Hemodynamic Changes of the Prefrontal Cortex during Functional Activation in Essential Hypertension Measured by Near Infrared Spectroscopy

by

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Abstract

Chronic hypertension induces microvascular changes in the prefrontal cortex (PFC) which could influence oxygenation status. However, hypertension-related changes in oxygenation in the PFC and cognition, especially during functional stresses, remain poorly investigated. This project consisted of three separate studies, evaluating and comparing normotensive and stage 1 hypertensive males (19 – 56 yrs.) for: (1) the reliability of the hemodynamic responses, namely, oxyhemoglobin (O_2Hb), deoxyhemoglobin (HHb), total hemoglobin (tHb) and hemoglobin difference (HbDiff) at the PFC during postural change and carbon dioxide (CO_2) rebreathing, (2) cognitive performance (digit span and auditory consonant trigrams - CCC) at rest, and (3) cognitive performance (modified Stroop task) at rest and during cycling at 50 Watts and up to 75%HR_{max}. Functional near infrared spectroscopy (fNIRS) was used to measure the bilateral PFC hemodynamic responses in real-time during these interventions. Delta values (peak minus baseline or peak minus control) were calculated for each hemodynamic variable and subjected to appropriate analysis to test the study hypotheses.

Moderate to high reliability coefficients were observed for all hemodynamic and CO_2 reactivity responses with intraclass correlation coefficients (ICCs) for O_2Hb and tHb ranging between 0.67 and 0.901 (normotensive, N=25), and 0.61 and 0.823 (hypertensive, N=15). No significant difference was noted in CO_2 reactivity with postural change between the groups after matching for age level. Significant impairment in digit span and CCC performance was observed in the hypertensives (P=0.027) after age matching 15 participants for each group. Both groups demonstrated similar trends in the acute hemodynamic responses during the digit span and CCC tests. However the delta values were not significantly different between the two groups.

Significant correlations were observed between digit span performance and delta values of O_2Hb as well as tHb, only in the hypertensive group in both the right and left PFC. During the cycling tests, no significant differences were observed in modified Stroop test performance on any of the hemodynamic responses, except tHb, which was higher in the normotensive group. Significant positive correlations were observed for the hypertensives in Stroop performance scores and O_2Hb and HbDiff changes at rest only. The conflicting findings in the hypertensive group could be due to the wide age range of participants and the period of hypertension which could influence microvascularity at the PFC. The evidence suggests a less than straightforward relationship between cognition and performance in hypertension and provides new perspectives that can be used in structuring rehabilitation programs for this clinical population.

Preface

This dissertation is an original work by Hercules Grant. The research project, “Hemodynamic Changes of the Prefrontal Cortex during Functional Activation in Essential Hypertension Measured by Near Infrared Spectroscopy”, of which this dissertation is a part, received ethics approval from the University of Alberta Health Research Ethics Board – Health Panel on January 23, 2012.

Project title: Hemodynamic Changes of the Prefrontal Cortex during Functional Activation in Essential Hypertension Measured by Near Infrared Spectroscopy

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Dedication

I dedicate this project to my maternal grandfather, Hercules Carty, who as an immigrant to New York in the early 1900's dedicated his life to my mother's education back in the Caribbean island of Antigua. His act of commitment has fostered a deep respect for learning in my family and his foresight remains instrumental in my own enlightenment.

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Chapter 1

The focus of this project was: (1) to evaluate the reproducibility of the acute hemodynamic responses of the prefrontal cortex (PFC) during postural change in normotensive and stage 1 hypertensive males measured by functional near infra-red spectroscopy (fNIRS), and (2) to examine the relationship between PFC hemodynamic changes in normotensive and stage 1 hypertensive males during cognition and exercise. Chronic hypertension is known to induce end organ damage (Grossman & Messerli, 1992) which can adversely affect PFC oxygenation status. Research has demonstrated oxygenation status of the PFC is associated with alterations in cognition in healthy men and women (Fallgatter & Strik, 1998; Hoshi & Tamura, 1993; Schreppel et al., 2008). However, such a relationship has not been demonstrated in hypertension, and therefore needs to be tested. Establishing such a relationship would increase the scope of cognitive rehabilitation strategies used by clinicians in the treatment of hypertension.

Rationale

Globally, illness and death due to hypertension related diseases result in an annual loss of 92 million disability-adjusted life years (one disability-adjusted life year is equivalent to one lost year of healthy life) (Kearney et al., 2005). Further, 70% of individuals with their first cerebrovascular accident (stroke) have had antecedent hypertension (Lawes, Hoorn, & Rodgers, 2008). In Canada, 23% of the adult population is hypertensive with young males least likely to be aware of their hypertension status (Robitaille et al., 2012; Campbell, McAlister, & Quom, 2012).

Pointedly, it is becoming evident that even in what is considered a normotensive blood pressure range (<140/90 mmHg), elevation of blood pressure can adversely affect health (Chobanian, et al., 2003; Maillard et al., 2012). Over five decades of research has clearly established that high blood pressure contributes to all major cardiovascular diseases. These include strokes, renal disease, heart ailments, peripheral artery disease, and more recently recognized, premature cognitive impairment focussing on PFC activities (Elias, Goodell & Dore, 2012; Kannel, 2000; Laragh & Brenner, 1995).

The PFC is integral to executive functioning such as planning and generally attending intelligently to daily life (Rabbitt, 1998; Miller & Cohen, 2001). Oxygenation levels in hypertension under different stressors are unknown, and indices of cerebrovascular reserve of the hypertensive remain unclear. Hence decisions about the disease with regard to functional rehabilitation and treatment in general, practical reflections of cerebrovascular reserve are poorly understood.

Essential hypertension, one of two types of hypertension (Laragh & Brenner, 1995), is idiopathic and defined clinically as repeated readings on separate occasions in excess of 139/89 mm Hg. This applies to individuals over the age of 18 years who are not on anti-hypertensive medication, and are not suffering from diabetes, kidney disease or otherwise acutely ill (Chobanian et al., 2003). Hypertension-allied cognitive dysfunction is consistent with the pattern of end organ damage as a sequel to this disease recognized in other organ systems (Laragh & Brenner, 1995; Raz, Rodrigue, & Acker, 2003; Arntzen, Schirmer, Wilsgarrd, & Mathiesen, 2010). Arterial stiffness and endothelial dysfunction suggest alteration in cerebral

hemodynamics resulting in reduced cerebral oxygenation. This view is being increasingly offered as an explanation for impaired cognitive function i.e. hypertension-related cognitive impairment and all cause dementia (Launer et al., 2010; Liu et al., 2014). The PFC, with its connection to executive function, remains central to the discussion on cognition and hypertension (Raz et al., 2003; Baddeley, 2003). Damage to the PFC significantly affects functional performance. This is the basic alliance which drives a hypertension-cognitive dysfunction–disability triad. Altered cerebrovascular reactivity and hypoperfusion within the PFC are being proposed as an underlying factor to disease-related cognitive changes (Hajjar, Zhao, Alsop & Novak, 2010; Liu et al., 2014).

Cerebrovascular reactivity, defined as alteration in cerebral blood flow to a defined stimulus (Madden, 1993), is said to be reduced in certain cardiovascular diseases including congestive heart failure and hypertension (Ainslie & Duffin, 2009; Xie et al., 2005; Hajjar et al., 2010). The decreased reactivity may be related to the altered cerebral perfusion that characterizes the hemodynamic dysfunction associated with end organ damage (Strandgaard & Paulson, 1995; Grossman & Messerli, 1992).

Hypertension research has made great strides in the past half century. First the negative effects of higher blood pressure on cardiovascular function were established in the 1930's (Kotchen, 2011). Sixty years later strong and consistent evidence implicating hypertension in various forms of cognitive dysfunction began to emerge with the Framingham Heart Study (Elias et al., 1993). In the Systolic Hypertension in the Elderly Program (SHEP), (SHEP Cooperative Research Group, 1991) active treatment reduced the incidence of cardiovascular events, but did not alter

cognitive decline and disability that was clearly established as a feature of the disease. The Perindopril Protection against Recurrent Stroke (PROGRESS) program, a large double blind placebo controlled study, demonstrated that treatment decreased the risk of cognitive decline from hypertension (Hansson, Hedner & Himmelmann, 2001). Others have demonstrated a link between hypertension and cognitive deterioration, including the Study on Cognition and Prognosis in the Elderly (SCOPE) (Lithell et al., 2003), the Feedback of Outcomes to Users and Staff (FOCUS) study (Jacobson et al., 2001), and Systolic Hypertension-Europe (Syst-Eur) Trial (Forette et al., 2002). Despite these studies, scientific literature addressing cognition in hypertension is not clearly articulated. A substantial challenge for health professionals and scientists is to explore and clarify the nature of the relationship not just between hypertension and cognition, but between hemodynamic responses in the disease and functional stressors. While hypoperfusion and impaired cerebrovascular reactivity may be responsible for cognitive decline associated with hypertension, aging could be a confounding variable. Most studies investigating cognitive decline in hypertension have been performed on the elderly (Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007; Anson & Paran, 2005). Despite the recent findings of Maillard et al. (2012) of decreased cognitive function in 40 year old hypertensives, it is not clear whether the features of altered cerebrovascular reactivity and hypoperfusion are typically present in younger hypertensives.

This project compared the hemodynamic responses and cerebrovascular reactivity between relatively young healthy normotensive and stage 1 hypertensive males (i.e. 56 years and younger) under postural and cognitive stress using functional Near Infrared Spectroscopy (fNIRS). The physiological hypothesis central to this project was that hypertension-related small

vessel damage results in hemodynamic alterations effectively inducing hypoperfusion measured at the microvascular level. The reduced blood flow instigates a relative attenuation of oxygenation of the cortical parenchyma which may be most demonstrable when the individual is physiologically challenged in some way; e.g., with physical or cognitive stressors. This issue is unresolved.

The *first study* examined the reliability of fNIRS in assessing PFC hemodynamic responses and reactivity in both normotensive and hypertensive participants. The following questions were addressed: (1) Can fNIRS be used to reliably examine the hemodynamic changes and cerebrovascular reactivity within and across testing sessions during interventions such as CO_2 rebreathing and postural change? Such interventions are known to alter these responses in normotensive and hypertensive participants (Xu et al., 2011; Mehagnoul-Schipper, Vloet, Colier, Hoefnagels & Jansen, 2000; Hajjar, Zhao, Alsop, & Novak, 2010) and (2) Is there a significant difference between normotensives and hypertensives for these acute hemodynamic changes during these interventions? After establishing the reliability of fNIRS-measured hemodynamic responses and reactivity in these two groups, the *second study* compared their hemodynamic responses during tests of working memory. The following research questions were conceptualized: (1) Does the introduction of higher forms of cognition significantly alter the PFC hemodynamic responses and working memory in normotensive and hypertensive participants? and (2) If so, what is the relationship between these variables in the two groups? The *third study* was designed to examine the following questions: (1) What is the effect of acute exercise on the PFC hemodynamic changes and attentional control in normotensive and hypertensive

participants? and (2) Is there a relationship between attentional control and alterations in PFC hemodynamics in these two groups?

Pertinent background information on hypertension within our conceptual framework and the results of the three investigations are presented in this dissertation as follows: *Chapter 2* provides a review of the relevant literature including the physiological parameters of cerebral circulation in hypertension that was applicable to our theoretical base. It also reviews the mechanisms of action of our main assessment technique, namely fNIRS. *Chapters 3 – 5* present the three investigations which are structured in paper format. Finally, a discussion and summation of the overall project, including implications for clinical practice, are presented in *Chapter 6*.

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Chapter 2

Literature Review

Evidence of the impact of hypertension on cognitive function is substantial and increasing. Therapeutically meaningful strategies, which emphasize functional performance, and undermine the hypertension-cognitive dysfunction-disability triad, are urgently needed. This chapter reviews trends in the hypertension literature and emphasizes hemodynamic coupling with prefrontal cortex (PFC) function pertaining to functional Near Infrared Spectroscopy (fNIRS) monitoring. A comprehensive deliberation of the pathophysiology of hypertension is beyond the scope of this dissertation and essential reviews of this area are present in Laragh and Brenner (1995). After reviewing pertinent information in the hypertension-cognition pairing, we describe fNIRS as an appropriate measurement technique for this project. The chapter then provides a brief preamble to the three studies that encompass the project.

