere with the EPR. More simply, it is possible that the EPR is not only a reflexive mechanism that increases cardiac output, but rather communicates important information on the metabolic condition of the skeletal muscle, influencing both systemic and cerebral responses vital to maintaining perfusion throughout the body. Further research into the 'selfish brain hypothesis' is required, likely consisting of examination cerebral stimulation, cerebellar stimulation and CBF changes during isolated stimulation of EPR. Examining CBF assessments during EPR stimulation may uncover a nuanced understanding of the EPR as more integrated than a simple reflex. It is essential to understand the complexity of the EPR to better treat those with an impaired EPR. Studying the involvement of the brain, by investigating differences in CBF during EPR stimulation (especially without the influence of central command) seeks to improve our understanding of the EPR response, and consequently inform the 'selfish brain hypothesis'. This thesis will compare regional differences in CBF with intra and extracranial arterial blood flow changes during EPR stimulation, to consider the legitimacy of the selfish brain hypothesis, as well as establish the

level of CBF control that is likely impacted by the 'selfish' redistribution (microvascular or arterial).

1.1.5 Afferent neurons

Afferent neuron fibers are typically classified into four groups: I ('a' and 'b'), II, III and IV (McCord and Kaufman 2010). Group I and II neurons are thickly myelinated neurons that innervate muscle spindles (group Ia and II) and Golgi tendon organs (group Ib). Evidence using selective blockade in humans, and direct stimulation in animals demonstrates that group I and II neurons do not contribute to EPR or sensation in the skeletal muscle but rather a limbs position relative to time and space (Tibes 1977). In contrast, group III and IV afferent neurons directly inform the brain of the metabolic and mechanical forces acting on the skeletal muscle and are the focal origin, responsible for triggering the EPR (Tibes 1977). Group III and IV afferent neurons are lightly and unmyelinated (respectively) multi-modal neurons that govern the pressor response to two types of exercise-induced stimuli: metabolic and mechanical. Despite being multi-modal, group III and IV afferent neurons generally respond to either mechanical (group III) or metabolic (group IV) stimulus. Stimulation of group IV afferent neurons, however, appears to sensitize group III afferent neurons to their respective stimuli, lowering their threshold for stimulation (Rotto et al. 1990). Direct invasive stimulation, either by metabolite injection, or in-vivo direct electrical stimulation, of these afferents has yet to be performed in humans, while assessing CBF. The effects of afferent neural stimulation have been extensively studied in animals. The reflexive cardiorespiratory effects of afferent stimulation observed in animals transfer more directly to the human model than the cerebrovascular effects. The robust effect on cardiac output is an easily definable reflex that is more consistent across species. As a result, the cardiorespiratory and

peripheral vascular effects of afferent stimulation are understood more completely than the cerebral effects, and the nuanced understanding of the whole impact of the EPR is lost.

Group III and IV neurons provide a pathway for pain sensation from the muscle fibers. Group III and IV afferent feedback also protects skeletal muscle tissue from harmful intramuscular conditions by depressing efferent muscle activation during periods of high afferent innervation (caused by either metabolic or mechanical stimulus); protecting muscle tissue while limiting force output (Hureau et al. 2019; Taylor et al. 2016). Motor neuronal output is limited (sometimes labeled central fatigue) either in corticospinal areas (McNeil et al. 2009), as a result EPR stimulation (Hureau et al. 2019), or as the result of a cortical 'decision' that sufficient force output isn't possible (Muddle et al. 2018). Blocking afferent feedback impairs these processes, risking intermuscular perturbation, as the regulatory process which minimizes intramuscular damage is compromised. The connection between central fatigue and afferent blockade further indicates the connected nature of these processes.

1.1.6 Mechanoreflex

The afferent neural response to exercise is not caused by a universal stimulus. The mechanoreflex represents the portion of the redundant EPR responsive to mechanical stimuli, mostly represented by group III afferent neurons. Mechanical stimulus in this context refers to *both* the passive movement of a joint through (or beyond) its range of motion and the mechanical force production from the skeletal muscles, even if there is no change in joint angle (isokinetic). During mechanical stimulation, such as passive muscle stretch, mechanoreceptive (group III) afferents stimulate increases in respiration and cardiac output (McCloskey 1972) and global

sympathetic nerve activity -mediated changes to the periphery (Drew et al. 2017). From an applied perspective, group III and IV afferent neurons, and therefore the mechano- and metaboreflex are stimulated simultaneously during exercise, especially given that metabolic stimulation, sensitises the mechanoreflex (Rotto et al. 1990). The effect of the mechanoreflex on BP (cerebral autoregulation), respiration (carbon dioxide reactivity) and sympathoexcitation (vasoconstriction) could all alter CBF, though specific study of this is limited due to challenges of stimulating mechanoreflex in isolation without inadvertently stimulating the metaboreflex.

1.1.7 Metaboreflex

The metaboreflex represents the portion of the EPR describing the afferent-mediated reflexive response to metabolite buildup in the active skeletal muscle. Metabolically sensitive group III and IV afferent neurons are stimulated by a variety of metabolites, such as, potassium ions, adenosine triphosphate (ATP), lactic acid, nitric oxide, bradykinin, as well as various prostaglandins and thromboxane's (Li & Sinoway, 2002; Luc Darques et al., 1998; Rybicki et al., 1985). Lactate, for instance, has been found to be a potent exercise product that elicits a large afferent response when injected (Kaufman, Rotto, and Rybicki n.d.; Sutherland et al. 2001). Despite this, human and animal studies suggest that no one metabolite is the driver behind the metaboreflex, rather the exercise pressor response is activated by the plethora of metabolites, that provide a redundant and synergistic afferent response to metabolic changes (Kaufman and Hayes 2002). Furthermore, much of the early research used higher than naturally occurring metabolite concentrations to stimulate group IV afferent neurons, which informed the capacity for neural stimulation but did not provide the physiological relevance to clarify how exercise stimulates group IV neurons. Applied assessment techniques, such as post exercise muscle ischemia (PEMI

– reviewed in 1.2.11) could perhaps address this issue, though most applied assessments lack a structured methodology, and even fewer assess CBF.

1.1.8 Baroreflex Regulation of System Exercise Response

Intrinsic cardiovascular mechanisms are also involved in the modulation of the systemic response to exercise. The baroreflexes, reviewed by (Joyner 2006; Raven 2008), regulates BP, as evidenced by increased stimulation to baroreceptors causing a vasodilation and slowed HR, and a reduction in baroreceptor stim causing the opposite response. Researchers have uniquely demonstrated that during exercise the arterial and pulmonary baroreflex shifts its control point to establish a new baseline with which to modulate changes in systemic cardiac responses in order to maintain BP. Therefore, both at rest and during exercise, the baroreflex mediates MAP through small sympathetic mediated changes in HR or total peripheral resistance and conductance (Ogoh et al. 2003). The operating point that the baroreflex maintains is set by central command and the EPR during exercise, but then maintained by baroreflex management. In populations with compromised baroreception, such as some stroke victims, MAP is more variable, though the MAP increase in response to exercise is maintained. This supports the theory that baroreflex is a regulatory mechanism that reduces variability in MAP, but does not impede compensatory governing of MAP by other mechanisms, such as EPR. The pulmonary baroreflex exists by responding to changes in pressure in the pulmonary tissues. It behaves similar to the carotid baroreflex and regulates pulmonary artery pressures by increasing or decreasing systemic sympathetic nerve activity output via a complex combination of positive and negative feedback loops (Fadel and Raven 2012; Fisher, Young, and Fadel 2015). The above mechanisms complicate the analysis of the EPR. Whereby the EPR adjusts cardiac output to the

demands of the periphery, with input from the brain, baroreflex adjusts cardiac output only in response to changes in intra-arterial pressure. Still, the regulatory pathway that baroreflex uses to alter systemic response is similar to EPR, given that sympathetic nerve activity from the brainstem acts as the main regulatory pathway. Secondly, systemic changes in breathing, MAP, and HR as a result of EPR are likely to influence the measured EPR, and the CBF response to the EPR. The complexity of multiple redundant homeostatic mechanisms working in concert, is that they respond to a multitude of stimuli, all of which are stimulated during exercise. This enforces the notion that the pressor response to exercise is likely less reflexive than currently reported, behaving more sophisticatedly than the 'traditionally reflexive' baroreflex. The complexity of these mechanisms also demonstrates the need for applied assessments that can seek to integrate the multitude of reflexive, and perhaps less reflexive mechanisms.

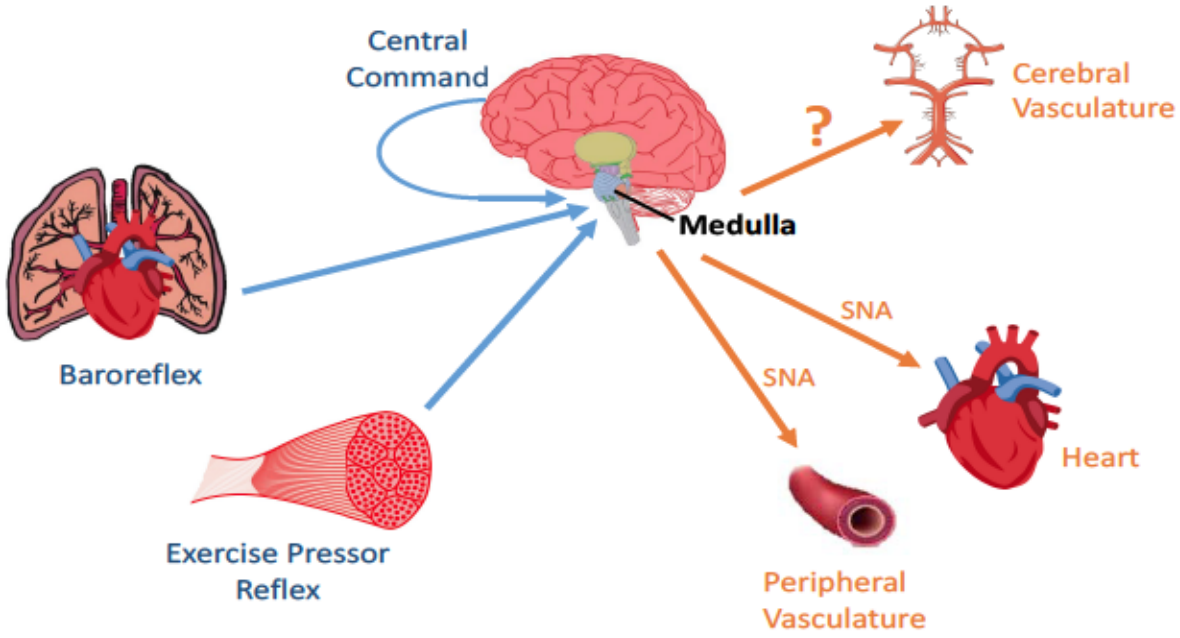

Figure 1. 1. Simplified schematic of the systemic exercise response (EPR) where central command integrates with afferent neural stimulation (blue) in the medulla causing efferent neural projection (orange) to the heart and periphery. The impact of this response on the cerebral vasculature is confounded by the multiple components of the EPR that also impact cerebrovascular regulation.

1.2 Cerebrovascular regulation during rest and exercise

Considering group III and IV afferent projections that travel from skeletal muscle to the brain stimulate autonomic centres involved in systemic and cerebrovascular regulation, where cortical integration also occurs, it is pertinent to discuss how the EPR and the cerebrovasculature interact. Direct EPR effects on CBF are likely disguised by the multitude of regulatory mechanisms that alter CBF. These relevant factors that modify CBF at rest and during exercise are discussed below. Specifically, the following sections describe how the EPR fits within the traditional model of cerebrovascular regulation during exercise. Whilst the CBF response to exercise is classically studied by manipulating only one relevant variable, and since the metaboreflex and

mechanoreflex are rarely included, understanding the independent and integrative components illustrated by foundational CBF research is crucial to bridging the gaps in our current approach to CBF research (Figure 0.1).

1.2.1 Physiological regulation of cerebral blood flow at rest

A multitude of mechanisms, influenced by a variety of factors work together and in opposition to maintain CBF. Due to complexity of cerebrovascular regulation, the controlling of relevant physiological stimuli is used to target specific cerebrovascular regulatory mechanisms. Furthermore, the redundant balance of these mechanisms means that changing, or removing the influence of one can alter the response of other factors. Involved in this balance, is the EPR, though the comparative lack of EPR research on CBF control mechanisms has reduced our capacity to account for its impact. Only once the variety of cerebrovascular regulatory mechanisms are understood independently, can their competing influences be integrated to understand physiological response to hemodynamic-stimulating conditions, such as exercise. An understanding of how exercise can modulate each CBF moderator should be understood so that the confounding effects of each CBF mechanism can be considered when interpreting CBF response to EPR. Below, a selection of relevant factors that regulate CBF at rest and during exercise is detailed. These factors represent confounds and/or mechanisms by which EPR stimulation can alter CBF.

1.2.2 Regulation of cerebral blood flow through arterial blood gases

The regulation of CBF is sensitive to a variety of environmental factors, including arterial gas concentrations of oxygen and carbon dioxide. Arterial gas concentrations are often manipulated

by changes in elevation, metabolism, or, specifically to this study, by exercise. An understanding of how fluctuating oxygen and carbon dioxide concentrations influence CBF control is required to grasp the intricacy of changing CBF during exercise.

1.2.3 Cerebral blood flow and Oxygen

Hypoxia, induced by a decrease in arterial O_2 results in cerebrovascular vasodilation and increased flow, if PaO_2 is reduced severely enough (hypoxemia) (Tymko et al. 2017; Willie et al. 2012). Due to the redundant mechanisms of hypoxic CBF control, it has proved difficult to block the vasodilatory response to hypoxia in *in vivo* human participants (Hoiland et al. 2016). An exception to these findings include a study that used glibenclamide to block 50% of the hypoxia mediated cerebral vasodilation (Rocha et al. 2020) likely due to the convergence of multiple signaling pathways on the blocked K_{ATP} channel (Smith, Neill, and Hoiland 2020). Exercise in normal populations, at sea level, does not reduce oxygen delivery to the brain enough to trigger hypoxia-mediated response in the cerebrovasculature. Specific to this thesis, CBF control related to altered PaO_2 concentration maintains O_2 delivery, even if PaO_2 changes due to altered respiration (such as during exercise). Oxygen may also influence arterial carbon dioxide concentration, which is known to have a more robust effect of CBF during exercise than oxygen. As PaO_2 increases during hyperoxic exercise, $PaCO_2$ is lowered via hyperventilation which is counteracted by a decrease in alveolar ventilation, which increases $PaCO_2$ (Asmussen and Nielsen 1946). Research on the hyperoxic exercise response has demonstrated increases in cerebrovascular arterial velocity (Smith et al. 2012), and regional CBF (Smith et al. 2016) likely related to $PaCO_2$. The Balance between PaO_2 and $PaCO_2$ has the potential to influence the CBF

response to exercise. Independent of oxygenation, when a hyperventilatory response lowers $PaCO_2$, a separate and robust effect on CBF is observed, (Lucas et al. 2011) described below.

1.2.4 Cerebral blood flow and carbon dioxide during exercise

Carbon dioxide plays a more evocative role in the regulation of blood vessel diameter than oxygen. All levels of the cerebral vasculature from small pial vessels, to intra- and extra-cranial arteries respond to changes in arterial carbon dioxide (Smith and Ainslie 2017; Willie et al. 2014). The CBF in response to changes in $PaCO_2$ is quite linear, and more sensitive to increases from rest. CBF decreases about 1-3% from rest with each mmHg reduction of $PaCO_2$, and increases 2-5% with each mmHg increase in $PaCO_2$ from rest (Willie et al. 2012) depending on the assessed artery (Sato et al. 2012). The CBF response to changing $PaCO_2$ has also recently been shown to occur irrespective of acidity (Caldwell et al. 2021) eliminating bicarbonate changes as a mechanism for the observed change.

If the effect of fluctuating CO_2 is not controlled it can mask the cerebrovascular contribution of other changing factors during exercise by provoking a counterbalancing response (Ainslie et al. 2005; Braz et al. 2014). This could potentially alter the CBF EPR, and is necessary to discuss in all studies investigating CBF regulation. During maximal exercise where CO_2 levels are not controlled (poikilocapnia), a hyperventilation-caused decrease in end-tidal CO_2 evokes vasocontraction of the cerebral arteries, although recent research has demonstrated that the cerebrovascular reactivity to CO_2 appears to be independent from the ventilation stimulus (Howe et al. 2020), at least in hypercapnia. Clamping $PaCO_2$ at ~1mmHg above baseline (isocapnia-

typically ~35-45 mmHg) mediates the vasoconstriction associated with changing respiration, uncovering the cerebrovascular impacts of conditions other than arterial CO_2 (Tymko et al. 2017) Some research has shown that exercise at 'low' and 'moderate' levels doesn't cause enough exercise-induced hyperventilation to cause hypocapnia. In fact, end-tidal CO_2 was measured to be the same at both low and moderate exercise intensities. It is suggested that at these levels of aerobic exercise, CO_2 levels could play less of a regulatory role (Witte et al. 2019). This contrasts earlier studies that attributed a proportion of the CBF response to exercise to changes in $PaCO_2$ (Willie et al. 2012). In research that alternates between controlling and not controlling $PaCO_2$ levels during exercise, there appears to be a strong regulatory role of carbon dioxide at all exercise intensities, that vanishes during isocapnia, when $PaCO_2$ isn't permitted to fluctuate (Prodel et al. 2016). The influence that the EPR has on ventilation must be considered when assessing the CBF response to EPR stimulation, and the resultant change in $PaCO_2$ should be investigated as a confound.

1.2.5 Cerebral Metabolism

The cortex consumes three primary substances to maintain organ function: glucose, oxygen, and lactate (Kety 1963). The rate of consumption of these metabolites increases locally with increased neural activity in regions of the cerebrum. Cerebral metabolic changes can influence CBF by a process defined as NVC (NVC). NVC describes the coupling of nutrient delivery, and metabolite clearance to local neural metabolic demand by a local endothelial response. Pressure changes due to local microvascular control causes down-stream macro arterial changes in CBF, meaning metabolic changes can influence global and regional CBF (Raichle 1976), though this often occurs with a level of regional specificity (Willie, Cowan, et al. 2011). During an increase

in cerebral metabolism, the local microvasculature dilates to facilitate nutrient delivery. When sufficient microvascular dilation occurs, the sum increase in flow compounds causing an increase in arterial flow, often attributed to an increase in arterial blood velocity (Aaslid 1987). NVC is most clearly demonstrated using an eyes open-closed test, whereby changes in posterior cerebral circulation are measured during acute changes in occipital lobe (posterior cerebrum) metabolism stimulated by alternating low and high visual input to the eyes (Willie, Colino, et al. 2011). Posterior intracranial circulation appears to follow the occipital lobe circulation, while anterior intracranial circulation remains largely unaffected, demonstrating the regional specificity of the NVC response (Phillips et al. 2016). NVC has yet to be studied as a mechanism for anterior CBF change during exercise, despite a well understood increase in motor and pre-motor cortex metabolism during exercise (Martin et al. 2008). Intracranial and extracranial flow rates do not support a contribution of NVC to the exercise pressor response. An assessed difference in anterior vs. posterior flow could perhaps indicate a NVC contribution, as could differences in ipsilateral and contralateral blood flow during a unilateral exercise task. This is perhaps due to a lack of specificity in the assessment, as NIRS assessments have identified changes in cortical flow during exercise. Given that EPR stimulation likely causes cortical stimulation, contrary to a traditional 'reflexive' model, NVC is a potential mechanism of direct cerebrovascular change during EPR stimulation. Furthermore, since there is a global sympatholytic vasoconstriction that occurs during exercise, an exercise-induced NVC response could be counter to that response, preserving blood flow to the cortex. The legitimacy of this theory is related to the extent to which sympathetic nerve activity alters cerebrovascular tone, reviewed in section 1.2.7.