Part 1: Hypertension: Classifications and Trends.

The worldwide prevalence of hypertension may be as much as 1 billion individuals (Chobanian et al., 2003). Ninety percent of Canadians will develop hypertension if they live an average lifespan (Health Canada, 2013). Further, the World Health Organization describes suboptimal blood pressure levels as the number one risk of death worldwide and projected that by the year 2025, 29% of the world population will have hypertension (Kearney et al., 2005; World Health Organization Report 2003). The awareness and treatment of hypertension has improved since the 1970's, but as the National Health and Nutrition Examination Survey shows, only 34% of treated hypertensives have control over their blood pressure and more strikingly, only 59% of those with the disease are being treated (Table 2.1) (Chobanian et al., 2003). Additionally, data

in a population based observational Swedish study have revealed only one out of four primary care patients in that country reach their target blood pressure (Qvarstrom et al., 2010). Put succinctly, a very large number of individuals are exposed to the complications of this disease.

Observational data from over 1 million study participants have clearly identified that death from ischemic heart disease and stroke increases progressively from blood pressure levels as low as systolic of 115 mmHg and diastolic of 75 mmHg (Lewington et al., 2002). The increased risk, reported in the 40 - 89 age group, is also associated with mortality from stroke and ischemic heart disease that doubles for every 20 mmHg increase in systolic and 10 mmHg increase in diastolic blood pressure (Chobanian et al., 2003; Elias, Goodell, & Dore, 2012).

These data are driving a clinical urgency in addressing hypertension. In this regard, a new classification of the disease has been advised to include a state called “pre-hypertension”. Since the damage caused by the disease is proportional to time since diagnosis (Elias et al., 2012), the prehypertension designation is an attempt to promote early treatment of the disease. The feeling is that this approach may forestall the typical sequel of target organ damage. See Table 2.2 for the most recent Joint National Committee (JNC 7) classification.

Consistent with target organ damage, a correlation between hypertension and vascular dementia is well known. It is also becoming clear that hypertension is a reversible factor in the development of most dementias (van der Flier et al., 2005; Veglio et al., 2009). Cardio- and cerebrovascular diseases are related to cognitive decline in large population based studies (Launer, et al., 2010; Elias et al., 1993). Indeed, according to Veglio et al. hypertension remains the most modifiable risk factor for heart and cerebrovascular disease. In the case of the brain,

this modifiable characteristic of the disease is likely the result of the functional coupling of brain activity and cerebral blood flow. Utilizing this coupling relationship is one approach to investigating the hemodynamics of the conditions related to brain dysfunction.

Hemodynamic Coupling and Brain Function

Global brain measurements of cerebral metabolism and blood flow have demonstrated the direct relationship between functional activity, metabolism and the flow of blood to the brain (Secher, Seifert & Van Lieshout, 2008). Almost a quarter century ago, Kuschinsky (1991) remarked that this relationship was locally heterogeneous within the brain. "Locally heterogeneous" implies different regions of the brain have their own local coupling features related to their individual type of neural activity. He further stated that adjustments to allow for this coupling occur in two ways. Firstly, in the short term, dynamic coupling is mediated by vaso-active influences that ensure immediate regulation in response to increased neural activity. Secondly, neurovascular coupling occurs over the long term, and this is mediated by alteration to capillary density that is developed in response to functional and metabolic demands. A coupling sequence can be stated as neuronal activity preceding increased metabolism followed by increased blood flow.

The coupling phenomenon and the regulation process of the brain in general are likely to be altered by conditions that affect cerebral blood flow and metabolism (Ide & Secher, 2000; Koike, et al., 2004). In this regard, cerebral blood flow is normally autoregulated. (See Figure 2.1) This means that the blood flow is kept relatively constant during variations in perfusion and intracranial pressure (Paulson, Strandgaard, & Edvinsson, 1990; Tiecks, Lam, Aaslid, & Newell,

1995). Such regulation is mediated by alterations in the aperture of small arteries and arterioles (resistance vessels – highly associated with hypertension) which dilate when blood pressure falls, and constrict when it rises (Ainslie & Duffin, 2009; Wahl & Schilling, 1993).

Recent Thinking on Autoregulation

Figure 2.1 presents the classical interpretation of the phenomenon of autoregulation in cerebral circulation. The absence of significant change in cerebral blood flow with mean blood pressure changes between ~60 and 150 mmHg is considered normal autoregulation (Lassen, 1959).This theoretical model has been widely used in the diagnosis and monitoring of cerebrovascular diseases. However, it has been criticized for not having valid quantification, and certainly not utilizing cerebral oxygenation measures in addition to measures of cerebral blood flow (Lucas, Tzeng, Galvin, Thomas, Ogoh, & Ainslie, 2010; Heisted & Kontos, 1983). Lucas et al. demonstrated that between 40 to 125 mmHg of mean arterial blood pressure in healthy humans, cerebral blood flow and oxygenation closely follows pharmacologically-induced changes in blood pressure. Hence, changes in the slope of the plateau region shown in Figure 2.1 may not imply defective autoregulation, as is usually the case. Such a change in slope has been reported in severe cases of hypertension and diagnostically interpreted as disruption of normal cerebral autoregulation (Immink et al., 2004). However, Lucas et al. reported that studies in the area of cerebral autoregulation have traditionally failed to consider arterial Pco_2, a potent regulator of cerebral blood flow. They further stated that such an important consideration is highly relevant to issues of blood pressure changes triggered by body position (i.e. orthostatic changes). In addition, Pco_2 reductions in orthostatic hypotension were noted to

trigger significant reduction in cerebral blood velocity, a surrogate for cerebral blood flow (Thomas et al., 2009). It is also noteworthy that most tests on cerebral circulation are done in supine lying in the case of Magnetic Resonance Imaging (MRI) studies, and sitting in the case of Transcranial Doppler Ultrasound. Hence, widespread comparisons of cerebral blood flow, or oxygenation for that matter, in different orthostatic conditions with the possibility of different compensatory mechanisms are largely untested. This fact is highly relevant to hypertension in which arterial stiffness, a known feature of the disease, and cerebral oxygenation are all altered by body position (Murphy et al., 2010; Nurnberger et al., 2011).

Brassard, Seifert and Secher (2009) using fNIRS reported changes in oxygenation with progressive increases in mean arterial blood pressure in norepinephrine induced hypertension in healthy humans. These findings corroborate those of Lucas et al. (2010) previously mentioned. However, the vasoactive effects of norepinephrine may confound studies that address hypertension, and may explain altered perfusion seen by Brassard and colleagues. Hence, the possible occurrence of changes in perfusion in this case, along with the effects of changes in Pco_2 and orthostatic positioning create questions about the minute variations within the limits of autoregulation itself. Nevertheless, despite the limitations in understanding of brain circulatory dynamics, the concept of some form of autoregulation of cerebral blood flow is widely accepted as an important protective mechanism. Regardless, adequate cerebral blood flow is controlled by neurovascular coupling related to cortical activity (Azevedo, Rosengarten, Santos, Freitas & Kaps, 2007; Iadeleco, 1993).

In hypertension, the upper and lower limits of autoregulation are shifted to the right (Veglio et al., 2009; Elias et al., 2012). This improves the tolerance of the hypertensive patient to relatively higher blood pressure, but impairs tolerance for lower blood pressure. Serrador et al. (2005) found that cerebral blood flow was preserved by changes in vascular resistance and that hypertensives retain cerebral blood flow despite acute changes in perfusion pressure. This is an apparent improvement in autoregulation in hypertensives compared to normotensives. That is, there is better attenuation of blood pressure fluctuations in the hypertensive. An explanation for the apparent improvement in autoregulation of hypertensives could be the well known changes that hypertension causes in the remodeling of cerebral vasculature (Veglio et al., 2009).

Vascular Remodeling in Hypertension

Using the animal model, Baumbach & Hajdu (1993) demonstrated that cerebral arterioles hypertrophy and become more distensible with chronic hypertension. Such an increase in distensibility may result in greater attenuation of pressure and suggests better autoregulation in hypertension as reported by Serrador et al. (2005). Cerebral autoregulatory response primarily occurs at the level of the arterioles and small arteries (Ainslie & Duffin, 2009), and interestingly, these cerebral small arteries are the targets of hypertensive damage (Veglio et al., 2009). The arteries of concern are lenticulostriate branches of the anterior and middle cerebral arteries referred to as “perforating arteries”, as well as branches of the basilar artery (Nolte, 2009). The lumen of these small arteries range from 100 to 400uM and are end-artery anatomy and unbranching in morphology resulting in them being subjected to significant hemodynamic forces. Such forces and the alteration of anatomy that comes with the disease are a classical

feature of the end organ damage caused by hypertension (Veglio et al.; Grossman & Messerli, 1992).

End Organ Damage

Hypertensive brain lesions resulting from small vessel changes may appear in two different forms in neuro-radiological and clinical findings. Firstly, they present as ischemic lesions referred to as “lacunar infarcts”, mostly occurring in the territories of the “perforating arteries”. They are usually the consequence of occlusion in these small vessels or simply post-stenotic hypoperfusion (Rosenblum, 1993). The lack of collateral circulation in the area of these mostly “end arteries” results in small infarcts that spread distally from the point of occlusion. It should be noted that these small diameter perforating arteries in the brain arise directly from main arterial trunks, which is unique to the cerebral circulation (Nolte, 2009; Veglio et al., 2009). Such a feature renders these small diameter vessels vulnerable to changes wrought by increased blood pressure levels. It is noteworthy that most lacunar infarcts are asymptomatic, but may eventually present clinically in various versions of stroke and cognitive impairment (Laragh & Brenner, 1995; Grossman & Messerli, 1992).

The second form of hypertensive small vessel disease is due to diffuse erosion of the white matter or myelin degeneration, also referred to as “leukoaraisosis” (Jacobs et al., 2013). There is brain tissue rarefaction, fibrosis of the wall of deep small vessels with coexisting cavitated or non-cavitated small deep infarcts (Pantoni & Garcia, 1995; Pantoni & Garcia, 1997). These changes are likely ischemic in nature caused by hypoperfusion in the deep arterial and arteriolar territories.

For the hypertensive patient, neuro-imaging demonstrating these lesions are usually subclinical (asymptomatic). They present no apparent functional alteration in the brain, i.e. cognitive impairment under normal stresses (Laragh & Brenner, 1995). Utilizing neuro-imaging techniques on the brain can be considered analogous to echocardiogram measures of cardiac hypertrophy in a hypertensive patient before symptoms of alteration in heart function appear, e.g. prior to heart attack. In the case of "leukoaraisosis", cognitive impairment is the clinical finding of note and the neuro-imaging findings just described can be a prelude to such cognitive dysfunction (Veglio et al., 2009).

Cognitive Impairment

The small vessel changes in the brain that typify hypertension cause vascular occlusion that decreases perfusion (Grossman & Messerli, 1992). Such changes precede varying degrees of cognitive impairment giving hypertension its emerging role in dementia (Dickinson, 2001; Faraci, Baumbach, & Heistad, 1990; Elias et al., 2012; Liu et al., 2014). Longitudinal studies, including the Framingham Heart Study, have shown cognitive levels to be inversely proportional to blood pressure measured 15 or 20 years previously (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Launer et al., 2010).

To allow for closer analysis of these findings, a recent past trend was to look at systolic and diastolic blood pressure separately as they relate to cognitive function (Elias et al., 2012). This was in large part due to the finding that elevated diastolic blood pressure is a more potent risk factor for cardiovascular complication before age 50 as opposed to systolic that continues to be a risk factor well into old age (Chobanian et al., 2003). Knecht et al. (2008) using a cross-sectional design found the relation between systolic blood pressure and cognitive function to

parallel the established linear relationship that exists between systolic blood pressure and vascular risk in general. These authors also found that the linear relationship exists not only between established hypertension and cognitive impairment, but also between so-called high normal blood pressure and cognitive impairment. This is consistent with the idea behind the "pre-hypertension" designation (Chobanian et al., 2003), which is an attempt to promote early management of the disease and forestall end organ involvement.