1.2.6 Blood Pressure (Cerebral Autoregulation)

Increase in BP is often associated in increased blood flow (especially in major non-cranial arteries). To maintain CBF, the cerebrovasculature appears to autoregulate with respect to changes in BP via vasoconstriction and dilation which modify intracranial pressure, and therefore maintain perfusion pressure (Eq. 1.1). It was initially believed the autoregulatory capacity of the cerebrovasculature minimised the impact of BP change on CBF for the majority of physiologically relevant BP levels (Lassen 1959). More recent research has demonstrated that the true autoregulatory buffer is much smaller (between 5-10 mmHg) and more effective at managing increases in MAP compared to reductions, (Lucas et al. 2010) while also being potentiated by cerebrospinal fluid pressure (Tarumi et al. 2021) (Eq. 1.2).

$$Eq\ 1.1.\ Cerebral\ Profusion\ Pressure = Blood\ Pressure - Intracranial\ Pressure$$

$$Eq\ 1.2.\ Intracranial\ Pressure = Arterial\ Blood\ Pressure + Cerebrospinal\ Fluid\ Pressure$$

In a recent study, mean arterial pressure (MAP) and MCAv amplitude were found to coincide, yet changes in MAP only accounted for less than 40% of variability of MCAv amplitude (Billinger et al. 2017). The impact of cerebral autoregulation on CBF during exercise is likely confounded by $PaCO_2$ changes that occur during increases in MAP (Numan et al. 2014). Despite this, MAP changes both in response to exercise, and is preserved during EPR stimulation, such as during PEMI (Delaney et al. 2010). The effect of MAP on CBF response therefore must be considered, especially when comparing CBF between exercise bouts and EPR stimulation(Smith and Ainslie 2017).

1.2.7 Neurogenic control of cerebral blood flow

Neurogenic innervation is one of the main regulatory mechanisms for peripheral arteries, reviewed in (Ainslie and Brassard 2014; Brassard, Tymko, and Ainslie 2017; Seifert and Secher 2011), but the role neurogenic innervation plays in modulating cerebral arteries is not obvious. Cerebral arteries have alpha (Edvinsson 1982) and beta (Tsukahara et al. 1986) cells, which are the cells that modulate vasculature in response to changing sympathetic nerve activity in the periphery. Alpha cells cause vasoconstriction in response to sympathetic stimulation, whereas beta cells cause vasodilation (Bevan et al. 1987). Differences in alpha and beta ratio would influence the extent and 'direction' (constriction/dilation) of vascular reaction to sympathetic nerve activity changes. There is evidence that blocking sympathetic nerve activity causes cerebrovascular dilation, but these claims are contradicted in some research (Willie et al. 2014). Assessment difficulties regarding the actual blockade of sympathetic nerve activity in human participants has hindered a more in depth investigation of sympathetic nerve activity control of cerebral arteries. Difficulties in assessing intracranial artery diameter with high temporal accuracy also make elucidating the effect of sympathetic nerve activity on intracranial arteries challenging. Nevertheless, there appears to be sympathetic control of cerebral arteries in humans, as evidenced by the cerebrovascular reaction to conditions of high sympathetic outflow, such as the cold pressor test (Tymko et al. 2017).

1.2.8 Central Command and Cerebral Blood Flow

Central command provides a potential area for direct and indirect cerebrovascular changes during exercise. The indirect effects of central command are clear; central command mediated changes in BP and respiration can alter CBF in the same way the EPR can, through evoking a

systemic exercise response. The extent of which the systemic-mediated CBF response to exercise is due to central command, compared to the EPR isn't fully understood. Investigation as to the relative contribution of each mechanism to the systemic response to exercise, could clarify the extent to which each system contributes to any associated CBF responses. Importantly, these CBF responses would not just be direct responses to central command or EPR, but also to the systemic changes that occur during exercise. In terms of a direct influence, however, increased cortical stimulation that evokes the central command of the periphery likely increases cortical metabolism, which would need to be met by increased nutrient delivery, at least in the microvasculature. Whether or not the changes in descending neural drive from the cerebrum cause a NVC mediated increase in CBF has not been studied. A study by Sato and colleagues studied the MCAv response to static arm exercise with a session of simultaneous exercise and mechanoreflex activation via spindle vibration. By artificially increasing metaboreflex activation during one trial, the regulation of central command compared to the mechanoreflex was possible. They demonstrated a decrease in MCAv response to exercise with lowered central command (Sato, Sadamoto, et al. 2009; Sato, Moriyama, and Sadamoto 2009) indicating the central command likely plays *some* role in increasing CBF during exercise. Work with imagined exercise, and scientific hypnosis has been used to determine the cerebral activation of central command activation (Williamson et al. 2002) but the evaluation of cerebral arteries during such a protocol remains to be performed. The influence of central command on CBF can potentially confound the response driven by the EPR. Understanding the cortical metabolic influence of central command, for example, is essential to discovering the cortical influence of the EPR. It is in likely that these two systems integrate, so the diligent stimulation of each in isolation is crucial to detecting where and how there is an integration.

1.2.9 Afferent Feedback and Cerebral Blood Flow

Changes in muscular metabolism influence the regulatory agents of CBF. Cellular respiration causes changes in oxygen and carbon dioxide levels in the blood. Metabolic by-products of exercise build up in skeletal muscle and stretch and pain receptors in the muscles are activated by dynamic or isometric contractions. The systemic manifestation of the EPR can be quantified *either* by the relative change from rest in the physical manifestations *or* in the initiation of increased sympathetic nerve activity. These peripheral changes in skeletal muscle trigger the autonomic centres in the brain through the afferent arm of the EPR, delivered via group III and IV afferent neurons. The efferent arm of the EPR is punctuated by changes in respiration, HR, BP, and a systemic vasoconstriction all mediated by increased sympathetic nerve activity to facilitate nutrient deliver to active skeletal muscle (Mitchell et al. 1983). The effect of sympathetic nerve activity on cerebral arteries (described in this section) is still an area of controversy (Brassard et al. 2017). Assessment of cardiorespiratory variables is more accurate and simple than cerebral variables because they are more physically accessible for direct assessment. Thus, the effect of changes in metaboreflex stimulation, including sympathetic nerve activity level are better understood in the periphery. The cerebrovascular implications of these interactions between afferent reflexive stimulus and cortical input is an area of very limited study.

The effect of metaboreflex on the cerebrovascular response to exercise has been an area of controversy for exercise physiologists. Early studies found sustained neural excitation from afferent signals, induced from fatigued skeletal muscle during PEMI did not preserve the

increase in CBF that occurs during exercise (Jorgensen et al. 1993). This evidence was initially interpreted to indicate the metabolic component of the EPR is not accountable for the cerebrovascular response (Pott et al. 1997). Contrarily, the blocking of skeletal muscle afferent feedback using anaesthesia was discovered to attenuate the normal increase in cerebral profusion (Friedman et al. 1992). However, early studies did not account for the counter influence of systemic cardiorespiratory factors such as hypocapnic vasoconstriction. The above research can be taken separately to implicate the metaboreflex, mechanoreflex, and central command each as the main driver of the CBF response to EPR. The present thesis intends to use more recent research to reconcile these findings.

Stimulation of the EPR likely influences all of the regulatory agents indicated above, which work in parallel and in opposition to maintain nutrient delivery to the cerebrum. Furthermore, when there exists a shortage of nutrients relative to whole body metabolism, the distribution of those nutrients is likely related, at least in part to the cerebral integration of the EPR. The way in which changes in afferent-mediated CBF effect that process is unknown, but it has been speculated the brain is 'selfish', diverting the required blood flow to maintain function, even at the detriment of the periphery. Despite this, research has been slow to evaluate the CBF response to afferent neural stimulation, likely due to the long-time status quo of treating the brain as a relay, rather than a cortical command center of the response. Extensive cardiorespiratory evidence has created a comprehensive understanding of the effects of the EPR on the periphery, but only studied the impact on CBF enough to indicate that there are EPR implications for CBF, without fully identifying them.

Disordered EPR exists in disease and other special populations, and often effects exercise capacity, and perceived exertion. When the EPR is altered, it can fail to sufficiently raise cardiac output to meet exercise demands, such as in patients with Down Syndrome (Dipla et al. 2013). Conversely, the EPR can also, in some cases be over-stimulated during exercise, causing a decreased tolerance to exercise, such as in participants with metabolic syndrome (Limberg, Morgan, and Schrage 2016). Some research has identified the cerebral impacts of disordered afferent neural feedback as limiting for the continuation of exercise (Doneddu et al. 2020). Other studies have demonstrated that athletes exhibit an increased exercise pressor response (Sato, Moriyama, et al. 2009), and an attenuated age-related decline of resting CBF (Ainslie et al. 2008). By addressing the cerebral impacts of EPR changes, treatment and outcomes in those with disordered EPR can improve, as can investigations into the 'selfish brain hypothesis' and the implications for athletic performance.

Thus, the EPR, at least in theory, likely affects CBF by stimulating both cerebellar and cerebral activity, while also modulating sympathetic outflow and systemic hemodynamics. Identifying the methodological and assessment difficulties that impede CBF and EPR research (both in isolation and when performed simultaneously), as well as mapping the current understandings will aid in bringing the CBF EPR to the forefront. Moreover, the variability in cardiac, sympathetic and cerebrovascular responses to PEMI have yet to be summarised, which likely effects CBF and non CBF PEMI research. The impact of the CBF EPR has also received limited attention regarding the impact on disease, and has not been investigated regarding athletic background.

1.2.10 Assessing the exercise pressor reflex in the brain

Individual factors and mechanisms of CBF have been identified, and outlined above, but to assess the interplay between these mechanisms during EPR stimulation requires a way to isolate the effects of the EPR from exercise itself. To assess the EPR contribution to the systemic and cerebrovascular response to exercise, the influence of central command innervation, which occurs simultaneously with EPR during exercise, must be controlled. First developed in the 1930's, PEMI is a practical technique that is often employed to stimulate metaboreflex in isolation (Alam and Smirk 1937).

1.2.11 Post Exercise Muscle Ischemia

PEMI is an assessment technique that isolates the effects of the metaboreflex from the effects of mechanoreflex and central command. When performing a PEMI protocol, rhythmic or isometric exercise is performed for specific duration or until failure (volitional or involuntary). While the dynamic movement has a central command component and group III/IV mechano afferent stimulation, 5-10 seconds before the cessation of exercise, a cuff, previously fitted on the limb of the exercising muscle is inflated above systolic BP, occluding blood flow to the active skeletal muscle, and then the dynamic exercise is stopped with only the metabo afferent group IV activation remaining. Given that the typical systemic response to the cessation of exercise is to return to baseline (Coote 2010) the preserved amplitude of the relevant physiological variables (ie., minute ventilation, BP) during 'occlusion' represent the proportion of the exercise response attributable to the metaboreflex (i.e., group IV afferents). The PEMI protocol offers the ability to observe the integrative response of metaboreflex to a physiological relevant concentration of the various metabolites present during exercise. During the 'occlusion' mechanosensitive afferents are not stimulated, because exercise is not being performed. Similarly, there is no descending

drive from central command stimulating motor units to perform exercise, thus the systemic effects of central command are, in theory, eliminated. Depending on which physiological response is measured during PEMI determines the corresponding physiological pathways explaining the phenomenon. Cardiorespiratory measures are commonly assessed, ranging from simply HR, systolic and diastolic BP, but extending to more complex cardiac measures such as ventricular filling, cardiac output, etc.

The conceptual approach to the PEMI protocol described above has been applied in a variety of different procedures. Skeletal muscles, exercise types, durations, intensities, occlusion type, and variables assessed vary between studies. The lack of universality between PEMI protocols confuses the interpretation of findings. The magnitude and duration of the metaboreflex response, for example, is difficult to interpret when differing PEMI protocols are used to stimulate the metaboreflex in different studies. This is especially important when metabolite concentration is not being directly assessed. The extent to which changes in exercise type, duration, intensity and modality change the pressor response to PEMI has received little attention, despite confusing our interpretation of the PEMI literature. To address this problem, a scoping review of the available PEMI literature across physiological disciplines (not necessarily to do with CBF) will be evaluated based on the systemic responses to PEMI and methodological differences in protocol (Chapter 4).

1.3 Refined Purpose

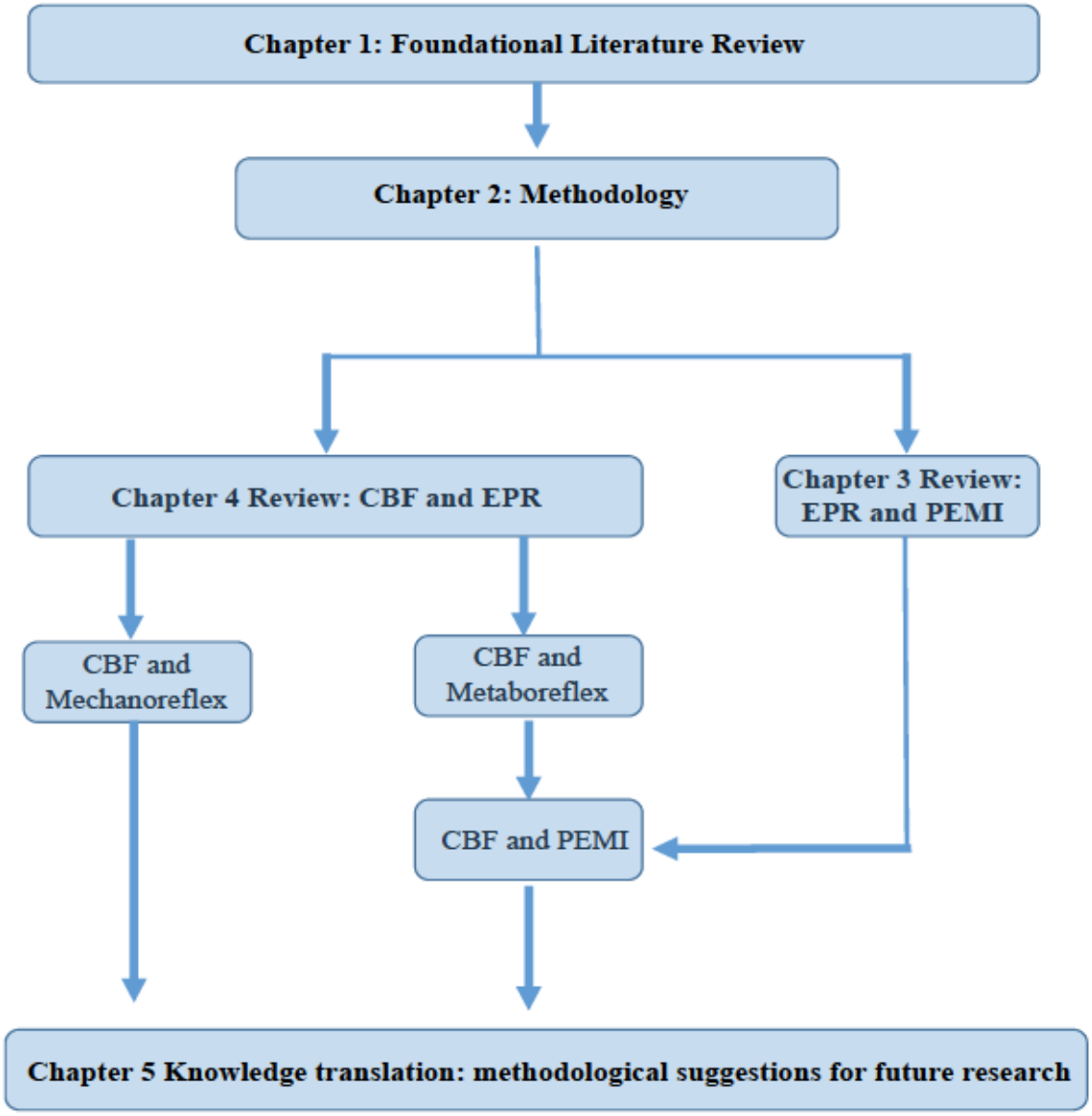

Figure 1.2. Conceptual thesis overview of the five thesis chapters. A foundational literature review of cerebral blood flow regulation during exercise (Chapter 1) is followed by a methodological section (Chapter 2) describing the thesis rational and methods. Then, a review of the use of Post Exercise Muscle Ischemia (PEMI) to study the exercise pressure reflex (EPR) and the importance of standardization of the PEMI methodology (chapter 3). Chapter 4 integrates the methodologies of chapter 3 with the foundational literature discussed in chapter one to comprehensively compare the mechanoreflex and metaboreflex components in cerebrovascular regulation during the EPR to discern their impacts on CBF regulation during exercise. A summary of these reviews is then provided to discuss the methodological suggestions for the continued use of PEMI in CBF research to improve knowledge translation (Chapter 5).

Given the multitude of influencing mechanisms that parallel CBF regulation and the EPR, and the lack of attention that EPR contributions receive in the majority of studies and reviews investigating CBF during exercise, it is important to discuss these factors in more detail. By comparing and contrasting the results and inferences of the various sources that have investigated the CBF and EPR relationship, the gap from exercise and rest to changes in CBF caused by direct influencing factors (Figure 0.1) can be addressed. Furthermore, once the EPR and CBF research has been mapped out, future investigation can be more effectively performed. The following sections will review the studies that have investigated the influence of metaboreflex and mechanoreflex on CBF, and provide a summary of the results and methodologies to clarify the gaps in the traditional approach to CBF regulation and exercise research. For the sake of guiding more efficient, comparable future studies, an element of the scoping review will discuss the influence that diverse CBF assessments, and EPR stimulation methodologies have on research outcomes. Below is the procedural strategy to developing the described review.

Chapter 2: Methodology.

The following sections will discuss the step-by-step procedure used to investigate the integrative relationship between CBF regulation and the EPR.

There are two primary review sources commonly used in physiology: systematic and scoping reviews. A systematic review is a way of extracting evidence from the available literature that can be used to conglomerate and summarize the current understanding, or to highlight gaps in the literature and reveal new theories and conclusions. A systematic review often follows a rigorous methodology, with a strict description of what constitutes the relevant literature, aiming to counteract and diminish author biases (Aromataris and Pearson 2014; Munn et al. 2018). A scoping review is tailored to describing the volume and focus of an area of research. Scoping reviews are excellent tools for mapping a broad subject of current research into a variety of sections, perhaps exposing areas of increased or decreased focus in the available literature (Anderson et al. 2008). Scoping reviews are also used to investigate methodological trends in research. For the proposed review, a scoping model is most useful because it affords the author the freedom to be exploratory in terms of evaluating the research assessing CBF in response to exercise. A topic containing such a variety of mechanisms requires a scoping inquiry to identify the relative importance between the mechanisms investigated, while perhaps exposing an imbalance in the current research priorities.

2.1 Methodological Framework

The following is the methodological approach to the scoping review, organized by the headings indicated by in the PRISM ScR checklist (Tricco et al. 2018). The chapter 3 and chapter 4 reviews also follow the headings indicated by the PRISM checklist.

2.2 Protocol and Registration

The protocol was drafted and submitted as part of thesis proposal document, submitted to Kinesiology Faculty at Lakehead University, and presented via a thesis proposal presentation, November 20, 2020 where it was accepted.

2.3 Eligibility Criteria

To be included in the proposed reviews, research studies had to be exclusively quantitative, peer reviewed, empirical studies, written in, or translated to, English. Only primary sources were eligible for inclusion. Cerebrovascular research was accepted only if performed in humans, using a direct assessment of CBF *or* cerebral blood velocity (including TCD, TCCD, MRI, NIRS, PET) and involved the manipulation of at least one physiological variable associated with the systemic exercise response (either at rest, during exercise, or using a targeted technique such as PEMI).

Neural physiology research was included if it was conducted in humans. The neural research was included if it investigated the impact of afferent neural stimulation on the systemic exercise response using PEMI (also referred to as Post Exercise Circulatory Occlusion, i.e. PECO, research using either is eligible for inclusion). PEMI is a technique that isolates the metaboreflex from an exercise bout, reviewed above. At least one measure of systemic exercise response had

to be directly measured for the research to be eligible (i.e. ventilation, sympathetic nerve activity, MAP, HR etc.). PEMI studies were only included in healthy participants, as the typical response was the question of interest.

Studies interrogating the cerebrovascular exercise response in diseased populations were not excluded, however, only the control data from the study was compared relative to other healthy population data, provided it contained otherwise healthy responses. No age or sex discrimination was used in exclusion criteria.

2.4 Information Sources

To identify the potentially relevant literature, a literature search was conducted using *PUBMed* and *Web of Science*. Boolean Search Criteria were used to specifically target the appropriate key words (Table 1). Sources that were cited by eligible sources, and that met the above inclusion criteria were also permitted for inclusion.

2.5 Search

Search strategy for both *Web of Science* and *PUBMed* engines was compiled by author, with help from committee members (Table 2.1) and performed October 1, 2020. A strategy to use a combination and a variety of Boolean search inputs that reflect the topic of the proposed literature review was used.

Table 2. 1. *Search inputs used to conduct literature search organized by search topic*.

Search Topic	Search inputs
Post Exercise Muscle Ischemia	"post exercise muscle ischemia" "post exercise circulatory occlusion"
Exercise Pressor Reflex and Cerebral Blood Flow	"cerebral blood flow" AND "metaboreflex" "cerebral blood flow" AND "mechanoreflex" "cerebral blood flow" AND "exercise pressor reflex" "cerebral blood flow' AND "metaboreceptor" "cerebral blood flow' AND "mechanoreceptor" "cerebral" AND "artery" AND "metaboreflex" "cerebral" AND "artery" AND "metaboreceptor" "cerebral" AND "artery" AND "mechanoreflex" "cerebral" AND "artery" AND "mechanoreceptor" "cerebral" AND "artery" AND "exercise pressor reflex"

2.6 Selection of Source Evidence

Decisions on the selection of source evidence were primarily performed by the lead author in cooperation with co- and senior authors. These decisions are a reflection of the degree to which the source evidence meets the topic of the review, and the evaluated score on the critical appraisal tool (outlines below).

2.7 Data Charting Process

Data was charted using Microsoft Excel, and SPSS software. Basic measures of central tendency were calculated, and data from multiple sources graphed in both absolute and relative values to visualize the scope of the data. Variety in source evidence assessment technique, and artery of choice limited the extent to which statistical analysis of significant differences can be used. Since the analysis aimed to determine the scope of the current literature, but not perform an in depth

meta-analysis, comparisons between source evidence was prioritized over the combination of data and use of complex statistics.

2.8 Data Items

The following data was extracted, charted and catalogued as indicated below:

In studies where multiple conditions were utilized (such as in sources studying the response of disease, intervention, pharmacology, etc. against a control) the control was recorded. In a source that stratified the results by sex, the male and female data was extracted separately and averaged.

2.8.2 Post Exercise Muscle Ischemia

The duration of exercise in the PEMI protocol was recorded in minutes (unless the protocol stated that exercise was performed until failure). The exercise intensity was recorded in either percentage of maximum voluntary contraction (%MVC) or target HR (bpm) as applicable. The exercise type was also recorded (i.e. Isometric handgrip, Rhythmic ankle flexion, etc.).

2.8.3 Cardiorespiratory

The HR (recorded in bpm) and MAP (recorded in mmHg) data were collected for every study during the rest, exercise, PEMI, and, if available, recovery portions of a sources testing session. If MAP data was not presented, systolic (SBP) and diastolic blood pressure (DBP) were recorded and MAP was calculated per Eq 2.1.

$$Eq2.1 \quad MAP = SBP + \frac{2(DBP)}{3}$$

When only resting data, and 'change from rest' data was available, the absolute values for each condition were calculated by adding the 'change' to the resting values.

2.8.4 Cerebral Blood Flow

Due to the variety of CBF assessment techniques, data was recorded in the units provided by the various sources (Table 2.2).

Table 2. 2. *Recorded units of cerebral blood flow (CBF) relative to assessment type*.

Assessment	Recorded Units
Intra/Extracranial arterial blood velocity	cm/s
Extracranial arterial blood flow	mL/min
Regional CBF	Not compared
Microvascular flow rate	Not compared

Resting, Exercise, PEMI and recovery CBF data was extracted from each source when available. When sources only included data changes from rest, along with resting data, the change was added to the resting data to calculate the absolute CBF values. Regional CBF, and microvascular flow was not recorded for secondary analysis, because these values are regionally specific, and should be analyzed in isolation.

2.8.5 Isocapnia

Two of the included studies had both poikilocapnic and isocapnic conditions. The cardiorespiratory and CBF data for these studies was recorded separately, and a separate entry for each condition was included into the data.

2.9 Critical Appraisal of Individual Sources of Evidence

Critical appraisal of all sources (neurogenic and CBF related) was completed the JBI critical appraisal checklists for the appraisal of research synthesis (Martin 2017), the AXIS appraisal tool for the evaluation of primary sources of cross sectional studies (Downes et al. 2016). The results of the appraisal process are displayed in Appendix A.

2.10 Synthesis of Results

The scoping review was grouped into two separate 'PEMI' and 'CBF' sections. To tackle the variability in EPR stimulation protocols, non-CBF EPR sources were analyzed with a methodological lens, to establish the extent to which methodological choices in EPR stimulation had a downstream effect on systemic outcomes, to indicate the extent to which these choices could influence the outcomes in the CBF based studies. Changes in MAP and HR during rest, exercise and PEMI were used to investigate the impact of different PEMI protocols on the cardiovascular response. The data extracted from the CBF sections was used to develop the expected CBF response to EPR stimulation, stratified by different manipulated variables across a variety of studies to elucidate the variables with the largest/most relevant impact.

2.11 Review Itemisation.

The following list provides the primary topics covered in the scoping review. Inclusion in any one literature set did not exclude a study from one of the other sets, and there was cross over between literature lists.

Review Sections:

A) Systemic response to post exercise muscle ischemia

- i. Methodological variability
- ii. Systemic response variability

B) Exercise pressor reflex control of cerebral blood flow

- i. Metaboreflex and CBF – PEMI studies
- ii. Mechanoreflex and CBF

Every study included in this review that investigates the effect of metaboreflex on CBF employed a PEMI protocol. These studies were analysed in both Chapters 3 and 4. To investigate the effect that the PEMI protocol has experimental outcomes, Chapter 3, which identified a number of PEMI studies using various protocols was conducted. Then, the studies that assessed CBF metrics were separately reviewed (Chapter 4). Conclusions based on the sum findings from both investigations precede an individual analysis of each literature review.

Chapter 3: Influence of Post Exercise Muscle Ischemia on the Cardiovascular response to Metaboreflex Stimulation

The majority of research assessing the CBF response to an EPR challenge has used PEMI to stimulate the metaboreflex. By controlling for the influences of central command and the mechanoreflex, PEMI is an elegant way of creating a robust but direct response to a known stimulus. Despite this, methodological diversity is prevalent in studies that employ PEMI. Exercise intensity, type, and duration often vary from one protocol to another. These variations are infrequently justified by the original sources and have implications to the EPR response as discussed below. In an effort to compare results between sources that employed PEMI to stimulate the metaboreflex, the influence of the prevalent methodological changes must first be addressed. In the following chapter, a number of studies that assessed CBF or other systemic responses to PEMI stimulation will be assessed. The systemic responses to PEMI from each source will be compared with the methodological details of the source's procedure, with the intention of identifying any potential influence that the methodological variability, and detecting an optimal PEMI protocol for future use. Find the accepted sources and their analysis in the chapter bellow, followed by a critical analysis of the influence of varying PEMI protocols, and whether the response provided by each protocol is valid and comparable. Finally, the present review provides a foundation for the interpretation of PEMI protocols used in the subsequent systematic review of CBF and the EPR (chapter 4).

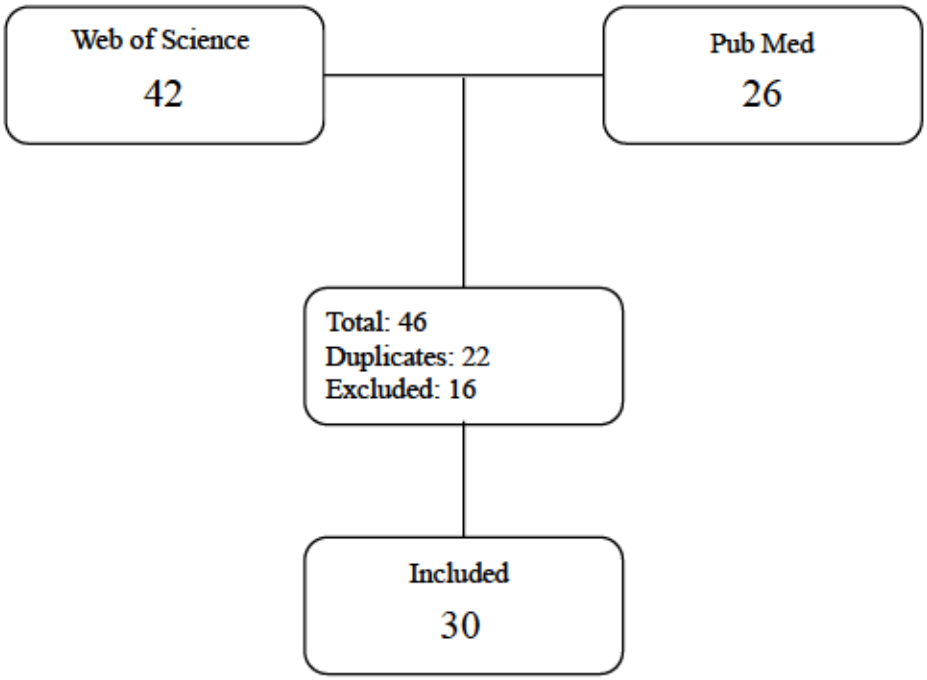

Figure 3. 1. Search results and inclusions of the literature search on metaboreflex stimulation. Included sources divided into studies who labelled their protocol Post Exercise Muscle Ischemia (PEMI) and those who labelled it Post Exercise Circulatory Occlusion (PECO).

3.1 Results - Characteristics of sources of evidence

The following Table will summarize each source of evidence used to perform the review of the methodological implications for PEMI.

Table 3. 1. *Individual sources of evidence, and the respective PEMI protocols.*

Author	Year	Exercise type	Exercise Duration (minutes)	Exercise intensity	Action
Amano	2018	Hand Grip	1	60%	Isometric
Badrov	2016	Hand Grip	5	20%	Isometric
Bell	2005	Plantar Flexion	1.5	30%	Isometric
Braz	2014	Hand Grip	Until Failure	40%	Isometric
Bruce	2016	Hand Grip	2	50%	Rhythmic
Carrington	2002	Plantar Flexion	2	30%	Isometric
Carrington	2001	Plantar Flexion	2	30%	Isometric
Carrington	2004	Plantar Flexion	2	30%	Isometric
Cristafulli	2011	Hand Grip	3	30%	Rhythmic
Doneddu	2020	Hand Grip	3	30%	Rhythmic
Figueroa	2009	Hand Grip	3	30%	Isometric
Figueroa	2016	Hand Grip	2	30%	Isometric
Figueroa	2015	Hand Grip	2	30%	Isometric
Fisher	1999	Plantar Flexion	2	30%	Isometric
Florian	2016	Hand Grip	Until Failure	40%	Isometric
Gama	2020	Hand Grip	3	30%	Rhythmic
Guicciardi	2019	Hand Grip	3	30%	Rhythmic
Incognito	2017	Hand Grip	3	30%	Isometric
Joshi	2019	Hand Grip	2	40%	Isometric
Karlsson	2009	Hand Grip	2	35-40%	Isometric
Kiviniemi	2010	Hand Grip	5	20%	Isometric
Millia	2015	Hand Grip	3	30%	Rhythmic
Mulliri	2020	Cycling	3	30%	Rhythmic
Mulliri	2019	Cycling	3	30%	Rhythmic
Ogoh	2019	Knee Extension	2	30%	Isometric
Ogoh	2019	Knee Extension	2	30%	Isometric
Prodel	2016	Cycling	13-15	120bpm	Rhythmic
Vianna	2009	Plantar Flexion	2	35%	Isometric
Williamson	2003	Hand Grip	3	40%	Isometric
Wong	2020	Hand Grip	2	30%	Isometric
Yamguchi	2014	Hand Grip	2	30%	Isometric

3.1.1 Post Exercise Muscle Ischemia and Post Exercise Circulatory Occlusion

Studies in the PEMI/PECO section with a protocol named PECO did not differ in approach to studies that labeled their protocol PEMI. Both types of studies employed exercise followed by occlusion with the intension of isolating metaboreflex stimulation, though both PEMI and PECO studies used a wide variety of protocols to do so. From this point forward, PEMI will be used to describe the entirety of the included studies. Despite roughly half of the studies employing a different moniker, there is not technical or methodological distinction between studies labeled PEMI and PECO.

3.1.2 Cardiovascular response to Post Exercise Muscle Ischemia

With the intent of capturing the scope of PEMI protocol variety, 30 sources of evidence were obtained that evaluated the cardiovascular response to PEMI. The exercises, duration, type, intensity, voluntariness and muscle groups used for the exercise portion of the PEMI protocols varied between studies. The occlusion pressure, and limb location of the BP cuff also varied, as did the duration that PEMI was maintained. Cardiovascular responses (MAP, HR) of all individual studies were extracted, when available. The responses were then grouped by protocol and graphed to represent the data, though statistical tests of significance were not appropriate, due to large variance between studies, and non-standard assessment techniques between studies. When grouped by MVC%, the MAP and HR responses did not differ, especially when exercise and PEMI response was quantified as change from rest (Figure 3.2). When the data was pooled into isometric and rhythmic groups, MAP response to exercise and PEMI did not appear to differ (Figure 3.3), nor did HR (Figure 3.4). There was no observable trend when data was grouped by MVC level on MAP during PEMI or exercise. Exercise duration did not appear to influence

PEMI MAP but exercise MAP appeared to change with duration. An exercise duration of 3 minutes appeared to cause a smaller MAP response than 2 minutes, or 4 or more minutes across all exercise intesities. When 2-minute exercise was compared to 3-minute exercise protocols, the difference is exaggerated (Figure 3.4). The observed difference is linked with a difference in variance between the 2-minute protocol data (119.1) and 3-minute (43.1) For PEMI MAP and 2-minute (81.9) and 3-minute (48.6) for exercise MAP. The variance in all data was massive between studies.

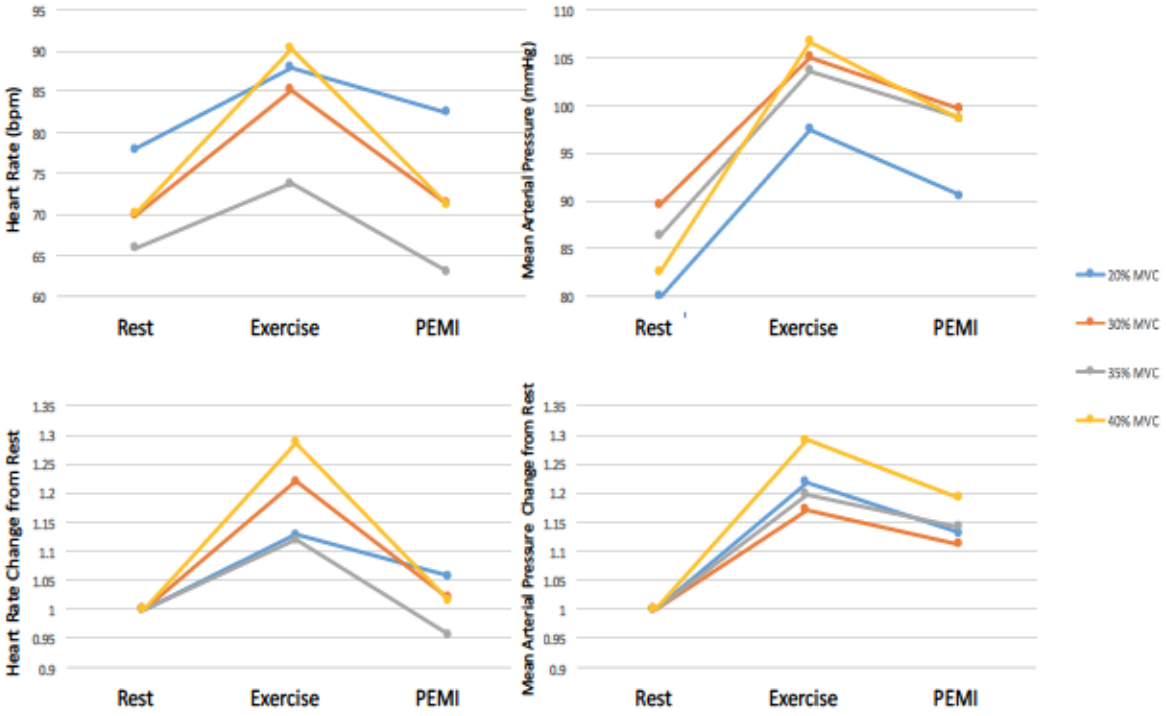

Figure 3. 2. Mean changes in Heart Rate (HR) or Mean Arterial Pressure (MAP) grouped by Maximum Voluntary Contraction (MVC) of the exercise stimulus in the PEMI protocol recorded as a proportion of baseline, where 1.0 indicates baseline levels.