Even more interesting, Lande, Kaczorowski, Auinger, Schwartz, and Weitzman (2003), later supported by Kupferman, Lande, Adams and Pavlakis (2013), found decreased scores on the digit span test among United States school children with higher systolic blood pressure measures (>90th percentile). The digit span test is a standardized neuropsychological measure of concentration and attention (Sattler, 2008). These findings mark a trend of functional involvement of the end organ (in this case, the brain) at increasingly younger ages associated with higher blood pressure. Intriguingly, as per Kupferman et al., neuropsychological testing is able to determine earlier stages in brain-end organ involvement associated with hypertension. Such early findings may anticipate eventual clinically evident cognitive impairment and the psychological entity referred to as "working memory" provides an opportunity to functionally assess individuals with probable impairment.

Working Memory

Various forms of memory testing have been used in the assessment of hypertension-related cognitive impairment (Scullin et al., 2013). The importance of working memory as a mark of individual intellectual capacity is largely unchallenged and clarifying its various

conceptualizations may shed light on its unique value in cognitive testing of the hypertensive patient. Cowan (2005) described the two common connotations of working memory. Firstly, there is the familiar description of working memory as a process of limited capacity that holds information which is readily accessible for use in a behavioral task. Secondly, working memory can be viewed as a multifaceted temporary holding system of mental processes hypothesized by Baddeley (1986). It is comprised of a phonological store, a visuospatial sketchpad and a central executive that shuttles information in and out of these two stores and other aspects of information processing. More recently, Baddeley (2003) included an "episodic buffer" in his system of working memory as a short term contextual receptacle of new information that parallels episodic memory. The expansion of Baddeley's model with the addition of the episodic buffer reduces the differences with other models of working memory such as Cowan's theoretical framework (Cowan, 2005).

Cowan (1988) developed the "embedded processes" model of working memory comprising two components. First he described working memory as a subset of processes in an activated mental state. Secondly, he hypothesizes the presence of a smaller subset of activated memory at the centre of individual attention. Cowan's connotations of working memory resemble the mid twentieth century work of Hebb who described the phenomenon as a "set of active, reverberating circuits of a neural cell assembly that carry the representation of a currently active concept in the brain…" (Cowan, 2005). Individual working memory capacity may prove to be valuable as both a functional measure and as a biomarker of neuronal activation in the hypertensive brain.

The concept of working memory is often controversial. However, its value as an objective measure of intellectual capability remains an industry standard capable of charting approaches to cognitive rehabilitation in various conditions including hypertension. Notwithstanding, in advance of such an impact, the functional sequelae of hypertension and high blood pressure on cognitive function requires further study to clarify conflicting findings as they arise.

Conflicting Results

Tsivgoulis et al. (2009) found an increment of a mere 10mmHg in diastolic blood pressure above normal ranges was associated with a 7% increased risk of cognitive impairment. These results are concordant with other cross-sectional studies (Cacciatore et al., 1997; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998). Pandav et al. (2003) in the Indo-US Cross National Epidemiologic Study reported a 10% decrement in cognitive function with a 10mmHg elevation of either systolic or diastolic blood pressure. The Framingham Heart Study found that elevated blood pressure levels in general were linearly related to decreased cognitive function (Elias et al., 1993). On the other hand, the East Boston Study (Scherr, Hebert, Smith, & Evans, 1991) and the Maastricht Aging Study (van Boxtel et al., 1997) reported contrary findings with no cross-sectional relationship between hypertension and cognitive function. One should be reminded however, that attributing causation is not associated with studies of a cross-sectional design, and the noted disparities in results may be related to design issues. Further, different blood pressure cutoffs and differences in age, ethnicity, education, and medication use may all influence results. Nevertheless, the association between decreased cognitive function and hypertension is well established (Elias et al., 2012). The likely basis of scientific investigation of

the disease going forward is at least twofold, and may include: (1) examination of the hemodynamics of focal brain oxygenation under ecologically valid models which utilize functional stressors, and (2) supplementing this dynamic examination with inter-hemispheric comparisons.

Inter-Hemispheric Influences

In exploring the effects of hypertension on brain function, hemispheric differences are likely to arise. It is well established that hemispheric differences are present in most mammals, and these differences are likely to be accentuated in humans with our reliance on complex behavior and use of language and symbols (Kandel, Schwartz & Jessell, 2000). Highlighting the importance of inter-hemispheric differences are cases of unilateral lesions of the brain that indicate memory processes being lateralized according to content (Golby et al., 2001) with left sided lesions interfering with verbal memory processes while non-verbal memory was affected by lesions to the right side. Meanwhile Cabeza, Locantore and Anderson (2003) demonstrated that the left prefrontal cortex was more involved in processing semantic information while the right side was involved in monitoring and verification. They referred to this latter feature as the "production monitoring" hypothesis which is essential for recall tasks, the most functional part of memory. Despite the examples highlighted by unilateral lesions of the brain, most cognitive processes are localized to specific areas with specific connections with other regions in cognitive control networks (Cole & Schneider, 2007). Localization of certain activities in specific brain areas, in addition to affirming the existence of such netwoks, allows study of cortical neurovascular coupling associated with functional challenges.

Harper, Bandler, Spriggs and Alger (2000) used magnetic resonance imaging procedures to investigate signal changes from multiple brain sites during blood pressure challenges. They found that signal responses to these challenges were highly lateralized especially in the frontal lobe with areas including the PFC demonstrating only unilateral activity. Given the frontal lobe's involvement in executive function (Kandell, Schwartz & Jessell, 2000; Rabbitt, 1998; Miller & Cohen, 2001), and its stated asymmetric response to blood pressure challenges for example, investigating inter-hemispheric differences is relevant to a functional study of hypertension.

Rationale for a Functional Study of the Prefrontal Cortex in Hypertension

Small vessel disease in hypertension takes the form of altered microcirculation and endothelial dysfunction (Grossman & Messerli, 1992; Elias et al., 2012). In turn, this affects the coupling of cerebral circulation and cerebral metabolism associated with neuronal activity. How do the normal features of the coupling phenomenon change with hypertension when the individual is under some form of functional stress - mental or physical? Answers to such questions may lead to strategies on treatment of hypertension-related cognitive decline. One method that may offer answers will be to investigate the changes in local oxygenation and other hemodynamic levels in select areas of the brain during functional activation. Such local oxygenation levels may reveal features resulting from the arterial disease that alters perfusion in these focal areas.

In summary, cerebral blood flow, brain metabolism and functional activities are linked in the phenomenon of neurovascular coupling of brain function (Leenders et al., 1990). Explicitly, functional activities are associated with particular brain regions which, when activated, demonstrate increased metabolic activity (Roy & Sherrington, 1890). This increased activity is associated with increased blood flow and oxygen consumption commensurate with that activity

in a strict coupling of blood flow in excess of oxygen utilization (Fox, Raichle, Mintun & Dence, 1988). This phenomenon may be affected by hypertension. Importantly, oxygenation and blood flow in the PFC are integral to a functional study in any pathological state that may affect human executive capabilities (Kupferman et al., 2013; Koike et al., 2004). This nexus between oxygenation/hemodynamic responses and the functional results of PFC activity is the "skeleton" of this project.

The conceptual framework for this proposition rested on the approaches in rehabilitation science that emphasize parameters of function and performance. In this case, the hemodynamic changes accompanying performance in postural stress, working memory, exercise and attentional control are the important points of analyses. The investigative technique used in this project was fNIRS, a procedure noted for its ecological validity in measuring brain hemodynamic responses under functional conditions (Desrosière, Mandrick, Dray, Ward, & Perrey, 2013; Hoshi, 2003; Strangman, Franceschini, & Boas, 2003; Sibbald, Messmer, & Fink, 2000).

Part 2: Functional Near Infra-red Spectroscopy

The appropriateness of fNIRS as the primary technique of assessment in this project rests with its physiological specificity in measuring microvascular responses and its ecological validity for multiple functional models (Derosière et al., 2013). The pertinent review of fNIRS that follows includes (1) an encapsulation of the theoretical basis of the technique, (2) limitations, (3) the validity and reliability of the technique, and (4) fNIRS measurement in cognitive function.

Methods to study end organ phenomenon in the brain associated with hypertension are limited. For the most part, they include the functionally restrictive testing procedures such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) scans, Computed Tomography (CT) Scans and Electroencephalography (EEG) (Veglio et al., 2009). With such limitations in investigative techniques, it is difficult to address questions of brain function with activities of daily living. In addition, these procedures have widely differing strengths in temporal and spatial sensitivity thus limiting research interpretation (Cui et al., 2011).

fNIRS is an investigative tool that is growing in popularity and usefulness. It has excellent temporal sensitivity and reasonable spatial sensitivity making it propitious for studying cognitive function (Hoshi, 2003; Strangman, Franceschini, & Boas, 2003). The procedure is simple, of relatively low cost, and allows free movement of the participant to engage in physical activities while testing. Given its flexibility, fNIRS provides information on disease processes in real time while the individual is engaged in meaningful functional tasks. In addition, near infrared light is non-ionizing, unlike CT Scans and X-rays, thus allowing safe scanning of the individual any number of times (Hoshi, 2003).

Theoretical Basis of Functional Near Infrared Spectroscopy

Prior to fNIRS, MRI, PET Scans and EEG, measuring the hemodynamics of the brain was not meaningfully investigated in select brain areas. Rather, the brain was looked at in a global sense for investigative function (Fox et al., 1988). Undeniably, measuring the global hemodynamics of the brain in conditions like hypertension is a poor substitute for localized measures of tissue oxygenation as offered by fNIRS. Further, measuring brain function while not meaningfully and

functionally engaging the brain will eventually result in a serious limitation in the transferability of research findings to therapy.

The brain demands relatively more blood than any other organ. It is only 2% of body weight, but utilizes 20% of the body's oxygen consumption (Mchedlishvili, 1986; Ainslie & Duffin, 2009). With regional brain activation, more oxygen is needed for glucose metabolism. The process results in energy in the form of Adenosine Triphosphate (ATP) to sustain neuronal activation. Measuring the change in oxygenation is a surrogate for the increase in the metabolic process accompanying increased activation of particular brain regions. Dilation of capillaries in neurovascular coupling occurs along with opening up of additional capillaries to accommodate the increased oxygen demand. Hence monitoring the increase blood flow that comes with vasodilatation and capillary recruitment during particular activities is a marker of cerebral activation (Villringer & Chance, 1997). A significant positive correlation has been noted between regional brain activation and regional cerebral oxygen consumption (Raichle, Grubb, Gado, Eichling, & Ter-Pogossian, 1976). The amount of oxygen delivered depends on the concentration of hemoglobin and its particular state of affinity for oxygen (Buxton & Frank, 1997).

In this regard, fNIRS, a non-invasive optical technique is becoming more established as a highly useful technique to measure localized oxygenation in both brain and muscle (Fallgatter & Strik, 1998; Obrig & Villringer, 1997; Villringer & Chance, 1997; Perrey, 2008; Ferrari & Quaresima, 2012). The principle of fNIRS arises from the observation of Jobsis (1977) that biological tissues have a relatively good transparency for light in the near infrared region of the light spectrum

(650-950nm) (Madsen & Secher, 1999; Perrey, 2008). This makes it possible to transmit sufficient light energy through organs, such as the brain, to allow in situ monitoring. In the near infrared region of the spectrum, hemoglobin shows levels of light absorption that is oxygen dependent. That is, it is possible to differentiate levels of oxygenation through levels of light absorption by the versions of the hemoglobin molecule – oxy- and deoxy-hemoglobin (Villringer & Chance, 1997). (Note that myoglobin and cytochrome C oxidase, not a part of this study, are also evaluated with fNIRS).

The usual fNIRS approach is to have an incident near infrared light striking the tissue being studied with the reflected light recovered by a receiving optode. The light energy transmitted to the tissue is either scattered in the tissue or absorbed by the chromophores (hemoglobin molecule in this case). The recovered light depends on the degree of tissue absorption and scattering properties. Changes in the light recovered reflect the relative amount of chromophores in the illuminated region (Colier, 1995).

The technique of fNIRS relies on the Modified Lambert-Beer law (Colier, 1995). The law states that the light recovered from the illuminated tissue depends on several factors: intensity of incident light, the separation of the optodes, the absorbency of the tissues, which is related to the concentration of chromophores, and the degree of light scatter within the tissue. The Lambert-Beer Law was intended for clear and non-scattering medium. When used in a highly scattering medium such as biological tissue a path length correction factor for the light must be incorporated. This factor is referred to as a Differential Path Length Factor and accounts for the increased scattering associated with biological tissue (Colier, 1995). In the most commonly used

fNIRS machine, the Continuous Wave instrument, this factor is considered constant allowing the conversion of the optical density of the medium to changes in concentration (Scholkmann et al., 2014). See Appendix A for further information on the Modified Lambert-Beer Law.