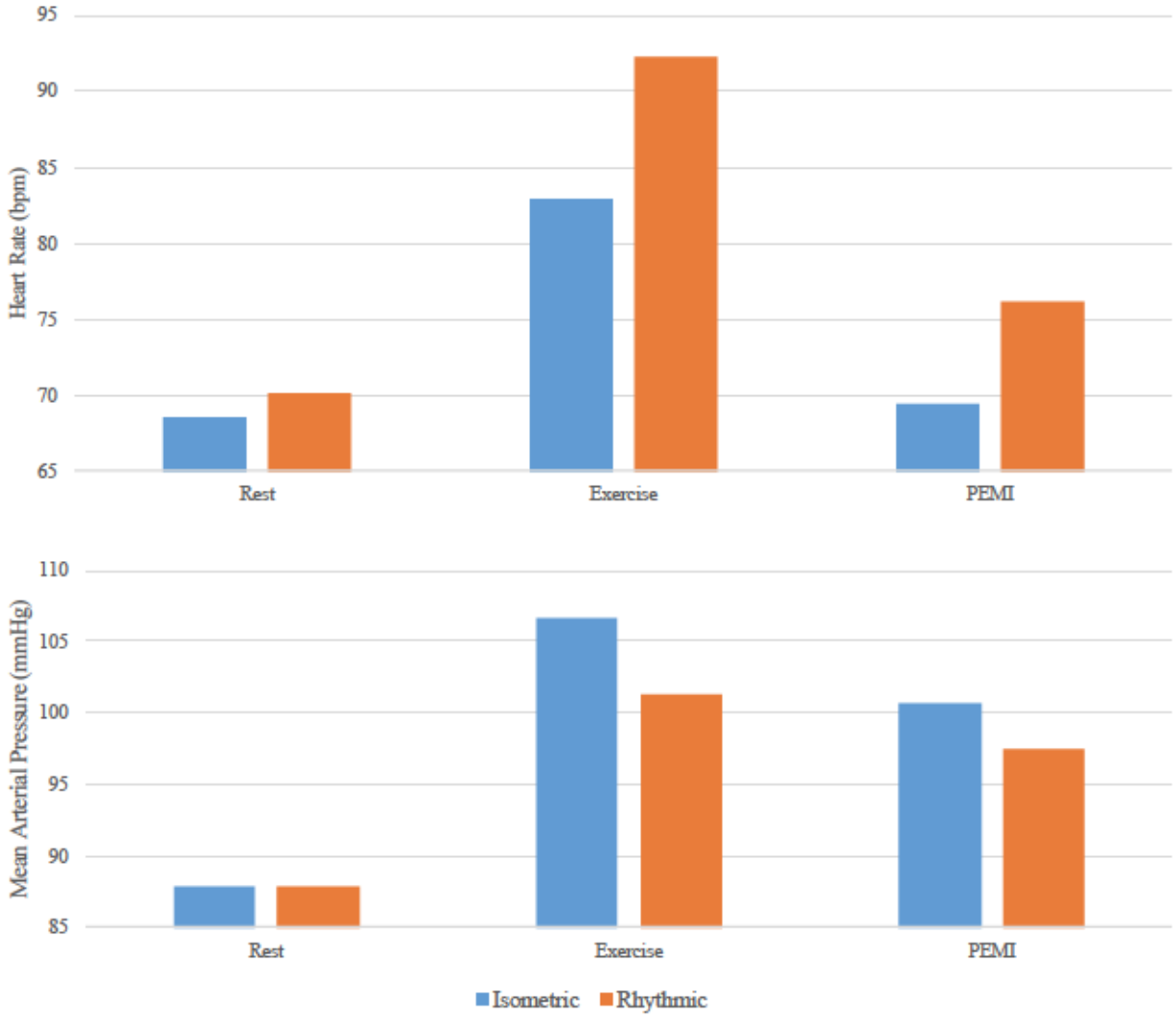

Figure 3. 3. Heart rate and mean arterial pressure differences between rhythmic and isometric exercise preceding post exercise muscle ischemia (PEMI) protocols during rest, exercise and PEMI.

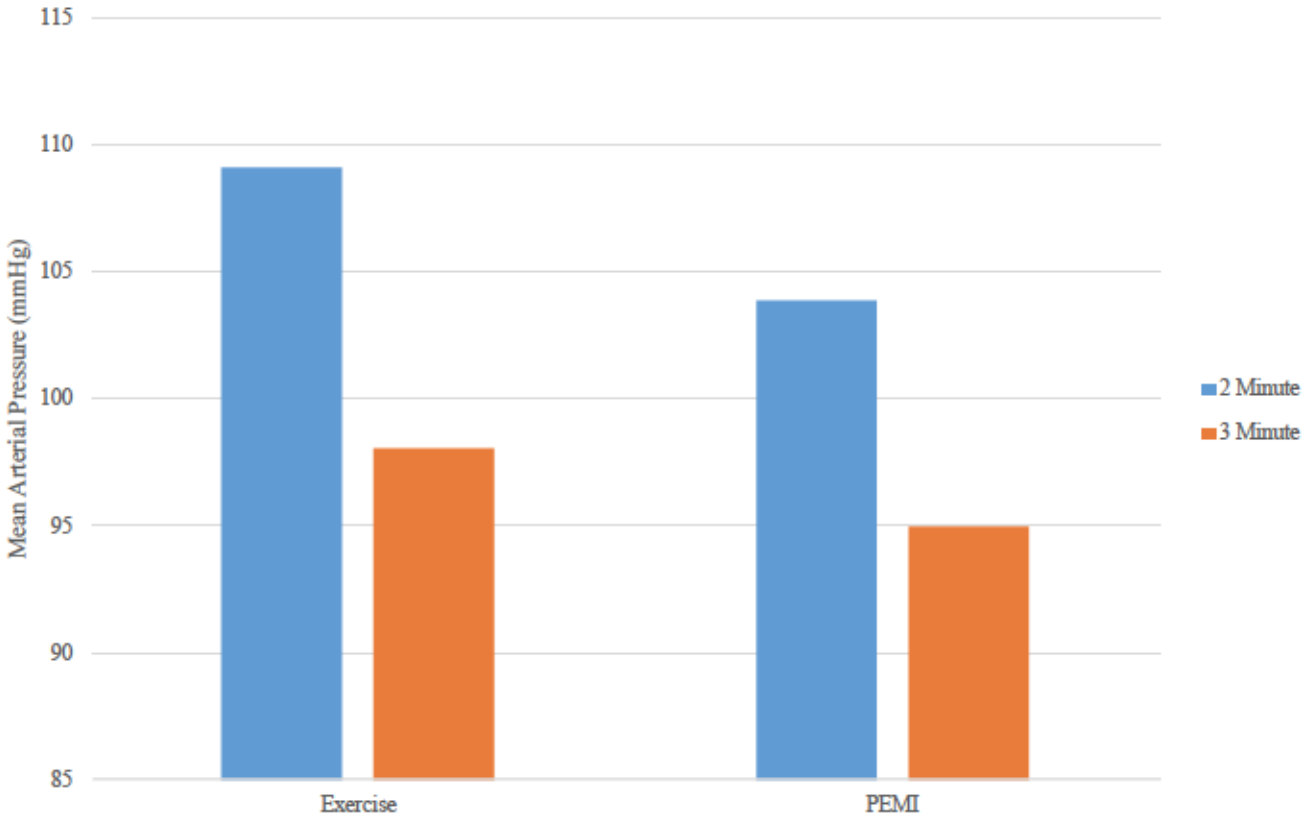

Figure 3. 4. Mean Arterial Pressure (MAP) differences during exercise (Ex) and Post Exercise Muscle Ischemia (PEMI) portions of 2 and 3 minute PEMI protocols.

3.2 Summary of evidence

The mean PEMI responses varied largely between studies, making accurate statistical analysis, and interpretation of the protocol variability challenging. Despite noticeable difference in PEMI protocols the summary was not able to reveal any effect of exercise type or MVC percentage on the systemic PEMI response. However, a possible effect of exercise duration on MAP during exercise and PEMI was revealed, though the effect was non-linear. Of note, differences in population age (Markel et al. 2003), sex (Jarvis et al. 2011) and strength (Saito et al. 2009), which influence EPR response exist between the studies. These confounds may have diluted the

effect any one methodological practice had on the acquired data set, limiting statistical interpretations. Both sex and strength appear to correlate with forearm volume, a factor which likely affects the local PEMI response. Research has shown that the local endothelial response to handgrip exercise is relative to forearm volume. Larger forearm volumes receive increase forearm blood flow at the same relative exercise intensities. Forearm blood flow plateaus irrespective of forearm size and handgrip strength at 14% MVC (Gonzales et al. 2007). No study to date has assessed active muscle size to evaluate the effect of size or strength of active muscle on cerebral hemodynamics. Research has also demonstrated that lower strength participants exhibit a larger pressor response to the same absolute workload compared to stronger participants, justifying the use of relative strength during PEMI protocols. Hand grip exercise time until task failure is longer in women than in men at the same relative intensity (Hunter 2014). As a result, men appear to stimulate more metaboreflex activation during the same duration of exercise as compared to women, as they complete a larger proportion of their maximal work (but not contraction) capacity. When hand grip exercise is performed at absolute intensities, the difference between sexes disappears, indicating that the basis for the sex differences in metaboreflex stimulation are likely due to strength and endurance related differences between sexes (Hunter 2014).

Despite the known differences above, the observed MAP difference during PEMI with exercise duration changes are difficult to interpret. There is no supporting evidence for a bimodal response to differing muscular contraction durations, in fact the response to exercise duration appears to linearly increase in another study (Gonzales et al. 2007). A potential explanation of the difference in MAP observed between 2, 3, and 4+ minute PEMI protocols is likely a function

of the variability between PEMI responses within each time-distinguished group. The 3-minute group exhibited roughly one third the variance as the 2-minute group. This likely indicates that a 3-minute exercise protocol more consistently increases metabolite concentrations relative to a 2-minute protocol, producing a less variable response despite capturing a weaker mean response among participants. Perhaps 4-minute exercise is prohibitive to less trained participants, thus inducing an increasingly varied response between participants of differing training levels. It is perhaps the case that a 3-minute exercise protocol is the best compromise between metabolite production, and maximal exercise capacity. 2 minute protocols likely are short enough to develop robust intramuscular metabolite concentrations via increased work rate in strong participants. Similarly, 4 minute protocols may provide stronger participants the opportunity to develop a larger response, that was not matched by weaker participants, increasing variability. Perhaps in between is an optimal level, where production of metabolites is more consistent irrespective of participants' strength. This is speculative, as the individual MVC of each participant in the sources of evidence was not provided.

Though beyond the scope of the current thesis, the present research revealed the need for a future meta-analysis. A meta-analysis of the systemic PEMI response and the influence of methodology is necessary to clarify the PEMI technique as metaboreflex stimulant. An in depth study of the PEMI response would clarify the dose-response relationship between the stimulation of the metaboreflex and the duration, intensity and modality of the PEMI protocol.

3.3 Limitations

Limitations in statistical power, and the inability to control for possible confounds such as sex and age perhaps hid the effect of methodological discrepancy between studies. Data was also collected in different intervals between each PEMI protocol. A future meta-analysis could more aptly identify the influence of PEMI methodology on response.

3.4 Conclusions

Variable PEMI responses due to different protocols will likely reduce the accuracy of the mechanistic inferences of cerebrovascular control. Despite this, the observed CBF responses to PEMI can be attributed to metaboreflex stimulation. Future research regarding PEMI protocol variance is just one of the ways researchers can sharpen the assessment of the CBF EPR.

Chapter 4: Scoping Review of Cerebral Blood Flow and the Exercise Pressor Reflex

The following is a scoping review of the accepted experimental sources investigating the cerebrovascular response to exercise pressor stimulation. The studies reviewed below stimulated the EPR using PEMI, electrically stimulated exercise and passive movement. In isolation, each of the sources reviewed in the following provide novel insight into the mechanistic control of CBF during EPR stimulation. When analysed together, the following sources of evidence, illuminate a pathway for future researchers to perform future studies that refine our understanding of mechanistic CBF control, CBF response to exercise, and the reflexivity of the EPR. The following will describe the sources selected, provide individual interpretations of the sources, and postulate what the outcomes from each source mean, when examined as a whole.

4.1 Selection of sources of evidence

The outcomes of the above-described literature search as represented in Figure 4.1.

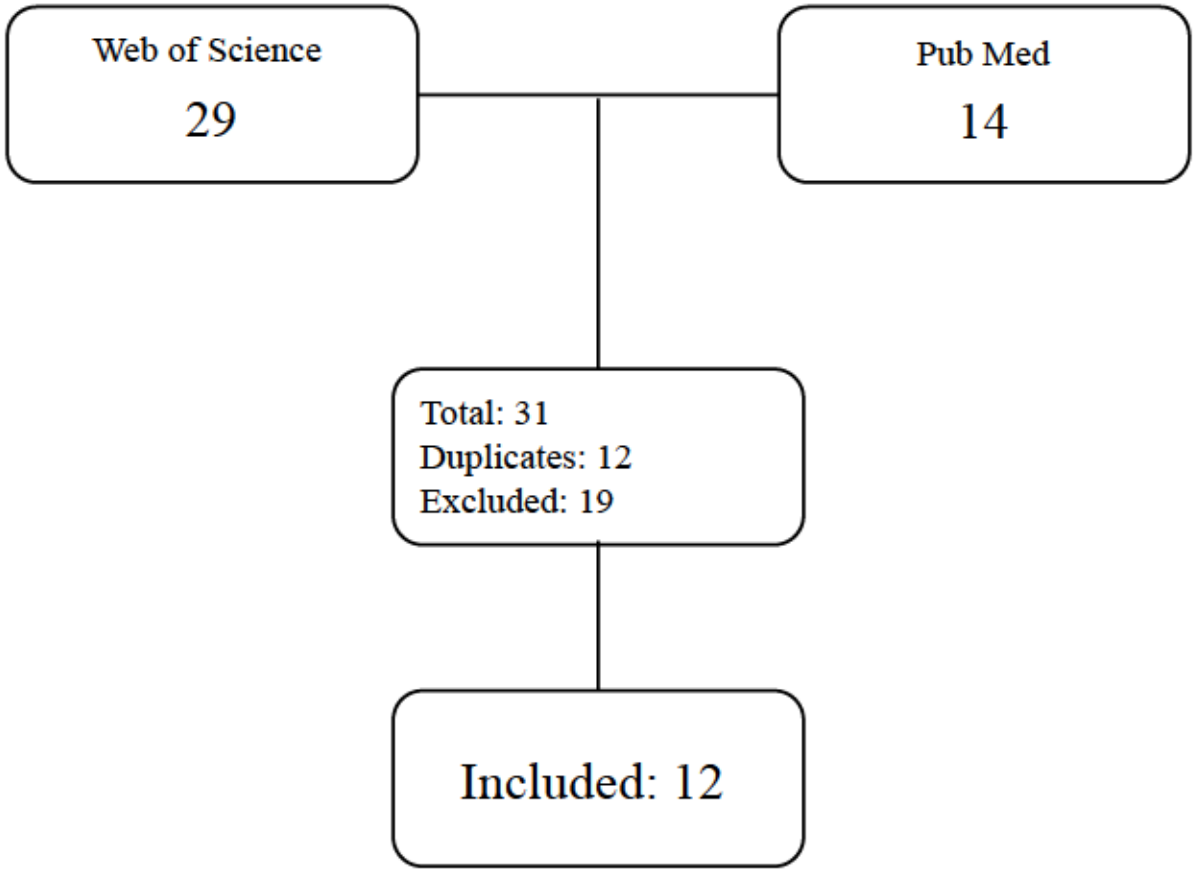

Figure 4. 1. Search results and inclusions of the literature search on cerebral blood flow and the exercise pressor response. Included sources divided into metaboreflex, labelled Post Exercise Muscle Ischemia (PEMI) studies and Mechanoreflex (Mechano) studies.

4.2 Characteristics of sources of evidence

The following section details the common characteristics from the included sources of evidence. The shared evidence from the sources is discussed further below.

4.2.1 Cerebral Blood Flow and Metaboreflex

Of the 31 sources of evidence identified using the search criteria, nineteen studies, including eight animal studies and seven review studies were excluded (Figure 4.1). Of the remainder, ten studies employed a PEMI protocol to assess CBF in response to metaboreflex activation, eight

did so in a healthy population, and two did so in a diseased population (participants with metabolic syndrome) (Doneddu et al. 2020; Guicciardi et al. 2019). A number of PEMI studies used specific controls while stimulating the metaboreflex. Two sources of evidence controlled for the regulatory effect of fluctuating arterial carbon dioxide concentration by clamping $PETCO_2$ near base line (Braz et al. 2014; Prodel et al. 2016). One source controlled for the vasoactive effects of female sex hormones by distinguishing between male and female participants (Joshi and Edgell 2019). One study controlled for the influence of central command output during exercise, by assessing electrically evoked exercise as well as volitional activation (Vianna, Araújo, and Fisher 2009). The same study that controlled for central command innervation also controlled for the possible confound of exercise modality by doing separate trials of rhythmic and isometric exercise (Vianna et al. 2009). All studies observed an increase in HR and MAP during exercise, with a persistent MAP elevation during PEMI, though HR returned to resting levels in all studies. Intracranial artery velocity was assessed in 5 studies, though none directly assessed intracranial artery diameter. The remainder of the studies assessed either extracranial arterial velocity and diameter (n=1) regional CBF (n=2) or cerebral oxygenation (n=2). The most common CBF assessment technique was TCD, with TCCD and NIRS being employed also (Figure 4.2).

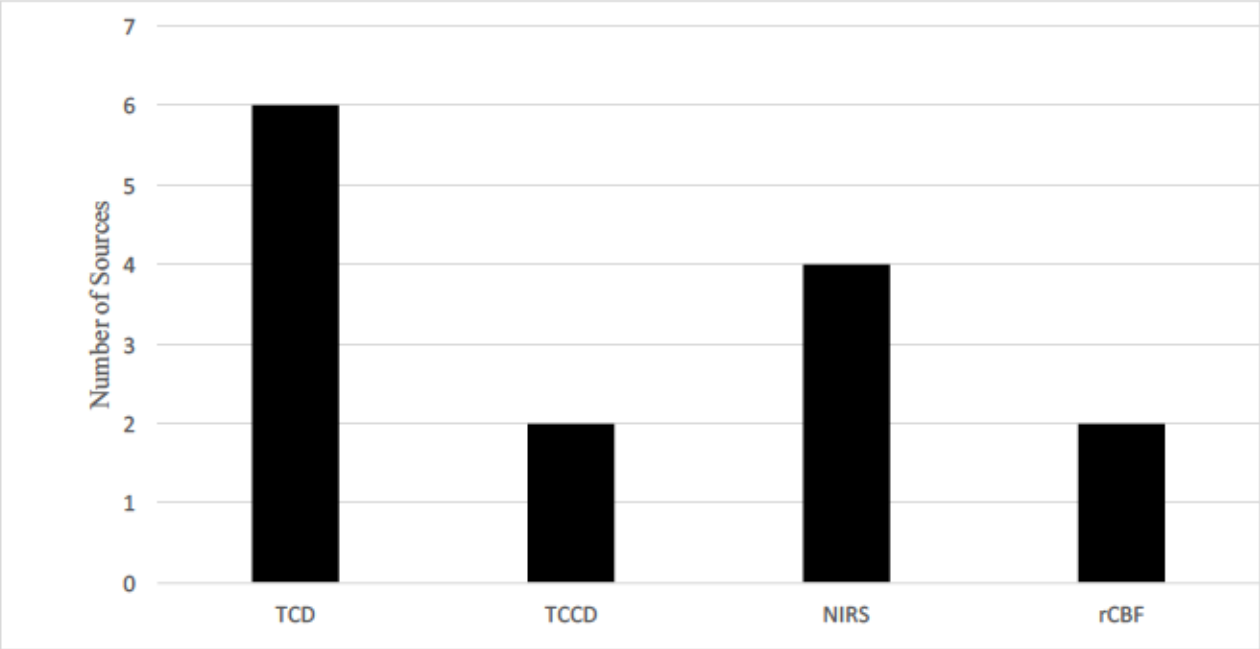

Figure 4.2. Prevalence of Transcranial Doppler (TCD), Transcranial Color-Coded Dupplex Ultrasound (TCCD) Near Infrared Spectroscopy (NIRS) and regional Cerebral Blood Flow (rCBF) assessment techniques employed in the source evidence of the scoping review. Included studies are referenced in tables 4.1 and 4.2.