The concentration of the chromophores (hemoglobin) in particular brain regions is dependent on levels of activation of that brain region. With increase glucose utilization from the metabolic activity there is increased oxygen consumption leading to increased hemoglobin concentration subsequent to vasodilatation and capillary recruitment (Buxton & Frank, 1997). Such changes in chromophore (hemoglobin) concentration can thus be monitored by fNIRS in accordance with the Modified Lambert-Beer law.

The phenomenon of the absorption of near infrared light allows monitoring of changes in tissue oxygenation at the levels of the small vessels (arterioles, capillaries and venules), (Rasmussen et al., 2006; Subudhi, Miramon, Granger, & Roach, 2009). At 760nm deoxyhemoglobin absorbs more light while at 850nm oxyhemoglobin has greater absorption. Hence, as hemoglobin becomes more oxygenated light absorption at 760nm decreases while that at 850nm increases. The difference of light reflected at the two wavelengths indicates the differing concentration of the two versions of hemoglobin (Colier, 1995). This in turn can be analyzed as levels of oxygenation of the particular brain region accompanying the functional activity, thus giving a working and valid representation of the brain in action. At this point, one should be aware of limitations associated with fNIRS measures.

Limitations of fNIRS

Quantification is an issue in Continuous Wave type fNIRS machines, the most common instruments in practice (Strangman et al., 2003; Scholkmann et al., 2014). In these instruments the differential path length of light entering the tissue is assumed constant, a proposition that is open to questioning, and for this reason these machines allow only a relative measure of oxygenation. Delta values are used for analysis, and comparing amplitudes of traces across participants is not valid (Strangman, Boas & Sutton, 2002).

Secondly, results can be rendered inaccurate if the position of the optodes (light source and light detector) changes with movement of the participant. Given testing with fNIRS can be accompanied by high levels of physical activity, movement and positioning of the optodes can be an issue (Perrey, 2008). Hence, close attention is required in securing the optodes and their placement to ensure accuracy and consistency of measures. Additionally, there are no clear standards in fNIRS data analysis (Hoshi, 2003). Though this in itself might not be a problem, it is necessary to ascertain reliability and repeatability of each method of analysis.

Finally, there are intuitive questions on scalp and skull thickness while measuring over the cranium (Hauessinger et al., 2011), but MRI findings have confirmed that these variables exhibit minimal effect on hemodynamics during task performance (Strangman, Zhang & Li, 2014; Alderliesten et al., 2014). Additionally, brain activation studies must account for the heterogeneity of the tissue composition of the human head. Despite the limitations, fNIRS remains a valid tool in measuring hemodynamic events.

Validity of Functional Near Infrared Spectroscopy

Biological tissue has a relative transparency in the near infrared region of the spectrum and this allows less light scattering, as well as light penetration up to 6 cm of the incident light (Edwards et al., 1993; Simonson & Piantadosi, 1996). In humans, fNIRS has been demonstrated to be a valid technique in evaluating cerebral oxygenation and blood volume (Holzschuch, Woertzen, Metz, & Brawanski, 1997; Pollard et al., 1996; Punwani, Ordridge, Cooper, Amess & Clemence, 1998; Quaresima, Sacco, Totaro, & Ferrari, 2000; Ferrari & Quaresima, 2012).

Holzschuch and colleagues (1997) demonstrated that with a stable fNIRS signal, changes in tissue oxygen pressure were highly correlated with fNIRS estimates of hemoglobin oxygenation at rest ($r>.07$). These measures were performed on severe head injury patients in whom a tissue oxygen monitoring pressure device was inserted into the frontal lobe tissue while oxygenation was being monitored by fNIRS from the surface of the head. In another validation study, Pollard et al. (1996), demonstrated that continuous monitoring of cerebral oximetry based on fNIRS could accurately determine decreasing cerebral hemoglobin oxygen saturation produced by hypoxia. Along these lines of inquiry, Quaresima et al. (2000) demonstrated that fNIRS measured on the forehead (either left or right side) correlated with intracranial venous oxygen saturation ($r=0.76$). The investigation was performed during partial occlusion of the jugular vein.

Similarly, when measuring cerebral oxygenation using fNIRS and PET simultaneously, Rostrup, Law, Pott, Ide, & Knudsen, (2002) demonstrated that fNIRS gave comparable and meaningful results in a brain reactivity study with carbon dioxide rebreathing when comparing the two

procedures. In another study using fNIRS simultaneously with Transcranial Doppler Ultrasound, Rasmussen et al. (2006) demonstrated that fNIRS is an adequate measure of cerebral oxygenation during handgrip strength performance and while inhaling different gas mixtures of oxygen and carbon dioxide.

Most recently, Alderliesten et al. (2014) reported correlation in the good to excellent range between cerebral circulation following respiratory challenge during the BOLD MRI signal and HHb measured by fNIRS. Over the past 30 years, the use of fNIRS as an investigative technique has grown widely and has found applications in psychology, muscle physiology and cerebral pathology (Ferrari & Quaresima, 2012). Validation of fNIRS under different functional conditions continues, and as the use of the technique grows, accompanying reliability at new levels of use will continue to evolve under different experimental conditions and clinical applications.

Reliability of Functional Near Infrared Spectroscopy

Bhambhani, Maikala, Farag, & Rowland (2006) demonstrated the reliability of fNIRS measurements in 25 participants with severe traumatic brain injury. They compared the test-retest reliability of fNIRS measurements performed at the left prefrontal area of cerebral oxygenation and blood volume during rhythmic hand gripping. Thirteen non-disabled participants were also a part of this study that involved two trials. Intraclass correlations between the two trials for the non-disabled group were 0.83 and 0.80 for cerebral oxygenation and blood volume respectively, while for the disabled group it was 0.70 and 0.64. (Blood volume was calculated as the sum of oxy and deoxyhemoglobin on fNIRS measurement.)

Under hypercapnia conditions (5% carbon dioxide), and simultaneously measuring with fNIRS and Transcranial Doppler Sonography, Totaro, Baratelli, Quaresima, Carolei and Ferrari (1998) demonstrated significant correlations between the cerebral blood flow velocity reactivity index and hypercapnia (0.60), reactivity index and oxyhemoglobin (0.68) and reactivity index and deoxyhemoglobin (0.76). These investigators demonstrated the reliability and reproducibility of fNIRS in measuring cerebral reactivity to carbon dioxide. (See section below, Functional Near Infrared Spectroscopy in Cognitive Function, for additional information on reliability in cognitive function.)

Functional Near Infrared Spectroscopy in Cognitive Function

The PFC is considered integral to "top-down" cognitive processing guiding intentional behavior (Miller & Cohen 2001). It is also among the most accessible regions for investigation using fNIRS. These circumstances have resulted in cognition and behavior becoming among the most widely investigated areas using this technique (Boas, Elwell, Ferrari & Taga, 2014). Aside from its easy access, the PFC is specifically involved in cognitive control processes which necessitate patterns of neuronal activity that modulates forms of attention. These patterns of activity are revealed through hemodynamic responses that can be monitored by fNIRS in varying states of health.

Two decades ago, Chance, Zhuang, UnAh, Alter, & Lipton (1993) reported changes in blood concentration in the frontal lobe using a simple dual wavelength spectrophotometer. Since then, fNIRS capability has grown to the present emphasis on measuring cognitive load for humans operating modern machines (Fishburn et al., 2014; Ayaz et al, 2012). Fishburn et al.

recently demonstrated a linear increase in neuronal activation in the bilateral PFC region with increasing load in working memory. In this same experiment they also identified increased inter-hemispheric fNIRS-measured hemodynamic activity as cognitive load increased. The issue of measuring cognitive load with fNIRS is presently driving developments in the field of neuroergonomics (Derosière, Mandrick, Dray, Ward, & Perrey, 2013).

The robustness and ecological validity of fNIRS is well known and the ease of application of the technique is promising for the study of attentional state in human-computer interaction (Derosière et al., 2014). Elaboration of the nature of this interaction is critical in issues around safety and human attention. fNIRS takes advantage of the "top-down" functions of the PFC in modulating attention and human behavior to monitor the day to day interactions of human with machine. The accurate measurement of mental workload is vital to improving human efficiency and identifying safe levels of human-machine interaction (Ayaz et al., 2012). To this end fNIRS is finding increasing usefulness in measuring attention-related metabolic activity.

The recent developments using this technique are a direct extension of earlier research on fNIRS-related PFC activity in cognitive function such as working memory. Schreppel et al. (2008) demonstrated PFC activity during a working memory task reflecting what these researchers described as being a reflection of both maintenance of presented information and attentional monitoring. Recent attempts to classify accuracy of attention in the study of concentration lapses (Derosière et al., 2014) is a reflection of growing confidence in fNIRS as a technique to monitor cognitive activity. It is also an admission of the important research around foundational

issues of the fNIRS technique provided by researchers like Schreppel et al. Yet another direction in the study of cognitive load with fNIRS is the area of aging and health.

In a review by Ferrari and Quaresima (2012) of the development in fNIRS over the past twenty years, the area of cardiovascular health appears to be underrepresented. However, the impact of changes in microvascular function as a direct result of arterial stiffening and endothelial dysfunction with age and diseases like hypertension present an important area of investigation using fNIRS. In a small but relevant study that might have presaged issues of cognitive load and cognitive activity compensation, Hoshi and Tamura (1993) reported an increase in both oxyhemoglobin and total hemoglobin in young subjects experiencing difficulty solving mathematical problems. The increase was greater than in subjects who had no such difficulty. These findings predated those of Fishburn et al. (2014), and might have introduced an important issue on compensatory activities in the brain with increments in relative cognitive load. Compensatory adjustments in brain function remain relevant to the aging process (Reuter-Lorenz & Cappell, 2008; Vermeij et al., 2012).

An increasing number of researchers in the area of aging are using the advantages that fNIRS offer to study age adjustments in brain function. Vermeij et al. (2012) reported impaired performance in healthy older adults (64 – 81yrs) on tests of increasing working memory load when compared to healthy younger adults (21 – 32 yrs). This is consistent with findings of Laguë-Beauvais et al. (2013) who reported bilateral PFC activity using fNIRS in older adults performing various tests of inhibition and switching mental tasks. No significant PFC activation was identified in younger participants by these researchers. These findings appear to support

other neuroimaging findings on age-related compensatory changes in brain activation (Reuter-Lorenz and Cappell, 2008). Changes in hemodynamics and related issues of laterality are highly relevant to this debate.

Vermeij et al. (2013) reported clear hemodynamic differences between younger and older adults in their reaction to increased cognitive load. In the younger group, very low frequency oscillations of cerebral hemodynamics and blood pressure reduced with increased cognitive load. These researchers postulated that age related systemic changes due to a decrease in microvascular smooth muscle activity and arterial stiffness require consideration in all discussions around cognitive neuroimaging.

In addition to quantitative changes in hemodynamics measured by fNIRS, the issue of laterality is relevant. Homae (2014) reported that most fNIRS studies revealed a functional differentiation between the hemispheres. This finding may be further strengthened through use of the versatility of fNIRS in functional tasks relevant to age and pathologies that may generate compensatory adjustments between the hemispheres. fNIRS is widely used in psychiatry in functional activation studies to investigate behaviors related to cognitive impairment. Please review Ehlis et al. (2014) for a comprehensive account of fNIRS in this discipline.

Changes in arterial stiffness and its impact on hemodynamic activity are relevant to most pathological conditions affecting cerebral circulation and cognition. An additional area of pathology that will likely find increasing use for fNIRS is the area of cardiovascular reactivity studies. Cummings, Swart and Ainslie (2007) studied changes in oxygenation as a measure of cerebrovascular reactivity using fNIRS in investigating diurnal changes in reactivity that may

trigger cerebrovascular accidents (strokes). This could be a prophylactic measure in cardiovascular diseases which fNIRS hemodynamic monitoring can provide.