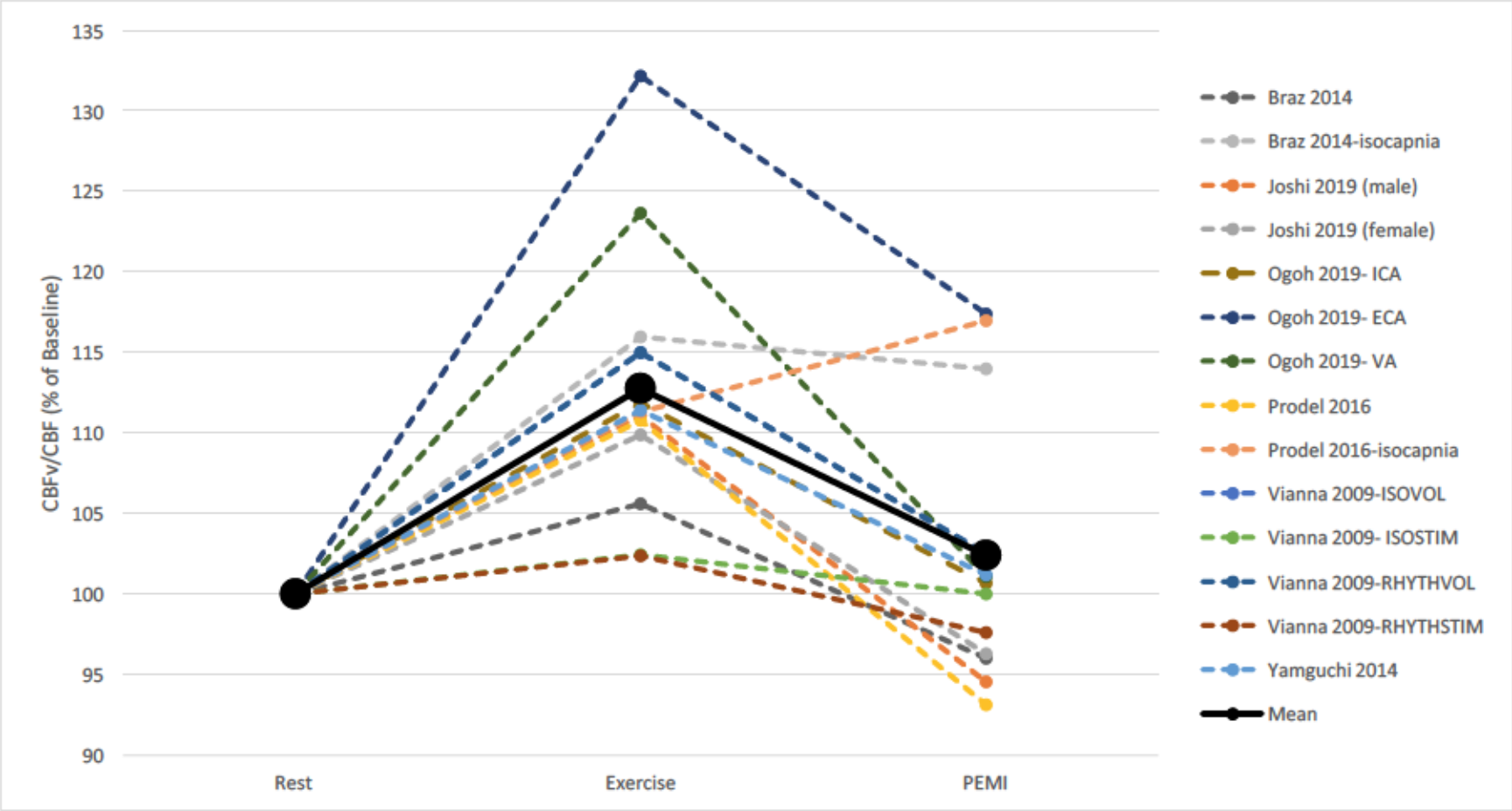

Figure 4. 3. Percentage of resting Cerebral Blood Flow (CBF) and CBF velocity (CBFv) during rest, exercise and Post Exercise Muscle Ischemia (PEMI) in various studies. Multiple groups were used to represent multiple data points in this figure. Isocapnia refers to an isocapnic trial, whereas others are poikilocapnic male and female represent data divided by sex. In a trial that modified the exercise portion of their protocol, ISOVOL is isometric voluntary exercise, ISOSTIM is isometric stimulated exercise, RYHTVOL is rhythmic voluntary exercise, and RHYTHSTIM is rhythmic stimulated exercise. ICA (internal carotid artery), ECA (external carotid artery) and VA (vertebral artery) were differentiated between for one study.

Figure 4.3 highlights the lack of congruency in the cerebrovascular response to metaboreflex stimulation among the compiled literature. HR increased during exercise in all studies, and returned to baseline levels during PEMI. All eight of the studies that assessed intra or extracranial CBF during PEMI found no change in CBF velocity between rest and PEMI (or a slight non-significant decline, as individually reported by each source of evidence), or regional CBF distribution during poikilocapnic trials, though they all demonstrated a change in cerebral vascular conductance index, mirrored by an elevation in MAP that persisted during PEMI. Two studies, completed control conditions and demonstrated a preserved increase in intracranial blood flow velocity during PEMI when the response-related decline in arterial carbon dioxide is avoided (Braz et al. 2014; Prodel et al. 2016). One also demonstrated an increase in extracranial CBF during isocapnic trials (Prodel et al. 2016).

4.2.2 Cerebral Blood Flow Responses to the Mechanoreflex

Only two studies controlled for the influences of central command and metaboreflex while stimulating mechanoreflex and assessing CBF (Asahara and Matsukawa 2018; Sato, Moriyama, et al. 2009). Both studies contrasted voluntary and passive exercise or movement to observe the differences between the activation of metaboreflex, mechanoreflex and central command simultaneously and the activation of mechanoreflex in isolation. Both studies reported no change in CBFv, but one study cited an increase in prefrontal cortex oxyhemoglobin concentration (Asahara and Matsukawa 2018). During voluntary exercise, which permits the input of central command, both studies observed increases in CBF compared to resting and passive exercise sessions.

4.3 Results of individual sources of evidence

The following indicates the basic findings of each individual source of evidence that used PEMI to assess the influence of metaboreflex (Table 4.1; n=10) and mechanoreflex (Table 4.2; n=2) stimulation on CBF are summarised below, including a simplified description of the CBF response to the EPR stimulation employed in each source.

Table 4. 1. *Methodology and results from studies investigating the cerebral blood flow (CBF) response to Post Exercise Muscle Ischemia (PEMI).*

First Author	Year	CBF Measure	CBF Assessment	Controlling	Effect of PEMI on CBF
Braz	2014	MCAv	TCD	PET_{CO2}	Elevated MCAv from rest during PEMI when CO_2 clamped
Donnedu	2020	COX	NIRS		Cerebral oxygenation unchanged in response to PEMI in patients with and without metabolic syndrome.
Guicciardi	2019	COX	NIRS		Cerebral oxygenation unchanged in response to PEMI in patients with and without metabolic syndrome.
Joshi	2019	MCAv	TCD	Sex	No change in CBFv in male or female participants
Ogoh	2019	ECA, ICA, VA flow	TCCD		Elevated extracranial CBF and CI
Prodel	2016	MCAv	TCD	PET_{CO2}	Increased MCAv and ICAf when CO_2 clamped
Vianna	2009	ACAv	TCD	Central Command	No change in CBFv from rest
Williamson	2003	rCBF	PET		No change in rCBF from rest
Williamson	1996	rCBF	PET		Sustained thalamus flow with PEMI after exercise
Yamaguchi	2014	PCAv	TCD		No change in CBFv from rest

Table 4. 2. *Methodology and results from studies investigating the cerebral blood flow (CBF) response to Mechanoreflex stimulation.*

First Author	Date	CBF Measure	CBF Assessment	Metaboreflex stimulation	Effect of metaboreflex on CBF
Asahara	2018	OxyHb, DeoxyHb, CCA, ICA,	NIRS, TCCD	Passive cycling	No CBF change from rest, increased oxyhemoglobin.
Sato	2009	MCAv, CCA	TCD, TCCD	Passive elbow flexion/extension	No change from rest

4.4 Synthesis of results

Control	PETCO	SEX (M)	SEX (F)	No Control
MAP response to Ex	Increase from baseline	Increase from baseline	Increase from baseline	Increase from baseline
MAP response to PEMI	Increase from baseline, decrease from exercise	Increase from baseline, decrease from exercise	Increase from baseline, decrease from exercise	Increase from baseline, decrease from exercise
CBF response to Ex	Increase from baseline	Increase from baseline	Increase from baseline	Increase from baseline
CBF response to PEMI	Increase from baseline, decrease from exercise	Return to baseline	Return to baseline	Return to baseline

Figure 4. 4. Synthesized Map of Cerebral Blood Flow (CBF) and Mean Arterial Pressure (MAP) response to exercise (Ex) and Post Exercise Muscle Ischemia (PEMI) when controlling for sex (M: male, F: female), percent end tidal carbon dioxide ($PETCO_2$). And without controls.

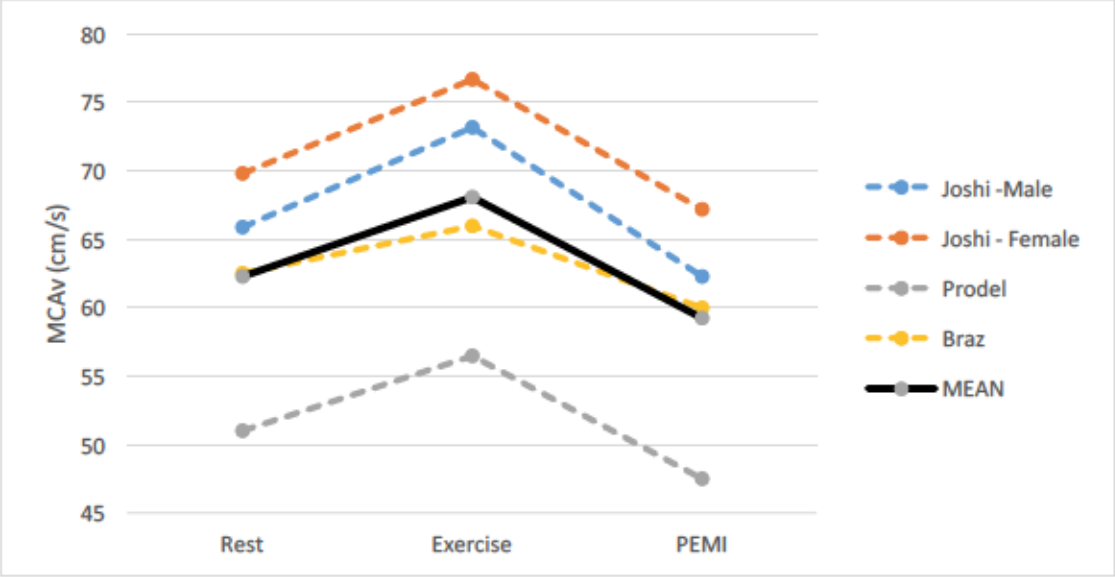

Figure 4. 5. Middle Cerebral Artery velocity (MCAv) during rest, exercise and Post Exercise Muscle Ischemia (PEMI) in poikilocapnic studies.

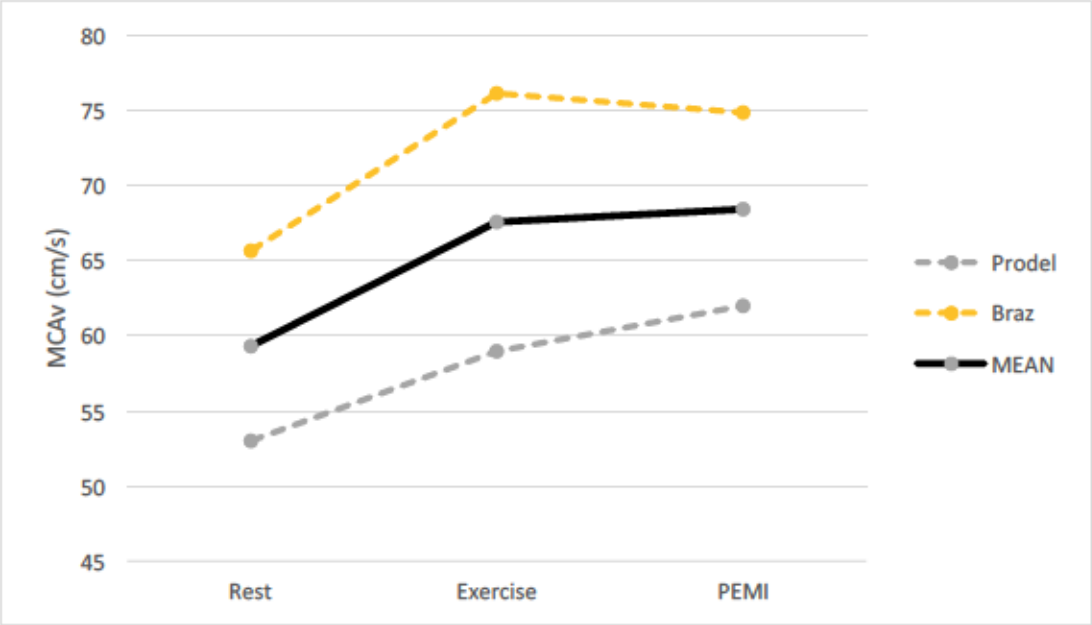

Figure 4. 6. Middle Cerebral Artery velocity (MCAv) during rest, exercise and Post Exercise Muscle Ischemia (PEMI) in isocapnic studies.

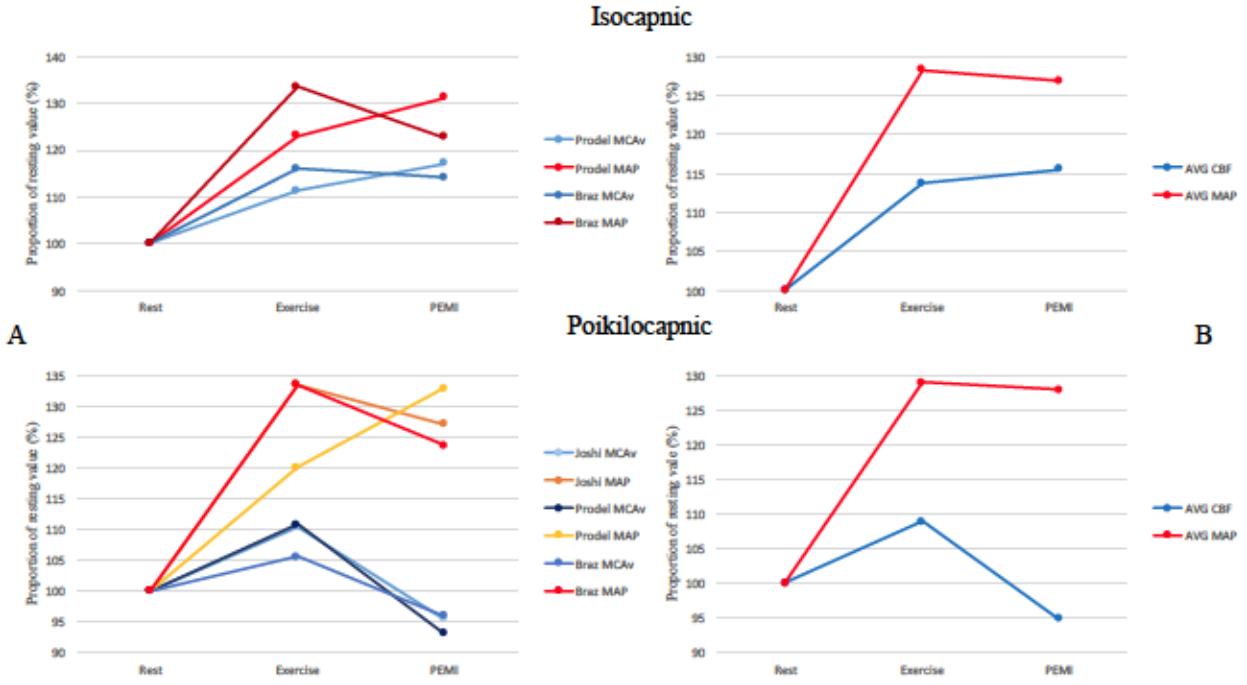

Figure 4. 7. Middle Cerebral Artery velocity (MCAv) and Mean Arterial Pressure (MAP) response to isocapnic and poikilocapnic exercise and Post Exercise Muscle Ischemia (PEMI) in individual sources of evidence (A) and next to the MEAN Cerebral Blood Flow (CBF) and averaged MAP responses (B).

4.5 Discussion - Summary of evidence

Interpretation of the included sources of evidence is discussed below. Inferences pertaining to CBF responses to metaboreflex, mechanoreflex and central command are discussed, and differences between sources of evidence examined. Differences between sources of evidence will be evaluated, and explanations for disagreement between sources of evidence will be proposed.

4.5.1 Cardiovascular Response to PEMI in CBF studies

The CBF response to PEMI is only important if the PEMI protocol sufficiently stimulated the metaboreflex. Observation of the cardiovascular response to the PEMI protocol assesses this. The included sources of evidence demonstrated a homogenous HR and MAP response at rest, during exercise, and PEMI. The impact of the varying PEMI protocols on central and peripheral outcomes remains unclear, and is presented above (Chapter 3). Despite there being a variety of PEMI protocols employed in the sources of evidence, all protocols appeared to stimulate the EPR. There was an increase in HR during exercise in all studies, but returned to baseline during PEMI. Furthermore, MAP increased during exercise, and decreased, but remained elevated from baseline during PEMI in all studies. Regardless of PEMI protocol variance, the CBF response to metaboreflex stimulation can still be analysed, firstly by looking at the main covariates of the response.

4.5.2 Cerebral Blood Flow Response

Several studies employed different assessment and modalities to assess the cerebrovascular hemodynamic response to EPR stimulation. This review reveals that the assessment approach and modality utilized (Figure 4.2) have divergent impacts on the cerebrovascular EPR (Table

4.1). In studies that employed NIRS to determine cerebral oxygenation or regional CBF, no changes in cerebral global oxygenation were observed (Doneddu et al. 2020; Guicciardi et al. 2019; Williamson et al. 1996). One study used Positron emission tomography and observed some small isolated increases in perfusion to certain regions of the thalamus and insular cortex during PEMI (Williamson et al. 2002). One study observed extracranial artery flow, and found that the external carotid artery blood flow increased during PEMI from rest in contrast to stable internal carotid and vertebral artery responses (Ogoh et al. 2019a). In studies that observed posterior CBF via the insonation of PCA velocity, no response to metaboreflex stimulation was observed (Yamaguchi et al. 2014). Lastly, in studies that observed anterior intracranial CBFv, a change in MCAv was not significantly different from rest in poikilocapnic trials. Because PEMI-induced hyperventilation lowers $PETCO_2$, there was an opportunity for $PETCO_2$ mediated vasoconstriction of the cerebral arteries to disguise the influence of other factors on the CBF EPR.

4.5.4 Cerebrovascular Conductance and Resistance

In studies using a direct measure of MCAv, cerebrovascular conductance (CVC) index was also calculated by dividing the mean cerebral blood velocity by the arterial BP signal, and interpreted as an index of the ease that blood moves through the cerebral vasculature (Smirl et al. 2014). Cerebrovascular conductance is a well-documented index of the cerebrovascular hemodynamic response to metaboreflex activation. CVC is largely determined by the vasomotion of downstream micro-vessels, and is inversely related to cerebrovascular resistance (CVR). Eight studies have used CVC to indicate a cerebrovascular response to metaboreflex stimulation, despite no statistical change in velocity. Because arterial pressure influences the perfusion

pressure that delivers CBF, any change in BP that is not met with a similar change in flow is viewed as indicative of a cerebrovascular response. If CBF and MAP rose proportionally (which appears to happen when the regulatory impact of carbon dioxide is controlled), the change in CBF could be the principal finding. Indeed, the only way the reviewed sources of evidence could find no effect of metaboreflex stimulation on CBF is if they failed to observe an increase in MAP. Changes in CBF can either be as a result of changing blood velocity in a vessel of a constant diameter, or as a result of changing diameter, perhaps disguising velocity as an indication of flow. Given that blood flow through a vessel is a product velocity and vessel cross-sectional area, any changes in vessel diameter can change blood flow velocity without affecting CBF. Blood flow velocity can be altered by a change in perfusion pressure, without a change in arterial diameter which would cause an increase in velocity. A recent study demonstrated that exercise induced increases in cerebrospinal fluid pressure trigger increases in intracranial pressure. The corresponding increase in ICP provides counter pressure on intracranial arteries, and thus in theory would stabilize cerebral perfusion pressure resulting in an increased CBF (Tarumi et al. 2021). Thus, using CVR as a reliable inference of arterial diameter without assessing intracranial pressure is challenging. When MAP increases as a result of PEMI, it is unclear whether the maintenance of a constant CBFv is the result of an unobserved dilation with an increase in CBF, or an unchanged CBF, due to increased cerebrovascular resistance. Since flow is being indirectly indexed from velocity, CVC is therefore an indirect measure, calculated from another indirect measure, which really limits the level of inferences that can be gained about arterial diameter from CVCi calculated using CBFv. When volumetric CBF is assessed, then CVC can be understood while only making assumptions regarding ICP, improves the inferences that can be made from CBF and CVC assessments.

Eight studies observed an increase in CVR during PEMI, meaning CBF returned to resting levels despite a persistent increase in MAP. In agreement with the traditional Monro-Kellie doctrine of constant intracranial pressure maintenance, this mechanism likely exists to protect the cerebral vasculature and the cerebrum from the damage associated with elevated levels of pulse wave pressure moving through the vessels. Despite this, Williamson and colleagues observed an isolated increase in regional CBF to left and right inferior thalamus as well as the right anterior insular cortex during PEMI (Williamson, McColl, and Mathews 2003). Taken together, these results indicate the potential for an increased CVR in response to PEMI, that is actually lysed in the microvasculature that supplies active centers in the brain. The increase in CVR would protect the brain from dangerous levels of intracranial pressure. The simultaneous lysing of the protective mechanism in the cerebral microvasculature could maintain flow to the most metabolically active portions of the brain during exercise. This theory mirrors the known response to the EPR in the periphery. During exercise, the peripheral vasculature experiences an increase in vascular resistance, which is lysed when the vessels that supply the more metabolically active parts of the body, such as the active skeletal muscles. This theory could be further developed by exploring the interplay of CO_2 and MAP with cerebrovascular control during EPR stimulation. It is also possible that the thalamus and insular cortex are exhibiting a NVC effect on the regional microvasculature, though that has yet to be investigated.

4.5.5 Influence of Carbon Dioxide on cerebral arteries during post exercise muscle ischemia

Interestingly, in poikilocapnic studies, where $PETCO_2$ was permitted to fluctuate with ventilation, no effect of metaboreflex on CBF was observed. In isocapnic studies, where

$PETCO_2$ was clamped near resting values, however, a CBF response to metaboreflex was detected (Figure 4.6). MCAv is known to respond to both changes in $PETCO_2$ fluctuation and MAP variation. The extent to which these mechanisms compete during metaboreflex stimulation wasn't clear. Taken together, these results suggest that the regulatory capacity of carbon dioxide potentially masks the influence of metaboreflex on CBF. The confounding nature of carbon dioxide, reviewed in chapter 2, appears to be specifically influential, because metaboreflex stimulation increases ventilation, lowering arterial CO_2 concentration. Thus, any changes in CBF due to neural control during metaboreflex stimulation will likely be mitigated by CBF changes due to $PETCO_2$ fluctuation. These findings coincide with the observation of decrease in CVCi in poikilocpanic studies, as increase CVR is likely indicative of cerebral artery vasoconstriction, which is likely the result of a hyperventilation mediated decline in $PETCO_2$.

Figures 4.5 and 4.6 display changes in MCAv during poikilocapnic studies contrasted with isocapnic studies. In the included studies, MAP was assessed alongside MCAv, providing a means for comparison in how end tidal changes in $PETCO_2$ alter MAP and CBF, but also how the CBF:MAP relationship changes with differing $PETCO_2$ levels.

4.5.6 Mean Arterial Pressure

In studies that control for the regulatory capacity of arterial carbon dioxide, the influence of MAP on the cerebrovascular response to exercise became increasingly apparent (Figure 4.7). The exercise induced increase in MAP was preserved during PEMI, and the response was mirrored by a maintained elevation in MCAv during PEMI (Figure 4.7). These results support other accounts of poikilocapnia disguising the cerebrovascular effects of conditions that increase

MAP, such as during the cold pressor test (Tymko et al. 2017). The potential impacts of MAP on the maintenance of elevated CBF during PEMI is varied. Changes in perfusion pressure are known to have direct impacts on CBF (Liu et al. 2013), dependent on changes of cerebrovascular conductance, and therefore resistance. It is possible the changes in hypocapnia to increased CVR, limiting the effect of increased MAP on downstream CBF. A once popular theory of cerebral autoregulation suggested that intracranial cerebral vasculature responded to changes in MAP to ensure a consistent blood flow and pressure to the brain despite large swings in systemic pressure (Lassen 1959). The extent to which cerebral autoregulation influences intracranial artery diameter is presently limited to a small regulatory window 10-15 mmHg of MAP. The lack of diameter assessment in the reviewed sources of evidence limits the analysis of metaboreflex mediated MAP changes on intra and extracranial arterial response.

4.5.7 Mean Arterial Pressure and Arterial Carbon Dioxide

Despite the evidence that the majority of the studies do not support a change in CBF during PEMI (Figure 4.3), the physiological counterbalancing of hypocapnia and hypertension on CBF during EPR needs to be considered. All studies that assessed MAP identified an increase during PEMI (Figure 4.7). Independent regulation of CBF solely through changes in perfusion pressure suggest intracranial artery vasoconstriction during EPR stimulation. Furthermore, hypocapnia induced by EPR stimulation likely causes a vasoconstriction in the intracranial arteries. Increases in CVR, observed in poikilocapnic trials, were not observed during isocapnia. No study to date has attempted to control for both MAP and CO_2 during EPR stimulation. The clamping of CO_2, and manipulation of MAP would provide insight into how these two mechanisms interact. Furthermore, by changing MAP independently of PEMI, other influencing factors on the CBF

EPR, such as sympathoexcitation, NVC, etc. could be observed. Whether or not the CBFv increase is a result of increased flow or vasoconstriction was not assessed by any sources of evidence.

4.5.8 Mechanoreflex

As discussed in detail previously (Chapter 2), the mechanoreflex describes the afferent neural excitation by skeletal-muscular mechanical activation and triggers an increase in cardiac output and BP. Though the effects of metaboreflex on CBF are understudied, the impact of mechanoreflex stimulation on CBF receives even less scrutiny. Early studies by Jorgenson and colleagues (1992) that failed to observe a maintenance of MCAv during PEMI, but did notice an attenuation of MCAv increase during afferent neural blockade. Since PEMI controls for the stimulation of mechanoreflex, they concluded that the whole of the CBF response to EPR stimulation was due to mechanoreflex (Friedman et al. 1992; Jorgensen et al. 1993), a theory that has since been refined by the inclusion of central command as a possible mechanism for CBF elevation (Williamson et al. 2003). Evidence from the research reviewed here, suggests that a role for metaboreflex on CBF exists. While the dynamic exercise preceding PEMI stimulates mechanoreceptors, the PEMI portion isolates the mechano stimulus and central command from influencing the metaboreflex.

Strategies such as passive stretch and muscle pressure are employed in an attempt to isolate the mechanoreflex, but the effectiveness of these strategies is tenuous, since the actual amount of stimulation that occurs at sub-painful levels is unknown in humans. The lack of universality between studies that assess the mechanoreflex makes comparison results between studies

difficult. Of the included sources, one study employed a passive cycling method to stimulate lower limb skeletal muscle mechanoreceptors (Asahara and Matsukawa 2018). By assessing prefrontal hemoglobin oxygenation, using NIRS, they determined that prefrontal cortex blood flow was diminished during mechanoreflex stimulation. They simultaneously assessed extracranial artery flow in the ICA and Common Carotid Artery (CCA), which remained unchanged during mechanoreflex stimulation. Taken together, these results suggest that mechanoreflex does not increase intracranial CBF, but likely redirects the unchanged global flow through microvascular dilation to cortical areas of need. One interpretation of these findings is that EPR stimulation increases the metabolic requirement of localised brain areas without increasing global cerebral metabolism sufficiently to raise global CBF by a NVC mechanism. A redistribution of blood flow supports the theory that the EPR is less reflexive than previously described, given that changes in blood flow through cerebral micro vessels are more likely to be related to cortical metabolism, especially when total CBF remains constant. The redistribution of blood flow to meet metabolic demand is more in line with a NVC-like mechanism, stimulated from afferent neural activation. If there was a large enough change in cortical metabolism, the expected response would be observable in the microvasculature, but also in the intra and extra cranial arteries just as there is in the posterior arteries during a typical NVC visual stimulus (Phillips et al. 2016; Willie, Cowan, et al. 2011; Yamaguchi et al. 2014). Perhaps, especially given that central command is unlikely to be active, the mechanoreflex causes a marginal, but not trivial, increase in cortical metabolism, large enough to change flow through the micro- but not the macro-vasculature akin to CBF redistribution. Other reports, however, have observed increases in intracranial CBFv, such as when a study observed increased MCAv during passive sensorimotor stimulation, which, although not intentionally, likely stimulated the mechanoreflex

(Matteis et al. 2001). The ventilator response to mechanoreflex stimulation appears reduced relative to the metaboreflex stimulation. Despite this, it is possible that the current mechanoreflex studies that do not control for the regulatory capacity of fluctuating arterial carbon dioxide concentration as a result of ventilatory changes are also understating the afferent neural influence on CBF.

The other reviewed study, which used passive elbow flection and extension determined that mechanoreflex likely maintains elevated CBF during exercise. They observed an increase in cerebral perfusion that occurs during the onset of exercise which was attributed to central command influence, since it occurred before mechanoreflex stimulation commenced but persisted during passive limb movement. (Sato, Moriyama, et al. 2009). Of note, MCAv and CCA flow increased before a bout of voluntary exercise commenced during voluntary exercise, but was unchanged during passive exercise. Towards the end of voluntary exercise, though, MCAv and CCA flow levels were similar compared to passive limb movement. Taken together, the two sources of evidence assessed in this review that stimulated the mechanoreflex demonstrated that the increase in HR, MAP, and CBF that occurs at the onset of exercise is likely not related to mechanoreflex stimulation, but that the mechanoreflex may play a part in the maintenance of elevated HR, MAP and CBF during exercise.

4.5.9 Cerebral Blood flow and Central Command

Though not the specific target of this review, most sources of evidence prudently identified the descending neural drive to regulate the systemic exercise response (central command) as a possible confound in observing the CBF response to exercise and the EPR. The mechanisms by which central command could alter CBF were identified as both a NVC mechanism that responds to changes in neural metabolism by increasing regional CBF and the systemic cardiovascular (increased cardiac output, Chapter 2) and ventilatory changes associated with the exercise response. The specific purpose of using a PEMI protocol is to separate the metaboreflex stimulation associated with exercise from the exercise bout, where central command input is pertinent. Despite this, studies assessing the effectiveness of PEMI at controlling for central command stimulation compared a traditional voluntary PEMI protocol with one where exercise was evoked using direct electric stimulation of the targeted muscles, avoiding the descending signal for the motor areas of the cerebrum (Vianna et al. 2009). All included sources demonstrate a higher MAP, HR and CBF during exercise compared to PEMI. The dip in these variables during PEMI likely represent the combined influence of mechanoreflex and central command, which are no longer stimulated during the PEMI portion of the protocol (Figure 4.8). The response to electrically evoked exercise was then compared to voluntary exercise, with any differences being attributed to the effect of central command activation. Vianna and colleagues (2009) studied both evoked and voluntary exercise PEMI protocols while assessing CBF. Their conclusion was that CBFv was unaltered during PEMI by the inclusion of descending neural drive from central command, as there was no CBFv differences between during PEMI following voluntary and evoked exercise sessions. The study did however observe a differential increase in CBFv during voluntary exercise, indicating that during exercise, the cerebrovascular response

was at least in part mediated by central command, but that PEMI adequately controlled for central command input. However, Vianna *et al*., (2009) did not control ventilation (or arterial partial pressure of carbon dioxide), meaning changes in ventilation and MAP, stimulated by either the EPR *or* central command could have confounded the CBF response. Secondly, Vianna and colleagues (2009) assessed only the anterior cerebral artery (ACA), which may provide less perfusion to the motor and premotor cortex (areas active during central command innervation) than the MCA. Lastly, without assessing diameter, ACAv can only provide an indication of blood flow under the assumption that vessel diameter remains constant. There is evidence of intracranial arterial diameter varying in response to a multitude of stimuli. As a result, a possible change in ACA diameter, either as a response to metaboreflex mediated increase in muscle sympathetic nerve activity (MSNA), arterial carbon dioxide (Verbree et al. 2014, 2017), MAP or as a result of NVC triggered by an increase in motor and pre-motor cortex metabolism (central command), was not assessed. As a result of not assessing arterial diameter, and the possible confound of central command on CBF cannot be explicitly identified, since variations in arterial diameter could be the result of central command via NVC. Furthermore, velocity differences that are a result of central command activation could be disguised by another mechanism altering ACA diameter, as CBF and diameter remain related. Despite not providing sufficient assessment for robust CBF inferences, the homogenous outcomes observed between evoked and voluntary exercise trials in the study by Vianna et al. indicate that PEMI is likely an effective tool for isolating the metaboreflex from the confounding impact of central command innervation, as it was designed to do.

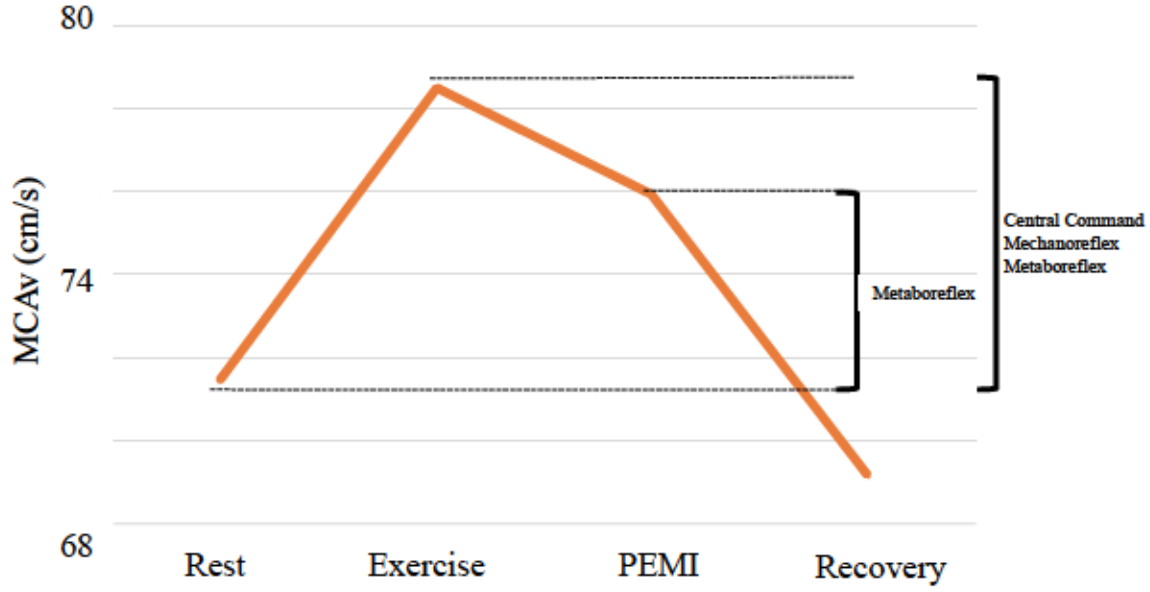

Figure 4. 8. Representative plot of middle cerebral artery velocity (MCAv) response to poikilocapnic Post Exercise Muscle Ischemia (PEMI – 30% MVC, 3 minutes' rhythmic handgrip). The influence of the metaboreflex is preserved via PEMI, but MCAv still declines from peak velocity due to the lack of central command and mechanoreflex stimulation (Neill & Smith, unpublished).

4.5.10 Influence of PEMI methodology on cerebrovascular outcomes

The variety of PEMI protocols (Figure 4.9) makes linear comparison across different sources difficult. Different exercise intensities, durations, and exercises all have the opportunity to elicit different responses during exercise and PEMI.

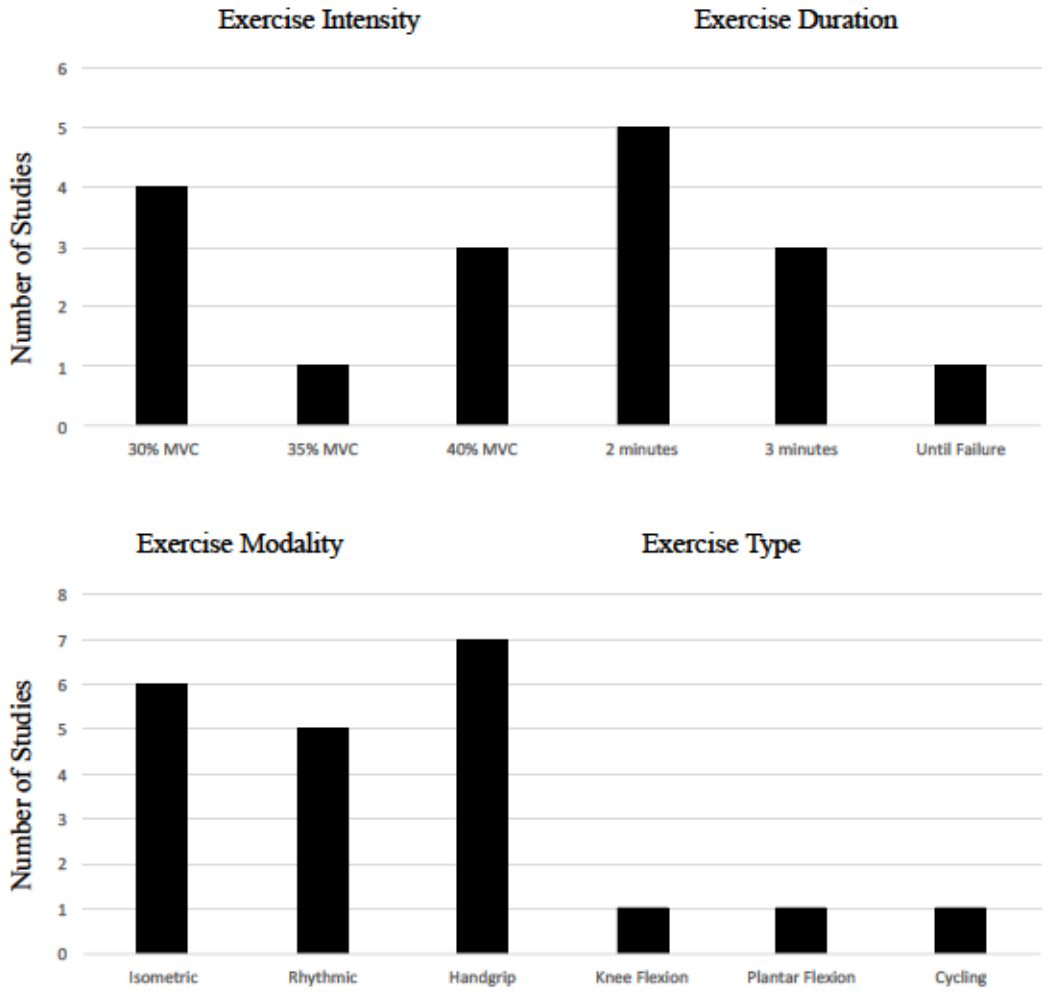

Figure 4. 9. Prevalence of methodological design elements in the Post Exercise Muscle Ischemia (PEMI) studies included in the chapter 4 scoping review. Exercise Intensity indicated in percentage of maximum voluntary contraction (%MVC). Included sources cited in Table 4.1

The same variety of PEMI protocols observed in chapter 3 was mirrored in chapter 4. Five studies used rhythmic exercise, while six employed isometric (static) exercise (Figure 4.9). Rhythmic exercise was contrasted with isometric exercise in a study by Vianna and colleagues, the only study to employ both techniques in this review (Vianna et al. 2009). They performed separate trials using isometric exercise and rhythmic exercise such that the effect of the exercise

modality could be observed. The observed cardiovascular or cerebrovascular responses to PEMI and exercise between the rhythmic and isometric trials were similar, although the exact impact a specific protocol had on systemic and cerebral responses remains illusive. Metabolite concentration, and MSNA was not assessed in any of the studies in this chapter, and thus the extent to which PEMI stimulated the metaboreflex was not directly assessed, though cardiovascular responses seemed to indicate a relatively uniform response. Only one study differentiated between male and female participants (Joshi and Edgell 2019), though the PEMI stimulation appeared to affect each sex uniformly, and none had participants perform hand grip exercise at the same absolute intensities.