In summary, fNIRS as a neuroimaging technique has demonstrated adequate validity and reliability in brain activation studies. It has grown exponentially over the past twenty years, and has been successfully integrated thus far in disciplines as diverse as neurology, psychiatry, psychology and education (Ferrari & Quaresima, 2012). The versatility of fNIRS has allowed advancement into the more recent area of neuroergonomics and is growing in all areas of the basic and health sciences (Boas et al., 2014). Its application in the study of hypertension will further advance its authenticity as a technique of assessment.

The ensuing chapters of this dissertation will report on three studies using fNIRS in normotensive and hypertensive males. Each of the studies will test PFC hemodynamic responses during carbon dioxide reactivity and postural change, working memory, and attentional control enhanced by exercise.

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TABLE 2.1: Trends in awareness, treatment, and control of high blood pressure 1976-2000

National Health and Nutrition Examination Survey (%)

	1976-80	1988-91	1991-94	1999-2000
Awareness	51	73	68	70
Treatment	31	55	54	59
Control*	10	29	27	34

(Adapted from Chobanian et al*.,* 2003)

TABLE 2.2: JNC 7 Classification of blood pressure

Systolic/Diastolic	JNC Classification
<120/80	Normal
120/80 – 139/89	Prehypertension
>140/90	Hypertension
140/90 – 159/99	Stage 1 hypertension
>160/100	Stage 2 hypertension

(Adapted from JNC 7, Chobanian et al., 2003)

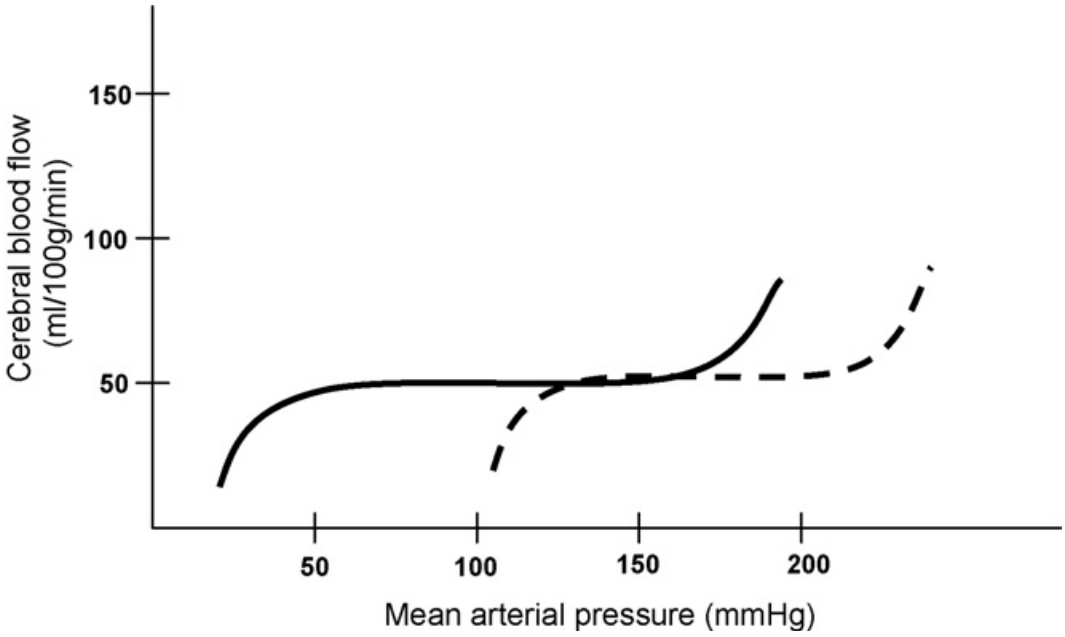

FIGURE 2.1: Autoregulation of cerebral blood flow: (normotensives = solid line; hypertensives = dashed line)

Note: In hypertensives autoregulation acts at a higher mean arterial blood pressure.

(Adapted from Veglio et al., 2009)

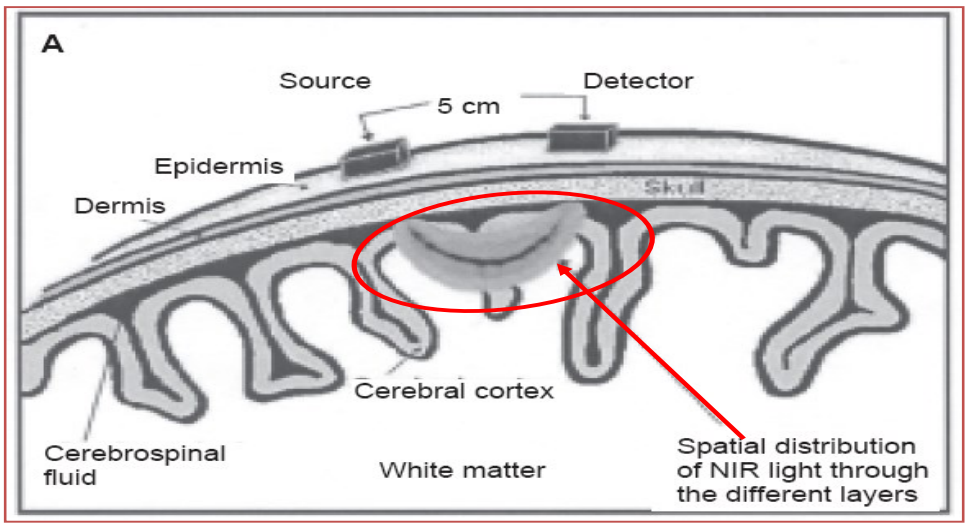

Figure 2.2: Propogation of NIR light through the Brain "Banana - shape"

(Adapted from Fukui, Ajichi & Okada, 2003)

Chapter 3

Reliability and Reactivity of the Prefrontal Hemodynamic Responses in Essential Hypertension: A Functional Near Infrared Spectroscopy Study

Introduction

A decline in cerebral hemodynamic responsiveness is associated with reduction in cognitive proficiency (Vincenzini et al., 2007). Hajjar, Zhao, Alsop, and Novak (2010), used magnetic resonance imaging (MRI), to demonstrate that hypertension was associated with impaired vaso-reactivity in all cortical zones, particularly the fronto-parietal region. These authors defined vaso-reactivity as the change in cerebral perfusion as a function of end-tidal carbon dioxide (CO_2). CO_2, a major by-product of cerebral metabolism, is widely known to alter cerebrovascular resistance, and $PaCO_2$ levels are usually indicative of the state of cerebral perfusion (Madden, 1993; Ainslie & Duffin, 2009). On that account, hemodynamic responses to changes in end tidal CO_2 can be considered an appropriate measure of cerebrovascular reactivity. Impairment in cerebral vaso-reactivity could be an important intermediary in the known affiliation between hypertension and cognitive decline (Veglio et al., 2009; Elias, Goodell, & Dore, 2012). Such a reduction in cognitive performance is considered central to the growing global loss in health and productivity associated with hypertension (Kearney et al., 2005; Vasan, 2009; Campbell, McAlister, & Quom, 2012).

Almost two decades ago, Ficzere et al. (1997) suggested that hypertension was associated with decreased cerebrovascular reactivity in the absence of neurologic deficits or demonstrable abnormalities on computerized tomography. These findings were subsequently supported using

advanced MRI technology (Hajjar et al., 2010). Despite this information, the impact of hypertension on the hemodynamic responses at the microvascular level (namely, arterioles, capillaries and venules) has not been extensively studied. Such a shortfall may be attributable to the investigative tools customarily used in assessing reactivity in cerebral hemodynamics. Further, the stated effects of hypertension on cerebrovascular reactivity were the result of testing in severe hypertensives (Hajjar et al., 2010). Consequently, these findings should be interpreted with caution in discussions involving mild to moderate (e.g. stage 1) hypertensives.

Until recently, cerebrovascular reactivity in hypertension and other cardiovascular/cerebrovascular diseases has been studied by investigating blood flow in the middle cerebral artery (Ainslie & Duffin, 2009). Transcranial Doppler sonography was often the technique of choice (Maeda et al., 1994) in monitoring blood flow changes triggered by interventions such as CO_2 rebreathing (Serrador, Picot, Rutt, Shoemaker, & Bondar, 2000). However, the technique of sonography, appropriate in measures of global cerebral blood flow (Ainslie & Duffin, 2009), is arguably not sufficiently specific to investigate microvascular changes within cortical parenchyma. Such adjustments may include hemodynamic responsiveness that accompanies small vessel disease pathology which is typical of hypertension (Olin, Dimmen, Subudhi, & Roach, 2011). Further, MRI investigation of the effects of hypertension on the brain provides limited information, in that it allows testing only in static positions (Fishburn, Norr, Medvedev & Vaidya, 2014). Thus, the consequences of hypertension-related cerebrovascular reactivity and hemodynamic responsiveness that may be relevant to general function, for example in postural changes, are poorly investigated. These modulations of stress on cerebral circulation in the hypertensive brought on by positional change are clinically relevant. For

example, avoiding posture-related brain ischemia during shoulder surgery in the beach chair position (Jeong et al., 2012; Moerman, De Hert, Jacobs, De Wilde, & Wouters, 2012), or altering intracranial pressure during neurosurgery (Lovell, Marshall, Elwell, Smith & Gladstone, 2000), highlight potential safety issues for clinical practice. Utilizing an appropriate technique to assess frontal hemodynamic changes in hypertension is fundamental to understanding how vaso-reactivity affects general function and care of these patients.

Functional near infrared spectroscopy (fNIRS) is a neuroimaging technique that has been validated with MRI, Positron Emission Tomography (PET) and other established techniques in the measurement of cerebral hemodynamic responses in a variety of disorders (for review see Ferrari & Quaresima, 2012). This non-invasive optical technique measures relative changes in oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) concentration associated with cortical activity and blood flow at the microvascular level. Its main advantage is that it allows real-time, in-situ testing in different body positions under varying functional stresses that resemble both clinical and prosaic scenarios. Utilizing the principles of the modified Beer-Lambert Law, this approach measures the absorption changes in near infrared light (700 – 1300nm) associated with the hemoglobin chromophore (light absorbing compound) to indirectly monitor changes in O_2Hb and HHb (Colier, 1995; Boas, Elwell, Ferrari, & Taga, 2014). fNIRS, as a neuroimaging technique, provides relatively higher temporal resolution (milliseconds) in measuring hemodynamic changes than fMRI (Arenth, Ricker, & Schultheis, 2007; Irani, Platek, Bunce, Ruocco, & Chute, 2007). Further, it offers biochemically specific information at the microvascular level that allows monitoring of the close association between hemodynamic responses and functional tasks (Ekkekakis, 2009; Fishburn et al., 2014). This renders the

technique ecologically valid for a variety of experimental situations that involve frontal lobe activation in different body positions (Derosière, Mandrick, Dray, Ward, & Perrey, 2013). Additionally, its relative cost effectiveness and robustness is a distinct advantage over other approaches in measuring the impact of functional stresses on the brain in a variety of clinical disorders including hypertension.

Over the past twenty years, test-retest reliability of fNIRS measurements has been established in both healthy and diseased populations under different experimental conditions. In areas of language and cognition on a group level, fNIRS has been demonstrated to be reproducible for periods up to a year (Ferrari & Quaresima, 2012). Additional areas where reliability has been identified include CO_2 rebreathing (Totaro, Baratelli, Quaresima, Carolei, & Ferrari, 1998), positional changes (Mehagnoul-Schipper, Vloet, Colier, Hoefnagels, & Jansen, 2000; Kurihara, Kikukawa, Kobayashi, & Nakadate, 2007), and motor testing (Leff et al., 2011). However, to our knowledge simultaneous testing of two of these procedures, CO_2 rebreathing and postural change for example, has not been performed. Moreover, testing of this nature in a group of stage 1 hypertensives has not been conducted. Hence information on the reliability of the known vaso-reactive changes that accompany alterations in $PaCO_2$ and body position in a healthy population (Ainslie & Duffin, 2009) is not available for hypertensives. Thus, one perspective in explaining the relationship between cognition and hypertension, in the form of cerebrovascular responsiveness, is unexplored. Therefore, clinically relevant questions on hemodynamic changes in the disease cannot be meaningfully contemplated. To address these enquiries and to confidently assess the hemodynamic changes and cerebrovascular reactivity in

hypertension, the reliability of fNIRS measured hemodynamic changes in different postures must be established.

The purposes of the present study were to: (1) examine the test-retest reliability of hemodynamic responses in a group of normotensive and stage 1 hypertensive participants, and (2) compare cerebrovascular reactivity, as determined by hemodynamic responsiveness, between these two groups during CO_2 rebreathing and positional stress. It was hypothesized that: (1) the hemodynamic responses of oxygenation (O_2Hb), deoxygenation (HHb), total blood volume changes (tHb), hemoglobin difference (HbDiff), as well as CO_2 reactivity scores for O_2Hb and tHb would be reproducible in the two groups; and (2) CO_2 cerebrovascular reactivity scores for O_2Hb and tHb would be significantly impaired in the hypertensives compared to the normotensives.

Methods and Procedures

Participant Recruitment and Inclusion/Exclusion Criteria

In order to recruit participants, several community organizations around the city of Edmonton were contacted and information sessions pertaining to the study were conducted between January 2012 and April 2013. As well, posters were placed at strategic locations at the University of Alberta campus and health clinics in south Edmonton requesting those interested in the study to contact the laboratory. The inclusion/exclusion criteria for the participants are summarized in Table 3.1. Recruitment was limited to males since the impact of gender on hemodynamic responses is unclear (Kastrup, Tie-Qiang, Glover, Kruger, & Moseley, 1999; Yang et al., 2009; Li, Luo, & Gong, 2010). The use of antihypertensive medication did not preclude

participation in the study. Potential participants contacted the laboratory by email or phone to clarify eligibility, and where appropriate, to book a time for testing.

Sample Size

Twenty four normotensive and 16 stage 1 hypertensive males in the age range 19 – 55yrs participated in this study. The hypertensive group included males with physician-reported controlled essential hypertension only (i.e. hypertension of no known cause). All participants were fluent in the English language and were right hand dominant except for two normotensives and one hypertensive. See Table 3.2 for a summary of salient participant characteristics. The calculated sample size based on effect size estimates of a similar study (Gatto, Hoffman, Mueller, Paisansathan, & Charbel, 2007) was 25 participants for each group with an estimated statistical power of 0.91.

Tests and Procedures

All the participants provided written informed consent (Appendix B.1 and C.1) prior to any testing which was conducted at the Work Physiology Laboratory, Faculty of Rehabilitation Medicine at the University of Alberta. Participants were advised to avoid a heavy meal and caffeinated drinks for two hours before testing. Each participant arrived one hour prior to test time in order to complete required forms and to be familiarized with test equipment and procedures. Each participant then completed the Medication History Form (Appendix D.1), Code for Physical Activity (Appendix E) and the Beck Depression Inventory, BDI II (Beck, Steer, & Brown, 1996). The examiner advised each participant that he may withdraw from the study at any time without percussions. Participant height, weight, head circumference, resting heart

rate and blood pressure were then measured using standard techniques (ACSM, 2010). In order to examine the inter-session reliability of the hemodynamic responses, each participant completed two test sessions approximately one week apart. During each test session, the procedures described below were repeated to examine the intra-session reliability of the hemodynamic responses. The experimental procedures were approved by the Health Research Ethics Board of the University of Alberta (Appendix F.1, F.2).

Participant Preparation

fNIRS optodes were attached bilaterally to the participant's forehead (Appendix G.1) just rostral to the supraorbital ridge with an emitter-detector distance of 4.5cm for each pair (Vermeij, van Beek, Olde Rikkert, Claassen, & Kessels, 2012; Bhambhani, Maikala, Farag, & Rowland, 2006; Obrig et al., 1996).There was a distance of 2-3cm on either side of midline for each optode pairing, the centre of which corresponded to FP1 and FP2 on the 10-20 International System (Jasper, 1957). These positions are thought to obtain the best signals from the dorsolateral prefrontal cortex (PFC) (Okamoto et al., 2004). The chest strap to monitor the heart rate with a remote device (Polar Global CS100, Finland) was then secured, followed by the blood pressure cuff placed on the left arm of the participant. To monitor end tidal CO_2, participants were attached to a metabolic cart (VMax 20, Sensormedics, USA) by a leak-free mask with a two way Hans Rudolph valve.

Test Protocol

Participants were randomly assigned to a starting position; either standing or supine lying on a plinth (head elevated 10 – 15 degrees from the horizontal on a firm pillow) (Appendix G.2).

Blood pressure was monitored in the starting position using the auscultatory method after a five minute rest. fNIRS recording began with the baseline, resting in the starting position for two minutes, and continued throughout testing. After baseline, the participant was asked to breathe for 30 to 90 seconds from a black 5L anaesthetic bag containing 5% CO_2 and balance N_2 via the Hans Rudolph valve attached to the metabolic cart. The time of rebreathing corresponded with the time that increase in cerebral blood flow would be detectable and time to reach steady state $PaCO_2$ (Shapiro, Wasserman, Patterson & Richmond, 1965) without participant discomfort. The participant was then moved from the original starting position to a new position of either supine lying or standing. This change in position took 15 – 20 seconds, and the participant remained in the new position for a further 3 minutes. The three minute timeframe was identical to the established physiological test for position change in orthostatic evaluation (Poda et al., 2012; Naschitz & Rosner, 2007). End tidal CO_2 was monitored during this period by the metabolic cart; blood pressure at the left arm was re-measured at the end of the trial. This procedure was repeated in the same session after five minutes of rest with mask removed. The entire procedure was repeated in a second session seven days later. See Figure 3.1 for the test protocol.

Cardiorespiratory Measurements

The VMax 20 machine was calibrated prior to each test according to manufacturer's specifications. The oxygen and carbon dioxide analyzers were calibrated using precision medical gases (4%CO_2, 16%O_2, balance N_2; and 0%CO_2, 26%O_2, balance N_2). The pneumotach was

calibrated for volume using a 3L syringe. Metabolic measurements were recorded in the breath by breath mode throughout each test session simultaneously with the fNIRS measurements.

Functional Near Infrared Spectroscopy Measurements and Data Analysis

O_2Hb, tHb, HHb and HbDiff changes were monitored simultaneously from the left and right prefrontal lobes using a continuous wave dual channel fNIRS machine (Artinis Oxymon Mk IV, Netherlands) with wavelength of 760 and 850nm (Boecker, Buecheler, Schroeter & Gauggel, 2007; Schroeter, Zysset & von Cramon, 2004). These hemodynamic responses were calculated from changes in optical density at the two wavelengths with the application of the principles of the modified Beer-Lambert law utilizing the manufacturer supplied software (Artinis Oxymon MKIV, Netherlands). The emitter-detector distance of 4.5cm corresponded to fNIRS penetration depth of approximately 2.7cm (Minati, Kress, Visani, Medford, & Critchley, 2011; Cui, Bray, Bryant, Glover, & Reiss, 2011) which was sufficient to reflect changes in prefrontal cortical grey matter (Fischl & Dale, 2000; Perrey, 2008). fNIRS sampling from both the left and right prefrontal lobes was conducted at 10Hz. The predetermined events were inserted in the fNIRS output for subsequent analysis. A moving average of five samples per second was applied to the output to smooth the traces of the four hemodynamic variables. Delta values (peak minus baseline) were obtained from the output trace and calculated for each variable. The peak used was that identified in the second (new) position (standing or supine lying for three minutes) after rebreathing. Delta values for end tidal CO_2 were calculated as follows: peak end tidal CO_2 in the new position after rebreathing CO_2 minus (-) resting end tidal CO_2 during baseline in the starting position. The use of delta values for hemodynamic measures in this experiment was

consistent with the practice for continuous wave fNIRS measurement (Hoshi et al., 2003; Cummings, Swart & Ainslie, 2007; Scholkmann et al., 2014).

Calculation of CO_2 Reactivity

According to the method described by Cummings, Swart and Ainslie (2007), the reactivity of hemodynamic responses to the hypercapnic challenge and postural change was calculated as the relative change from baseline in the values of O_2Hb and tHb (delta values) per increase in end tidal CO_2.This approach to calculating CO_2 reactivity is consistent with the research of Hajjar et al. (2010) who used blood flow as a function of end tidal CO_2 in calculating cerebral vaso-reactivity.

Statistical Analysis

Normality of the data were initially exmained using the Shapiro-Wilks test. Independent t-tests were used to compare the mean characteristics of the normotensive and hypertensive participants. To examine the differences and interaction between the repeated trials and side of the PFC in the hypertensive and normotensive groups, a three way (Group X Side X Trial) repeated measures analysis of covariance (ANCOVA) was performed for each of the four hemodynamic changes. To address concerns on scalp to cortex distance biasing fNIRS measurements, head circumference was used as a covariate for all comparisons between the groups, as advocated by Hauessinger et al. (2011). Test-retest reliability was calculated for all four hemodynamic variables in the groups using the two-way mixed intra-class correlation coefficient (ICC). This reliability was examined between the two trials in one session and between the two sessions using mean values for each trial. Bland-Altman analyses (Bland &

Altman, 1999) were performed using the MedCalc software (MedCalc version 13.1, Belgium) to verify the agreement of the hemodynamic responses in the trials. This procedure is a plot of the differences between two trials against their averages. A horizontal line represents the mean difference and the limits of agreement are defined as the mean difference ±1.96SD either side of the line (Bland & Altman, 1999). Data points outside the limits of agreement on these plots were considered as outliers. Common variance and derived regression equations were obtained from Pearson correlations between the two trials within the session.

To compare hemodynamic reactivity between the groups, 13 hypertensives were first matched on age levels with 13 normotensives, as advocated by Green and Salkind (Green & Salkind, 2011). ICCs of the reactivity scores of both groups were then calculated for the O_2Hb and tHb variables. Thereafter, a repeated measures MANCOVA (head circumference included as a covariate) was performed to compare the two groups with the dependent variables of CO_2 reactivity calculated for O_2Hb and tHb. 'F' ratios were adjusted using the Greenhouse-Geisser procedure and the Bonferroni correction was applied to control Type 1 error. Statistical significance was established at an α level of 0.05. Statistical analyses were completed with the Statistical Package for the Social Sciences, Version 21 (SPSS, Inc, Chicago, USA).

Results

Participant Characteristics

Relevant physical characteristics of the two groups are presented in Table 3.2. After matching on age levels there was no significant difference between the groups on BMI, head circumference, years of formal education, and BDI II scores. However resting systolic and

diastolic blood pressure were significantly higher in the hypertensive group (P<.05). The time period from the initial hypertension diagnosis to testing ranged from 1 - 20 years (mean 5.53 ± 5.59). Five hypertensive participants were taking calcium channel blockers while another seven were on angiotensin receptor blockers. Four other particpants were being treated with a combination of medication including angiotensin converting enzyme inhibitors and diuretics. They were evenly split on the usual time of day for taking the medication - morning or evening.

Hemodynamic Trends during CO_2 Rebreathing and Positional Change in Hypertensives and Normotensives

Traces of the hemodynamic trends in the two conditions, (1) standing-supine lying and (2) supine lying-standing, are represented for both groups in Figure 3.4. The trends were similar for both groups with higher concentrations noted for the normotensives, though it should be cautioned that comparing traces across groups may not be accurate in fNIRS measurment (Hoshi, 2003). During baseline, the trace exhibited a stable and uniform pattern with minimal change in O_2Hb, tHb, HbDiff and HHb. During CO_2 rebreathing, fNIRS trace concentrations of the first three variables systematically increased during the 30 - 90 seconds and peaked in the supine lying-standing condition immediately prior to the participant being moved to standing. After standing, there was a sharp decline in the first three variables (O_2Hb, tHb, HbDiff) towards baseline. HHb remained relatively unchanged in the rebreathing procedure and across both positions. During the standing-supine lying condition, the initial trend during baseline and CO_2 rebreathing was similar to the other condition. However when moved to supine lying there was a sharp systematic increase in O_2Hb, tHb and HbDiff. These variables remained elevated for

more than the three minutes of supine lying while trending towards the baseline. In both conditions and groups there was a trend for O_2Hb and tHb to parallel each other in the trace.

Similar to the hemodynamic responses, the end tidal CO_2 rose during the rebreathing and continued to increase until peak in the standing-supine lying condition for a further 110 seconds in the normotensives and 156 seconds in the hypertensives. In the supine lying-standing condition, end tidal CO_2 continued to rise until peak for a further 102 seconds in the normotensives and a further 135 seconds in the hypertensives after rebreathing termination. In both conditions, end tidal CO_2 returned to baseline within three minutes in the two groups. A comparison of the times to achieve peak end tidal CO_2 and peak O_2Hb in both conditions across the groups are demonstrated in Figure 3.5.