4.5.11 Metaboreflex in Health and Disease

Although not the specific target of this review, two sources assessed differing EPR and CBF relationships in those with metabolic syndrome. Metabolic syndrome describes a cluster of conditions that put an individual at risk for heart disease, stroke and diabetes. The cerebral vascular response to PEMI in participants with metabolic syndrome was assessed by two studies included in this scoping review, though both appear to be based on the same source data. The studies by Doneddu and colleagues (2020), and Guicciardi and colleagues (2019) compared cerebrovascular responses from participants with metabolic syndrome and age-matched controls to exercise, PEMI, a mental task, and combined exercise and mental task, and PEMI and mental task. Their results indicated that although both participant groups were able to increase their cerebral oxygenation during PEMI, there was an impedance of this process in participants with metabolic syndrome during a mental task, causing poorer mental performance. This research supports idea that the metaboreflex has cerebral implications, and that changes in metaboreflex

in health and disease have effects on participant quality of life. This research, although preliminary, demonstrates that the interplay between the EPR and CBF can fill the gap between the deficits observed with aging and disease at rest and during exercise and the mechanistic changes in the exercise response, systemically and centrally.

4.6 Limitations

There are a number of strengths and limitations in above review. Firstly, despite including all sources investigating CBF during the EPR in humans, there was not a large amount of source evidence. Many sources were unique in their methodology, and many conclusions were supported by a few sources of evidence. As a result, conclusions regarding the physiology of the EPR as it relates to CBF and sex, CO_2, central command, are still largely speculative. Furthermore, CBF assessment differed widely between studies, making it difficult to compare outcomes. Ultrasound assessments that indicated the velocity of blood cells through an artery could not be compared to studies that employed infrared spectroscopy to identify different oxygenation values, because the measures were too far apart in the cerebrovascular system. Comparisons of CBF assessed in different arteries has the potential for misleading outcomes regarding regional CBF differences, if the CBF response does not demonstrate regional homogeneity.

4.7 Conclusions

Variability in CBF responses in PEMI is likely the result of four major factors: arterial carbon dioxide, MAP, CBF assessment techniques, and PEMI protocol variability, and is potentially influenced by NVC. Hyperventilation was observed to mask changes in intracranial velocity, but produced an increase in CVR, likely due to hyperventilation induced hypocapnic vasoconstriction. Furthermore, the apparent linear relationship between CBF and MAP was observed once the effect of fluctuating $PETCO_2$ was controlled. The CBF response to PEMI was not homogenous between the intra and extracranial arteries, and the intracranial response appeared to be regional. Studies that manipulated the mechanoreflex were unsuccessful at determining a consistent response, especially compared to the metaboreflex. Lastly, variance in PEMI protocol likely did not hamper the interpretation of the included sources of evidence, because larger trends in the response were the primary focus, and the variance between PEMI stimulations is unlikely to have provided a completely different outcome. Despite this, some studies may have inadvertently decreased the statistical power of their studies with the use of a sub optimal PEMI protocol. The plot of the current EPR and CBF research has uncovered holes and uncertainties regarding the regional CBF response, the difference between extra and intracranial flow, and dose-response to metaboreflex stimulation. In the following chapter, future research aiming to fill these gaps will be directed with suggestions to maximise the effectiveness at addressing the still-plentiful unknowns regarding the CBF response to the EPR.

Chapter 5: Methodological Suggestions, Conclusion

Having provided analysis of the influence of methodology on the PEMI response, and interpreted the influence of the EPR on CBF, this final chapter represents the translation of the knowledge developed in chapters 3 and 4 into methodological suggestions and recommendations for future research. Based on the above chapters, the optimal CBF assessment and EPR stimulation methods will be discussed. Study designs that could identify the gaps exposed in chapter 4 will also be outlined. Lastly, a concluding summary of the thesis' intent, results and projections will be summarised in a concluding section.

5.1 Methodological Suggestions

5.1.1 Cerebral Blood Flow Assessment

Interpretation of the sources investigating the CBF response to the EPR is complicated by the differing approaches to technical and regional assessment of CBF, and perhaps is desensitised my varying PEMI protocols. Assessment of CBF varied widely between sources of evidence, which may explain some of the discrepant findings observed. The following section will compare the different assessment approaches, varying in terms of assessment technique, targeted arteries, velocity and diameter assessment and distribution in order to provide an evidence-based recommendation for CBF assessment in future EPR studies.

5.1.2 Near infrared spectroscopy.

Technical CBF assessment varied between studies. Some studies used Near Infrared Spectroscopy (NIRS) to quantify the regional cerebral blood flow CBF and cerebral oxygenation

differences during exercise and PEMI. Many studies instead evaluated CBF by assessing the blood flow through a targeted artery. NIRS assesses changes in oxyhemoglobin in upstream cerebral regions. The absorption/reflection of near infrared light differs based on the oxygenation of the hemoglobin the light is contacting. By investigating the absorption of the near infrared light, the presence and quantity of red blood cells, as well as the oxygenation of hemoglobin can be assessed, and used to index blood flow. By evaluating the change in oxygenation of specific cortical areas using NIRS, the change in metabolism of the targeted areas can be evaluated (Ferrari and Quaresima 2012). The benefit of understanding the differences in oxygenation in response to EPR stimulation is that questions regarding the influence of the EPR on cortical centers can be evaluated. Despite this, inferences on direct arterial influence cannot be assessed, and therefore it is difficult to reconcile between oxyhemoglobin redistribution in the cortex, and global CBF changes that are observed in the cranial arteries. NIRS provides insight into cortical changes during EPR stimulation, but in terms of studying blood flow regulation, is less perceptive.

5.1.3 Insonation of Cranial Arteries.

The other standard approach to assessing CBF demonstrated in the literature review, was to assess CBF in cranial arteries. Ultrasound insonation of major cranial arteries was used to identify the blood flow velocity, and in some cases the diameter of the targeted vessel. Intracranial vessels, such as the middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) provide blood to specific areas of the brain, anterior, middle, posterior. As a result, insonating these arteries allowed for inferences on the homogeneity of CBF changes to the larger areas of the brain during metaboreflex stimulation. Extracranial

arteries, such as the internal carotid artery (ICA), common carotid artery (CCA) and vertebral artery (VA) deliver blood flow to a plethora of intracranial arteries, via the circle of Willis. Changes in blood flow in these arteries, while they do indicate changes in intracranial flow, provide a less precise understanding of the regional differences in CBF response to metaboreflex activation. The changes in CBF due to afferent neuron stimulation is likely regional, since afferent neuronal stimulation during exercise stimulates motor and pre-motor cortices specifically, as well as brain stem areas. Direct assessment of CBF requires the assessment of both blood flow velocity, and arterial diameter. Using velocity as an index of flow, although common, is not accurate due to the known capacity for arterial vasoconstriction and vasodilation (Giller 2003). Though diameter assessment is possible in both intracranial and extracranial arteries, it is methodologically simpler and more accurate to assess diameter in extracranial arteries, which provides and assessment of blood flow. Higher accessibility due to a lack of cranium makes duplex ultrasound insonation of the extracranial arteries less challenging. As a result, the use of transcranial color coded duplex ultrasonography (TCCD) is more popularly used to assess extracranial arteries.

5.1.4 Transcranial color coded duplex ultrasonography

TCCD, a non-invasive, portable, imaging technique allows for the assessment of both artery diameter and blood flow velocity at multiple intervals across a number of cardiac cycles. The TCCD technique employs a B-mode ultrasound imaging and Pulse Wave Doppler sonography congruously. An arterial blood velocity trace is acquired with high temporal resolution akin to typical TCD ultrasonography. The novel application of TCCD is its spatial resolution mode in which the diameter of the target artery can be imaged with similar temporal frequency as

velocity (i.e, throughout multiple cardiac cycles). The imaging and quantification of intracranial artery diameter, also allows for a more standardized approach to arterial velocity quantification by enabling more consistent and valid artery land marking. TCCD has been used to assess MCA diameter and velocity by insonating the temporal window, an area of lower cranial density in the skull, permitting B-mode imaging, with varying levels of specificity (Wilson et al. 2011). The assessment of other intracranial arteries using TCCD has yet to be performed, or validated. The technique of using TCCD to assess intracranial arteries is currently not well documented due to high levels of difficulty using the technique; to date, TCCD sonography requires continuous manual use of the ultrasound wand. An unpublished study from our laboratory performed the first known assessment of TCCD specificity and reliability in assessing MCA diameter and velocity. That study demonstrated an Interclass correlation (ICC) between sonographers of 0.593 ($p=0.001$) for assessment of velocity and 0.98 ($p<0.001$) for diameter assessment congruent with a roughly 5% error in large samples. No studies in the current review used TCCD to assess intracranial artery CBF, though it was employed to assess extracranial CBF. Moving forward, an assessment of intracranial artery diameter in response to EPR will be crucial for evaluating the influence of intracranial arterial diameter on the cerebrovascular response to EPR stimulation.

5.1.5 Transcranial Doppler Ultrasound

Transcranial Doppler Ultrasound, on the other hand, was used heavily to assess intracranial arteries by the sources of evidence present in the current review. TCD is unable to assess arterial diameter, only the velocity of blood cells moving through the targeted artery. TCD assessment is methodologically simpler because it does not require the continuous hand-held insonation of the artery, and therefore can take place during a wider array of experiments. The benefit of TCD

assessment is that it assesses arterial blood velocity with high temporal resolution providing data on the dynamic responses that lower temporal resolution assessments, such as MRI, miss. The TCD assessment is also less invasive, and can be performed while a participant engages in dynamic movement while maintaining an accurate signal, something other techniques cannot. Despite being useful in the current reviews, having to indirectly assess intracranial diameter severely limits the inferences of the current cerebrovascular research. To address this, standardizing the use of TCCD to assess MCAv and MCA diameter will solidify the cerebrovascular assessment of the following study designs.

5.1.6 Study Designs

Future research examining the CBF EPR risks repeating some of the studies designs employed by sources of evidence in chapters 3 and 4. To target the literature gaps identified in chapter 4, specific studies designs, not yet present in the CBF EPR literature will be required. The optimal PEMI protocol, and study designs to advance our understanding off the CBF EPR are summarised below.

5.1.7 Post Exercise Muscle Ischemia Protocol

It remains unclear the extent to which PEMI protocol variances directly confuses cerebrovascular results (Chapter 4). What was observed is that a 3-minute exercise protocol caused a less variable MAP response during exercise *and* PEMI compared to other protocols, irrespective of exercise type, muscle group and intensity. Although the following methodological suggest should be explored perhaps by a meta-analysis or experimental trial, the following protocol is being

suggested as a possible standard. A 3-minute exercise protocol during consisting of rhythmic hand grip at 30% of MVC should be used, such that smaller variances between conditions are amplified when they aren't lost in the noise of different exercise protocols. Future research on the impact of exercise type, muscle group, and intensity on cardiovascular and cerebrovascular responses will help clarify a future direction for more concise, comparable PEMI studies.

Future studies should intend to assess dynamic changes in CBF via the insonation of intracranial arteries using a technique that evaluates velocity *and* diameter during periods of EPR stimulation, such as PEMI. To this end, it appears that an exercise protocol of 3 minutes provides minimal variability in the exercise and PEMI response, and may stimulate the metaboreflex more reliably.

5.1.8 Manipulated Variables

The sources of evidence reviewed in chapter 4 revealed a few common controlled variables. CO_2, sex, and central command innervation were all controlled for in at least one source. Specific manipulation of variables such as CO_2 and BP has yet to be performed, despite these variables appearing to be the largest cerebrovascular influencers. Research has already compared the poikilocapnic CBF EPR contrasted with an isocapnic trial, but no study to date has used a variety of clamped CO_2 levels to investigate the CBF EPR during Hypercapnia, or varying levels of hypocapnia. Furthermore, the studies in chapter 4 clamped CO_2 levels just above baseline, likely due to mechanistic constraints, including the influence of different carbon dioxide levels on cerebral stimulation of respiratory centers. Any hypercapnic change from baseline appears to

influence arterial compliance, distorting the true CBF response at rest CO_2 levels (Moir et al. 2021). With this in mind, the first study design suggested for future studies includes the use of a dynamic end-tidal forcing device to maintain multiple levels of CO_2 during a PEMI protocol, including a true baseline resting level. Different trials of isocapnic normocapnia, hypercapnia and hypocapnia during PEMI while assessing CBF could address the influence of CO_2 more clearly. Furthermore, using an assessment technique that assesses intracranial arterial diameter, such as TCCD insonation of the MCA, would provide valuable indication regarding the vasoaction associated with various levels of CO_2 during a PEMI protocol.

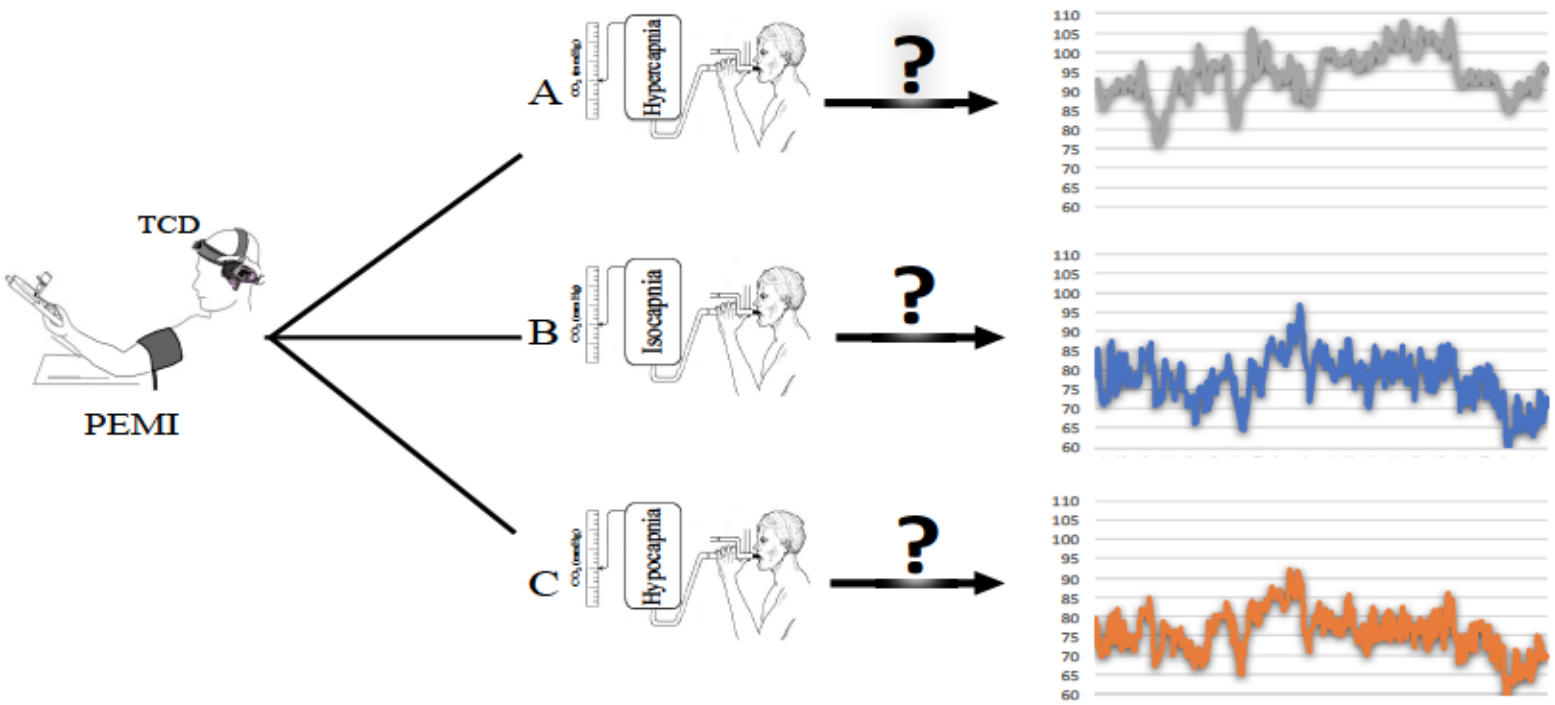

Figure 5. 1. Schemata of study designs to manipulate arterial carbon dioxide while assessing cerebrovascular response to Post Exercise Muscle Ischemia (PEMI). The Hypercapnic (A, +10mmHg above resting) Isocapnic (B, 1 mmHg above resting) and Hypocapnic (C, -10 mmHg below resting) experiments manipulate arterial carbon dioxide levels using end tidal gas forcing.

Secondly, the next most influential factor on CBF during EPR stimulation is BP. Chapter 4 identified an association between MAP and CBF when the influence of CO_2 was controlled. With this is mind, future research should investigate the relationship between MAP and the CBF EPR by manipulating BP. By specifically inducing different MAP levels during a PEMI protocol, while controlling for carbon dioxide levels, the synergistic influence of PEMI can be observed. A study design that permits the raising of MAP using a non-EPR stimulating mechanism, such as the Cold Pressor Test (CPT) contrasted with a PEMI protocol, both while CBF is assessed could indicate the extent to which the PEMI CBF response is mediated by sympathoexcitaiton. Furthermore, an investigation using a pharmacological alpha receptor blockade could uncover how the CBF response to MAP change differs as a result of PEMI stimulation independent of SNA. Using a pharmacological block of alpha receptors which inhibit the sympathoexcitatory increase in MAP, and have previously been employed in CBF research (van Mil et al. 2018). If the CBF EPR is the function of CO_2 and MAP, then no change in CBF would be observed. If CBF does change, metabolic and NVC mechanisms could be investigated as the cause. Since an alpha blockade could perhaps impact cerebral arteries, which are under a currently debated level of sympathetic control (Seifert and Secher 2011), a complementary study using a lower body negative pressure apparatus could mechanically lower MAP below baseline levels during a PEMI protocol, which could provide insight into the importance of MAP for the CBF EPR. The differences between a lower body negative pressure trial and an alpha receptor block trial has the potential to address the sympathetic control of the cerebral arteries, as well, by assessing the cerebrovascular response under periods of high and low sympathoexcitation.