Reliability of Hemodynamic Responses in Normotensive and Hypertensive Participants

The three way analysis of covariance was interpreted as per the procedure described by Keppel and Wickens (2004). If no three way interaction (Group X Side X Trial) was identified a two way interaction was examined (Group X Side) to compare the groups across sides. With no further significant interaction or main effect of side, both sides were pooled thus doubling the number of sample measurements. There was no significant interaction or group differences on the three way repeated measures ANCOVA (Group x Side x Trial) for any of the hemodynamic responses, and the use of head circumference as a covariate did not affect the results. The trial-retrial and intersession ICCs for the four hemodynamic variables in the two body positions with right and left sides pooled are reported in Table 3.3. The trial-retrial ICC for O_2Hb in the normotensive group ranged from 0.630 (P=.018) to 0.901 (P<.000) in the supine lying-standing

condition. In the hypertensive group, trial-retrial ICC in O_2Hb ranged from 0 .627(P=.044) to 0.823 (P<.000) across the two conditions.

The trial-retrial ICC in the normotensive for tHb ranged from 0.646 (P=.014) to 0.806 (P<.000) across both conditions. In the hypertensive group the ranges for tHb were from 0.610 (P=.051) to 0.900 (P<.000) across both conditions. For the HHb and HbDiff variables, as noted in Table 3.3, all ICCs within each group were moderate to high with α levels <.05.

Bland-Altman plots for O_2Hb and tHb in normotensive and hypertensive groups are illustrated in Figure 3.2A, B. For both groups, the data points in the plots clustered around the horizontal line of mean difference and no systematic bias was evident. In the normotensive group, there was one outlier above and below the 95% confidence interval for tHb during standing-supine lying. In the hypertensive group, there were no outliers for O_2Hb in standing-supine lying. All the other plots were characterized by a single outlier across all conditions in both hypertensive and normotensive groups. The removal of the outliers did not affect the significance level of any of the ICCs. Figure 3.3A, B illustrates representative scatterplots, common variance and regression equations for both groups on the O_2Hb and tHb variables.

ICCs of reactivity scores in the normotensive group, across both the O_2Hb and tHb variables, was higher in the standing-supine lying trial-retrial with ranges of 0.68 (P=.003) to 0.762 (P=.000). The trial-retrial ICC for the normotensive in the supine lying-standing condition ranged from 0.438 to 0.520 (P=.059). For the hypertensive group, ICCs across both conditions and variables ranged from 0.643 (P=.037) to 0.870 (P<.000).

Comparison of Reactivity Measures for Oxyhemoglobin and Total Hemoglobin between Normotensive and Hypertensive Groups

Figure 3.6A, B illustrates the trends in cerebrovascular reactivity in both groups. The hemodynamic reactivity measures, for O_2Hb and tHb, as compared on the repeated measures MANCOVA, showed a non-significant higher normotensive score for both positions (P>.05). An additional estimate of reactivity of the cardiorespiratory system is the time to peak changes in end tidal CO_2, and in the case of PFC reactivity, time of change in hemodynamic responses. Figure 3.5 is an illustration of the times to peak concentration levels for both O_2Hb and peak end tidal CO_2 in the two groups. Group differences were not significant on these variables.

Discussion

The association of hypertension with alteration in cerebrovascular reserve and consequent impairment in cognitive function (Hajjar et al., 2010) demands appropriate measurement techniques to chart disease impact and changes over time. In this context, establishing the reliability of the prefrontal hemodynamic responses during fNIRS in different postures will be an important contribution to the current research in the area. The main findings of this study were: (1) the test-retest and intersession reliability of the hemodynamic responses is moderate to high in both normotensive and hypertensive participants; (2) similarly test- retest of CO_2 reactivity scores were moderate in both groups, and there were no significant differences between the two groups for the CO_2 reactivity measures during postural changes. The physiological and clinical implications of these findings are discussed below.

Reliability of Hemodynamic Responses in Normotensives and Hypertensives

Supporting the initial hypothesis of this study, hemodynamic responses over the PFC, as measured by fNIRS, were reproducible in both normotensive and hypertensive groups. This reliability was demonstrated for both the within session and intersession trials conducted seven days apart. To our knowledge, this is the first study to demonstrate the reproducibility of fNIRS-measured PFC hemodynamic responses in normotensive and hypertensive participants. There was also moderate level test-retest reliability noted for CO_2 reactivity scores. Over the past twenty years of fNIRS research, the five areas of emphasis according to Ferrari and Quaresima (2012) included neurology, psychiatry, education, psychology and basic research. There has been minimal attention given to cerebrovascular reactivity changes in highly impactful conditions such as hypertension. This is a major oversight. The findings of the present study establish the reliability of fNIRS as a technique in assessing the disease and in part address the current shortfall in research. This is an important development if the functional limitations resulting from hypertension are to be reliably measured as a prelude to guiding appropriate therapies.

Additionally, this study focussed on relatively young men with stage 1 hypertension and was designed to present stresses on the cerebral circulation that would identify changes in hemodynamic responsiveness relevant to function. In Canada, 40% of those above 25 years old have hypertension. Of this group, young males in the prime of their productive lives are less likely to be aware of their disease, and thus more likely to go untreated (Campbell et al., 2012). To this end, being able to reliably measure hemodynamic responses to various stressors in this

group of hypertensives may help to reinforce the urgency for intervention which in turn may ameliorate ensuing disability.

The use of postural changes combined with the known vasodilator of cerebral circulation, CO_2, provided a unique approach to stressing the cerebrovascular reserve. Bright, Donahue, Duyn, Jezzard and Bulte (2011) demonstrated that in a "pre-dilated" state of the cerebral circulation, such as after experimental hypercapnia, the vasoconstrictive reactivity to hypocapnia is enhanced throughout the gray matter. These researchers postulated that a higher vasodilation in the baseline state is known to naturally occur in some cerebrovascular diseases such as forms of stroke. They postulated that an enhanced vasoconstirctive tendency in the cerebral cortex that is seen in these patients is the result of the resting "pre-dilated" state in their cerebral vasculature. The approach in the present study utilized the aforementioned experimentally induced pre-dilated state with CO_2 rebreathing, and followed this state with orthostatic stress to determine hemodynamic reactivity in a group not previously tested in this manner. The approach attempted to focus on smooth muscle related issues of vascular compliance in the cerebral circulation that are possibly part of the hypertension-stroke continuum. The reliability of the hemodynamic responses using fNIRS as demonstrated in this study may provoke further novel approaches to testing, predicated on the impact of the disease on the microvascular cerebral circulation.

Hemodynamic Reactivity and Implications

Reactivity implies the readiness of the cerebrovascular circulation to adjust to the functional demands that necessitate dilatation or constriction of cerebral vasculature (Madden, 1993).

The second hypothesis in this study postulated an impaired hemodynamic reactivity in the hypertensive group. Statistical significance for this assertion was not achieved. However, there was a trend for decreased reactivity in the hypertensives for both test position changes and most remarkably with regard to tHb. The non-significant findings are possibly the result of a large age range in the groups, protracted time since initial hypertension diagnosis, and more importantly, stage 1 hypertensives may in fact have less impairment in reactivity than do severe hypertensives as reported by Hajjar et al. (2010). Nevertheless, the identified trends in this study appear to support prior research findings, using severe hypertensives, suggesting impaired cerebral vaso-reactivity (Ficzere et al., 1997; Hajjar et al., 2010). Additionally, in the hypertensives, there was a trend for longer time to peak for both O_2Hb and tHb responses. This was also the case for time to peak end tidal CO_2. These changes may be indicative of impairment in hypertensive cerebrovascular responsiveness which may be consistent with stiffness in vessels and a blunted nitric oxide response (Veglio et al., 2009).

The test positions in this study, standing-supine lying and its reverse, are standard orthostatic stress test positions (Naschitz & Rosner, 2007) designed to diagnose orthostatic hypotension. This is highly pertinent to chronic hypertensive patients in whom the cerebrovascular autoregulatory curve is shifted to the right (Veglio et al., 2009; Elias et al., 2012). This change assents to orthostatic symptoms indicative of cerebral hypoperfusion in hypertensives, namely, light-headedness and syncope, at perfusion pressures well above the lower limit of autoregulation in the normotensive (Naschitz and Rosner, 2007). Importantly, episodes of hypoperfusion that accompany orthostatic tress are predictive of ischemic stroke (Eigenbrodt et al., 2000). Poda et al. (2012), investigating postural hypotension and cognitive function,

reported impaired cognitive function while standing for three minutes in patients with neurogenic orthostatic hypotension. Though none of these patients had hypertension as the only diagnosis, the admixture of cerebral hypoperfusion, postural stress and impaired cognition in any population warrants comparison with hypertensive patients in whom the loss of cognitive abilities is becoming increasingly associated with the disease (Veglio et al., 2009).

The more sudden and dramatic complication of hypertension, however, is ischemic and hemorrhagic stroke. These conditions may result both from hypoperfusion and vessel rupture associated with excessive blood pressure (Naschitz & Rosner, 2007). In either case, the reserve in the cerebrovascular system is unable to accommodate the demands put on the system in part due to impaired vaso-reactivity. Such alteration in reactivity within cerebral circulation has been associated with the tendency for cerebrovascular accidents (strokes) to occur in the early morning, a time of day usually coinciding with impairment in cerebrovascular reactivity (Atkinson, Jones, & Ainslie, 2010). This diurnal effect on cerebrovascular reactivity may be additive in the case of hypertension, further increasing the likelihood of cerebrovascular accidents (Cummings, Swart & Ainslie, 2007). Contemplation of hemodynamic responsiveness associated with the disease may help alter approaches to complications and treatment in general. The subject population in this study, younger males, was chosen to identify PFC reactivity changes as a mark of cerebrovascular reserve that may presage decline in cognitive performance. Given that this life period is arguably the age of greatest productivity, any health deficits may be that much more socially significant.

Limitations of the Study

The testing of cerebrovascular reactivity was limited by low statistical power in the present study. Given the demonstrated trends and the importance of CO_2 reactivity as a measure of cerebrovascular reserve, further testing is warranted with a larger sample. In this regard, more attention should be paid to the length of time since diagnosis. The wide range used in this study, 1 -20 yrs, was a poorly explained variable in the impact of vessel changes that parallel duration of the disease (Veglio et al., 2009). Measurement of ischemic changes in the PFC with fMRI would strengthen this part of the study. Medication use may also affect vessel reactivity and should be controlled, where ethically feasible, in a subsequent experiment.

The device used was a continuous wave fNIRS machine which does not determine path-length of light in the illuminated tissue. Hence absolute hemodynamic values could not be used in the analysis; and the delta values, as used in the analysis of the present study, limit the ability to utilize findings. A time-resolved or frequency-resolved device would provide path-length information that permits use of absolute hemodynamic measures. This would provide unambiguous interpretation of the hemodynamic response impact in hypertension with more ready translation of findings into patient care.

Finally, confounding signals may arise from scalp circulation and arterial blood pressure thus obscuring PFC activation (Strangman et al., 2014). The magnitude of these effects are unknown in this study and requires being accounted for in a future examination of the subject.

Conclusions

In the present study, the robustness and versatility of fNIRS was demonstrated with strong reliability estimates of hemodynamic responses in a dual procedure of simultaneous CO_2 rebreathing and positional change in both normotensive and stage 1 hypertensive participants. Cerebrovascular reactivity in hypertensives, increasingly associated with cerebrovascular accidents and likely altered cognitive performance, was not significantly different from the normotensives, possibly due to a large age range and range of time since diagnosis in the hypertensives. However, given the noted trends in vaso-reactivity in this group of stage 1 hypertensives and that identified in severe hypertensives, further research is warranted to control for vaso-reactivity as a variable across levels of hypertension. The findings of the present study support the use of fNIRS as a neuroimaging technique that will promote understanding of cerebral hemodynamic responses under meaningful functional stresses.