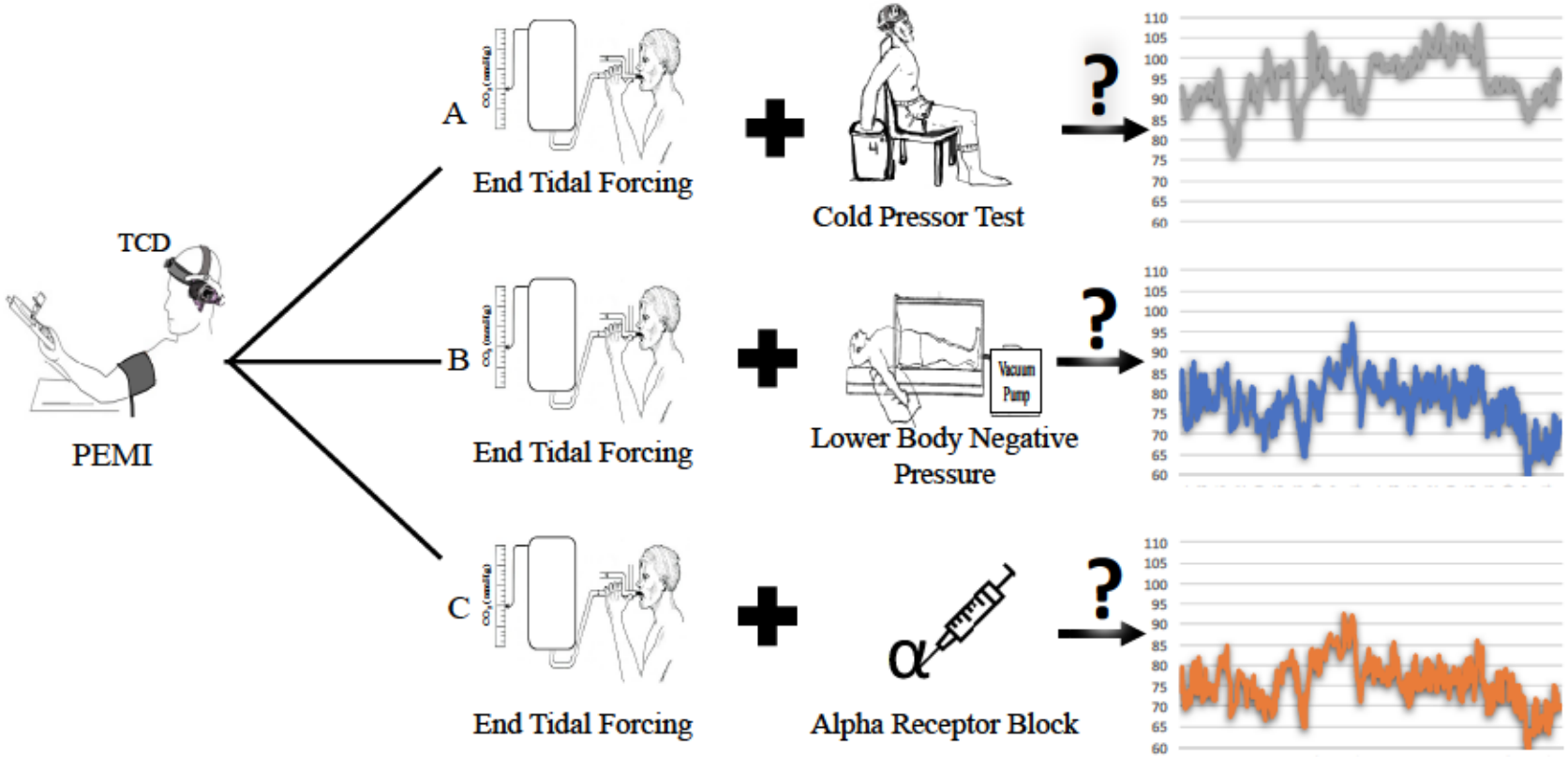

Figure 5. 2. Schemata of study designs to manipulate blood pressure while assessing cerebrovascular response to Post Exercise Muscle Ischemia (PEMI). Isocapnic Sympathetic Hypertension (A), Isocapnic hypotension (B) Isocapnic Sympathetic Blockade (C) studies manipulate blood pressure using neurogenic and mechanical control to elicit the cerebrovascular response to varying levels of blood pressure and sympathetic control of the cerebral arteries.

The last, most complex study design that could improve our understanding of the CBF EPR, is the combination of the above ideas. Manipulating MAP while controlling CO_2 simultaneously could uncover the influence of the other purported influences, identified in Chapter 2 and Chapter 4. Isocapnic PEMI trials using different conditions to modulate MAP, would the most prominent influencing variable identified in this thesis, while determining the influence of the other. Doing this, while assessing intracranial flow and diameter, would provide insight into the possibility of SNA mediated changes in vasoaction and NVC influences on CBF during EPR stimulation.

The above study designs target the gaps identified in a scoping review of the literature. Studies that vary the influence of MAP and CO_2, or simply control it, will advance our understanding of these complex mechanisms, including the way in which they alter all the other mechanisms of CBF control during exercise.

5.1.9 Special Populations

The above study designs are composed with the intent of improving our understanding of the CBF EPR in normal populations. Once the proposed research above addresses the current gaps in the CBF EPR research, application of mechanistic cerebrovascular understandings can be applied to special populations with differing EPRs. Research has identified that changes in afferent feedback during EPR stimulation differentially affect populations such as those suffering from metabolic syndrome (Limberg et al. 2016) and Down Syndrome (Fernhall and Otterstetter 2003). Investigation into the CBF profiles of these special populations could indicate the cerebral

implications of the EPR and also improve exercise capacity in these populations, many of which experience altered perceived exertion during exercise. The relationship between perceived effort, EPR impairment and CBF is unstudied but seems linked. Other populations, such as participants with Chronic Obstructive Pulmonary Disease (COPD) suffer from increased pulmonary afferent influence (van Gestel and Steier 2010), but the connection between pulmonary afferent feedback, and muscle afferent input has not been evaluated, especially in terms of CBF. As a result, there is an opportunity to learn about the mechanistic control of CBF during exercise, and improve the exercise capacity of those living with specific diseases by studying the EPR and CBF in the relevant populations. Applying the knowledge gained from the targeted mechanistic studies outlined in Figures 5.1 and 5.2 could then be translated to the applied settings of working with those that have EPR impairments.

The region of EPR CBF study that appears to receive even less attention is athletic performance. Afferent neural feedback appears to improve performance, in two ways. Firstly, the EPR facilitating the cardiovascular system being able to meet metabolic demands. Secondly, afferent neuronal feedback provides a cognisable feedback that has been demonstrated to improve pacing in cycling time trials (Blain et al. 2016). Despite this, afferent blockade improves performance when cardiac output is artificially maintained (Hureau et al. 2019). It is currently understood that afferent stimulation leads to central fatigue (Sidhu et al. 2018). Despite this, there is no current research that relates the cerebral effects of changes in afferent feedback to the differences in motor unit output during intense exercise, and the differing levels of failure from exercise between individuals. The link between afferent feedback from the EPR and performance could

also clarify the reflexivity of the EPR, and perhaps develop a model of cognitive input independent from central command.

5.2 Conclusion

The purpose of this thesis was to examine the literature studying the effects of the exercise pressor reflex on CBF, and derive conclusions about CBF control and future research pathways. Research assessing CBF during metaboreflex and mechanoreflex stimulation was included and summarised. Studies using a PEMI protocol to stimulate the mechanoreflex while assessing CBF were specifically compared, including the analysis of different variable manipulations. Studies using a PEMI protocol in contexts other than CBF research were evaluated to investigate the influence of protocol variance on outcomes. Then, CBF assessment techniques were outlined, and study designs described, such that future research can optimally target the present gaps in knowledge.

The analysis of sources investigating CBF and EPR revealed a few characteristics. Firstly, the effect of fluctuating arterial carbon dioxide, as a result of both EPR stimulation and likely central command stimulation, appears to mask the changes in intracranial arterial velocity during metaboreflex stimulation, in both men and women. As a consequence, most studies were unable to observe the effects of EPR stimulation on CBF independent of fluctuating carbon dioxide. Also, since studies did not assess the intracranial arterial diameter, the changes in diameter, which are associated with carbon dioxide could not be assessed, and CBF could not be properly quantified. Secondly, the influence of the BP on CBF changes during EPR stimulation was

observed. In isocapnic studies, CBF and MAP seemed to coincide, indicating that perhaps changes in BP are a primary driver of the CBF response, when carbon dioxide does not fluctuate. A lack of diameter assessment hampered this finding, also. Another interpretation is that the mechanisms that drive the change in BP, such as sympathetic nerve activity simultaneously alter CBF and MAP. No included sources of evidence distinguished between these alternatives.

Chapter 4 also revealed a discrepancy between micro and macrovascular function. In large vessels during poikilocapnic PEMI increased CVR, which is suggestive of an intracranial vasoconstriction. This was interpreted as a protective mechanism to guard the brain from a dangerous spike in intracranial pressure during exercise. Quite the opposite, one study assessed regional microvascular oxygen hemodynamics employing NIRS. They showed an increase in hemoglobin volume during PEMI to local regions within the brain. These results were taken together to suggest the novel theory that the cerebral protective vasoconstriction that occurs during a PEMI-mediated increase in MAP is lysed in the micro vessels that supply areas of high cortical metabolism. This is a theory that mirrors the global increased vascular resistance, and isolated decreased vascular resistance observed in peripheral vessels in response to EPR stimulation.

An ambition of the thesis was to provide a direction for future research to address the gaps identified by this thesis. Firstly, research using graduated arterial CO_2 clamps that investigates whether the effects of the EPR on CBF are masked by carbon dioxide or directly influenced by it. Secondly, the manipulation of MAP during EPR stimulation using a variety of techniques.

Technical suggestions to enhance approaches that aim to investigate CBF and EPR include the use of novel assessment techniques such as TCCD to investigate intracranial arterial velocity *and* diameter during EPR stimulation. A direct measure of arterial diameter is required to assess the theorised vasoaction in response to changing MAP, CO_2 and SNA, and address the observed changes in CVR during EPR stimulation.

A variety of PEMI studies were assessed in terms of their methodology during chapter 3 of this thesis, with the goal of differentiating between PEMI protocols. We noticed that protocols varied widely between studies, and that a 3-minute exercise protocol produced a smaller MAP response compare to 2 and 4-minute exercise protocols, punctuated by lower variability between responses. To deepen the understanding of the CBF EPR, decreasing variability in the stimulus is especially important, because variability in the stimulus can cause small variabilities in the response, and the assessments of CBF often lack the precision necessary to differentiate between small changes in cerebral profusion. Though the current research seeks mainly to identify directional changes from resting and exercising levels, precise assessment of CBF to a precise stimulus will improve the elegance of future interpretations. Improvements in the rigor of PEMI protocols and CBF assessments will increase the sensitivity to CBF changes, and ease the difficulty of conducting future research.

For the above proposed future research, the following design is suggested. The TCCD assessment of MCA velocity and diameter during 3 minutes of isometric handgrip exercise at 30% MVC followed by PEMI with various CO_2 clamps of true baseline, hypercapnia, and hypocapnia. A further study would include MAP modulation using sympathetic hypertension

(cold pressor test), hypotension (lower body negative pressure) and sympathetic blockade (pharmacological MAP clamp). Lastly, performing these methodologies in participants with disease such as Down Syndrome, COPD, or metabolic syndrome along with age matched controls would provide the upmost insight to continue building our understanding of EPR reflexivity, and EPR influence on CBF.

Better understanding of the CBF changes during EPR stimulation could provide clarification to ideas such as the selfish brain hypothesis; that the brain can divert blood flow away from the periphery and towards the brain in conditions where metabolic demand is increased everywhere, and blood flow is at a premium. Furthermore, changes in CBF during stimulation of the EPR could provide answers to the questions revolving around EPR reflexivity. Elevations in CBF, especially if they are stimulated to feed metabolic demand in cortical areas during PEMI, would provide evidence that afferent neural feedback in fact does influence the cerebrum, independent of descending drive from central command, perhaps casting doubt on the reflexivity of the EPR. Lastly, for special populations, where the ability to exercise is often hampered by a disordered EPR, understanding the cerebral influence of the EPR is crucial to treating the impairment.

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APPENDIX A

Author	Year	Title	Citations	Experimental	Human	CBF	Healthy control	PEMI	HR	MAP	AXIS	Accept or Reject
Amano	2018	β-Adrenergic receptor blockade does not modify non-thermal sweating during static exercise and following muscle ischemia in habitually trained individuals	2	Y	Y	N	Y	Y	Y	Y	Y	Accept
Asahara	2018	Decreased prefrontal oxygenation elicited by stimulation of limb mechanosensitive afferents during cycling exercise	4	Y	Y	Y	Y	N	Y	Y	Y	Accept
Badrov	2016	Central vs. peripheral determinants of sympathetic neural recruitment: insights from static handgrip exercise and postexercise circulatory occlusion	17	Y	Y	N	Y	Y	Y	Y	Y	Accept
Bell and Whi	2005	Cardiovascular responses to external compression of human calf muscle vary during graded metaboreflex stimulation: Cardiovascular responses to muscle compression	24	Y	Y	N	Y	Y	Y	Y	Y	Accept
Braz	2014	Influence of muscle metaboreceptor stimulation on middle cerebral artery blood velocity in humans	8	Y	Y	Y	Y	Y	Y	Y	Y	Accept
Bruce	2016	Ventilatory responses to muscle metaboreflex activation in chronic obstructive pulmonary disease: Ventilation and muscle metaboreflex in COPD	12	Y	Y	N	Y	Y	Y	Y	Y	Accept
Carrington	2002	Spontaneous baroreflex sensitivity in young and older people during voluntary and electrically evoked isometric exercise	13	Y	Y	N	Y	Y	Y	Y	Y	Accept
Carrington	2004	Muscle afferent inputs to cardiovascular control during isometric exercise vary with muscle group in patients with chronic heart failure	11	Y	Y	N	Y	Y	Y	Y	Y	Accept
Carrington a	2001	Exercise-induced muscle chemoreflex modulation of spontaneous baroreflex sensitivity in man	13	Y	Y	N	Y	Y	Y	Y	Y	Accept
Cristafulli	2011	Role of heart rate and stroke volume during muscle metaboreflex-induced cardiac output increase: differences between activation during and after exercise	48	Y	Y	N	Y	Y	Y	Y	Y	Accept
Donoddu	2020	Effect of Combined Mental Task and Metaboreflex Activation on Hemodynamics and Cerebral Oxygenation in Patients With Metabolic Syndrome	1	Y	Y	Y	N	Y	Y	Y	Y	Accept
Figueroa	2009	Cardiovagal baroreflex and aortic hemodynamic responses to isometric exercise and post-exercise muscle ischemia in resistance trained men	22	Y	Y	N	Y	Y	Y	Y	Y	Accept
Figueroa	2016	Influence of low and normal appendicular lean mass on central blood pressure and wave reflection responses to muscle metaboreflex activation in postmenopausal women	2	Y	Y	N	Y	Y	Y	Y	Y	Accept
Figueroa	2015	Impact of age on aortic wave reflection responses to metaboreflex activation and its relationship with leg lean mass in post-menopausal women	5	Y	Y	N	Y	Y	Y	Y	Y	Accept
Fisher and W	1999	Training-induced adaptations in the central command and peripheral reflex components of the pressor response to isometric exercise of the human triceps surae	65	Y	Y	N	Y	Y	Y	Y	Y	Accept
Florian	2016	Caloric restriction diminishes the pressor response to static exercise	3	Y	Y	N	Y	Y	Y	Y	Y	Accept
Gama	2020	Blood Pressure Response to Muscle Metabore ex Activation is Impaired in Men Living with HIV	0	Y	Y	N	Y	Y	Y	Y	Y	Accept
Guicciardi	2019	Effects of Metabolic Syndrome on Cognitive Performance of Adults During Exercise	13	Y	Y	Y	N	Y	Y	Y	Y	Accept
Incognito	2017	Ischemic preconditioning does not alter muscle sympathetic responses to static handgrip and metaboreflex activation in young healthy men	6	Y	Y	N	Y	Y	Y	Y	Y	Accept
Joshi	2019	Sex differences in the ventilatory and cardiovascular response to supine and tilted metaboreflex activation	4	Y	Y	Y	Y	Y	Y	Y	Y	Accept
Karlsson	2009	Central command and metaboreflex cardiovascular responses to sustained handgrip during microgravity	4	Y	Y	N	Y	Y	Y	Y	Y	Accept
Kiviniemi	2010	Frequency of slow oscillations in arterial pressure and R–R intervals during muscle metaboreflex activation	7	Y	Y	N	Y	Y	Y	Y	Y	Accept
Matteis	2001	Changes in cerebral blood flow induced by passive and active elbow and hand movements	38	Y	Y	Y	Y	N	Y	Y	Y	Accept
Millia	2015	Effect of aging on hemodynamic response to metabore ex activation	21	Y	Y	N	Y	Y	Y	Y	Y	Accept
Mulliri	2020	A brief bout of exercise in hypoxia reduces ventricular lling rate and stroke volume response during muscle metabore ex activation	0	Y	Y	N	Y	Y	Y	Y	Y	Accept
Mulliri	2019	Effects of exercise in normobaric hypoxia on hemodynamics during muscle metabore ex activation in normoxia	7	Y	Y	N	Y	Y	Y	Y	Y	Accept
Ogoh	2019	The e ect of muscle metabore ex on the distribution of blood ow in cerebral arteries during isometric exercise	2	Y	Y	N	Y	Y	Y	Y	Y	Accept
Ogoh	2019	The effect of muscle metaboreflex on the distribution of blood flow in cerebral arteries during isometric exercise	2	Y	Y	Y	Y	Y	Y	Y	Y	Accept
Prodel	2016	Muscle metaboreflex and cerebral blood flow regulation in humans: implications for exercise with blood flow restriction	18	Y	Y	Y	Y	Y	Y	Y	Y	Accept
Sato	2009	Influence of central command on cerebral blood flow at the onset of exercise in women	26	Y	Y	Y	Y	N	Y	Y	Y	Accept
Vianna	2009	Influence of central command and muscle afferent activation on anterior cerebral artery blood velocity responses to calf exercise in humans	26	Y	Y	Y	Y	Y	Y	Y	Y	Accept
Williamson	2003	Evidence for central command activation of the human insular cortex during exercise	166	Y	Y	Y	Y	Y	Y	Y	Y	Accept
Wong	2020	Attenuated aortic blood pressure responses to metaboreflex activation in T older adults with dynapenia	0	Y	Y	N	Y	Y	Y	Y	Y	Accept
Yamguchi	2014	Cerebral blood flow and neurovascular coupling during static exercise	16	Y	Y	Y	Y	Y	Y	Y	Y	Accept