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Table 3.1: Inclusion and exclusion criteria for the normotensive and hypertensive participants for reliability study

Group	Inclusion	Exclusion
Normotensive	• Males • Age 18 – 55 • No history of hypertension or cardiovascular disease • No history of neurological or psychiatric disorder	• Smoker • Regular use of prescription or non-prescription medication or illegal drugs • English language communication difficulty • Participating in similar study • Beck Depression Inventory (BDI II) score >13 (Beck, Steer & Brown, 1996).
Hypertensive	• Males • Age 18 – 55 • History of high blood pressure > 1 year – (confirmed by a physician licensed in the province of Alberta) • No history of dementia, stroke, heart attack or kidney disease • No history of neurological or psychiatric disorder	• Smoker • English language communication difficulty • Participating in similar study • Hypertension beyond stage 1 (above 159/99mmHg) (Chobanian et al., 2003), or hypertension deemed not to be fully controlled • Beck Depression Inventory (BDI II) score >13 (Beck, Steer & Brown, 1996).

Table 3.2: Participant characteristics for reliability study of normotensive and hypertensive males (Mean±SD)

Group	Age	Body Mass Index	Code of Physical Activity	Years of Formal Education	Resting Systolic BP (mmHg)	Resting Diastolic BP	Resting Heart rate (bpm)
Normo (N=24)	36.46±9.01	27.84±4.30	5.46±1.45	16.23±1.96	116.69±11.6	78.15±6.6	69.85±8.9
Hyper (N=16)	40.23±10.51	29.77±4.84	4.69±2.53	17.54±2.60	127.15±8.12*	83.54±6.17ʃ	72±11.18

Normo= normotensive; Hyper= hypertensive

*significant at P=.013 (hypertensive with higher resting SBP)

ʃsignificant at P=.042 (hypertensive with higher resting DBP)

Code for Physical Activity = /7 (as per Ross and Jackson, 1990).

Table 3.3: Test-retest reliability (ICC) of hemodynamic responses during CO_2 rebreathing and positional change in normotensive and hypertensive participants

Group (N= sample measurements with both sides pooled)	Position	Trial 1 vs Trial 2		Session 1 vs Session2
		Session1	Session 2	
		Oxy-hemoglobin		
Normotensive N=26	**Standing-Supine**	**.857****	**.855****	**.814****
N=20	Supine-Standing	.630*	.901**	.724**
Hypertensive N=14	Standing-Supine	.711*	.627*	697*
N=18	Supine-Standing	.762**	.823**	.560*
		Total Hemoglobin		
Normotensive N=26	Standing-Supine	.806**	.670**	.863**
N=20	Supine-Standing	.646*	.690**	.913**
Hypertensive N=14	Standing-Supine	.744**	.610*	.493
N=18	Supine-Standing	.787**	.900**	.690*
		Deoxy-hemoglobin		
Normotensive N=26	Standing-Supine	.862**	.631**	.665**
N=20	Supine-Standing	.780**	.654*	.779**
Hypertensive N=14	Standing-Supine	.727*	.780**	.798**
N=18	Supine-Standing	.882**	.644*	.899**
		Hemoglobin Difference		
Normotensive N=26	Standing-Supine	.933**	.504*	.702**
N=20	Supine-Standing	.770**	.744**	.675**
Hypertensive N=14	Standing-Supine	.826**	.811**	.652*
N=18	Supine-Standing	.824**	.704**	.685*

*P<.05; **P<.01

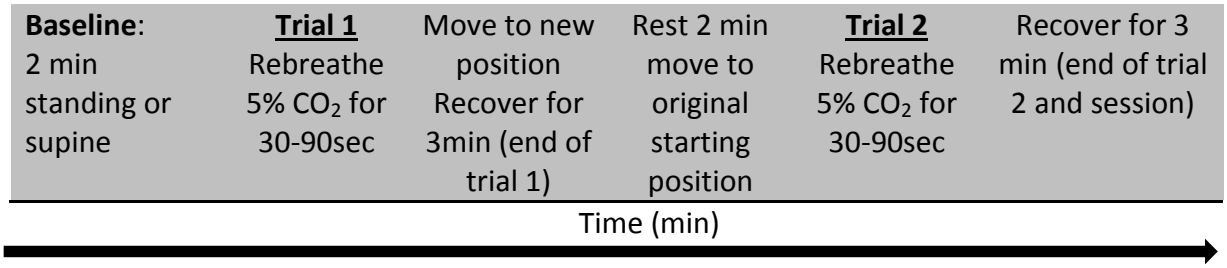

Figure 3.1: Test procedure for evaluating the reliability of two trials during one testing session in normotensive and hypertensive participants

Note: Participant completed two sessions to allow examination of intra-session and inter-session reliability. fNIRS and heart rate recording was throughout procedure; BP recorded before baseline and at end of each trial

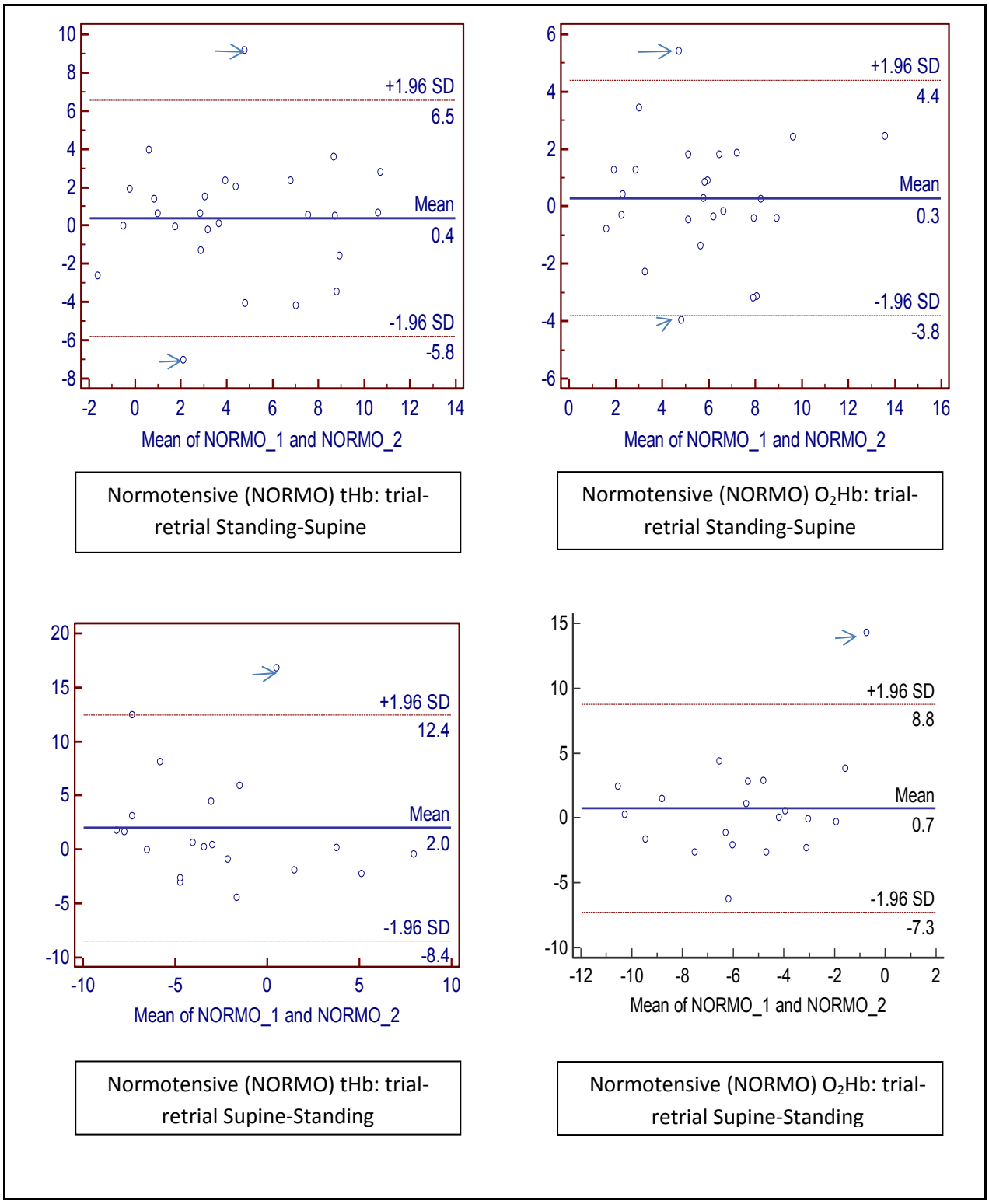

Figure 3.2A: Bland-Altman Plots of hemodynamic responses in normotensives during repeated trials of carbon dioxide rebreathing and postural change. Note outliers identified by arrows.

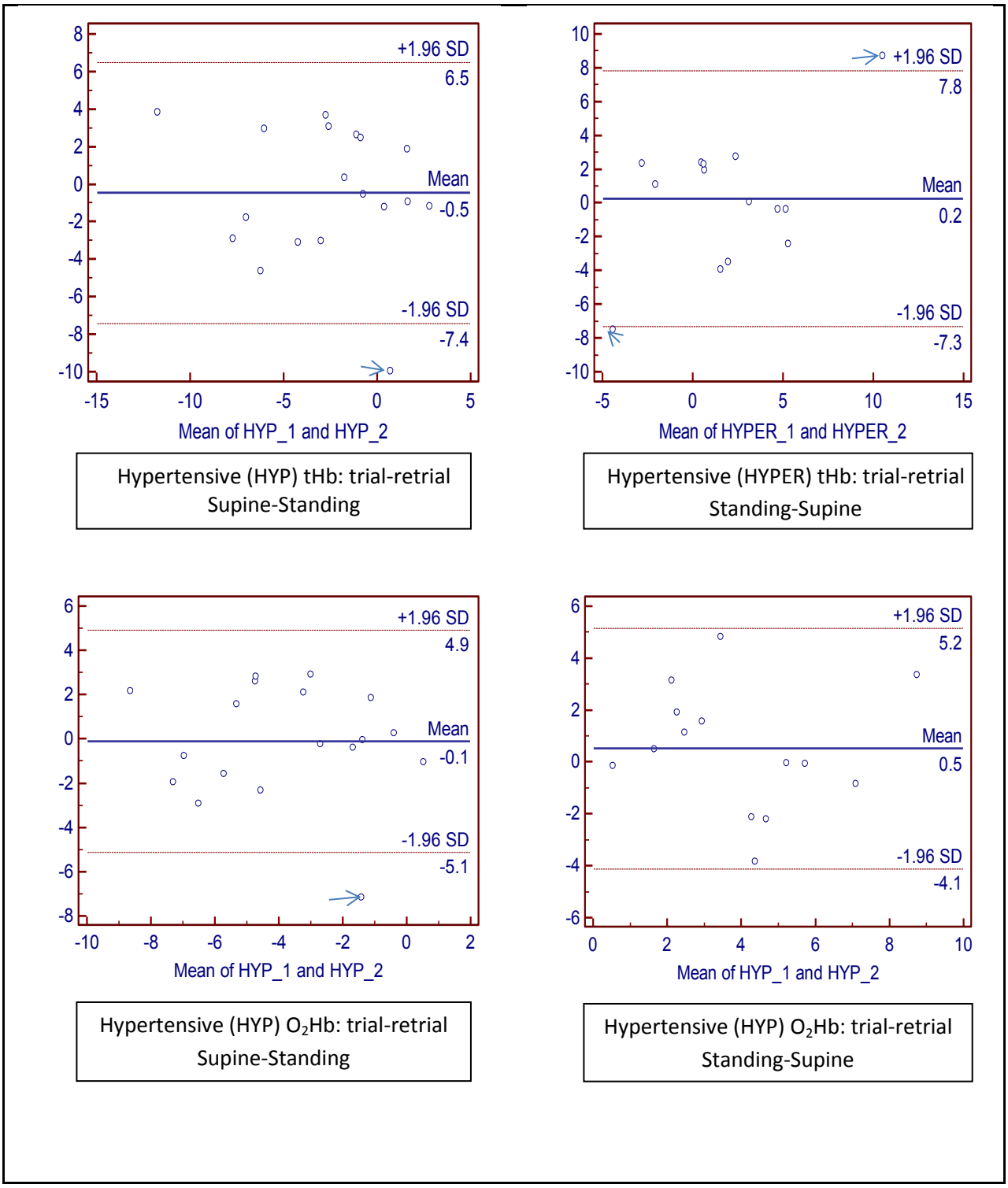

Figure 3.2B: Bland-Altman Plots of hemodynamic responses in hypertensives during repeated trials of carbon dioxide rebreathing and postural change. Note outliers identified by arrows.

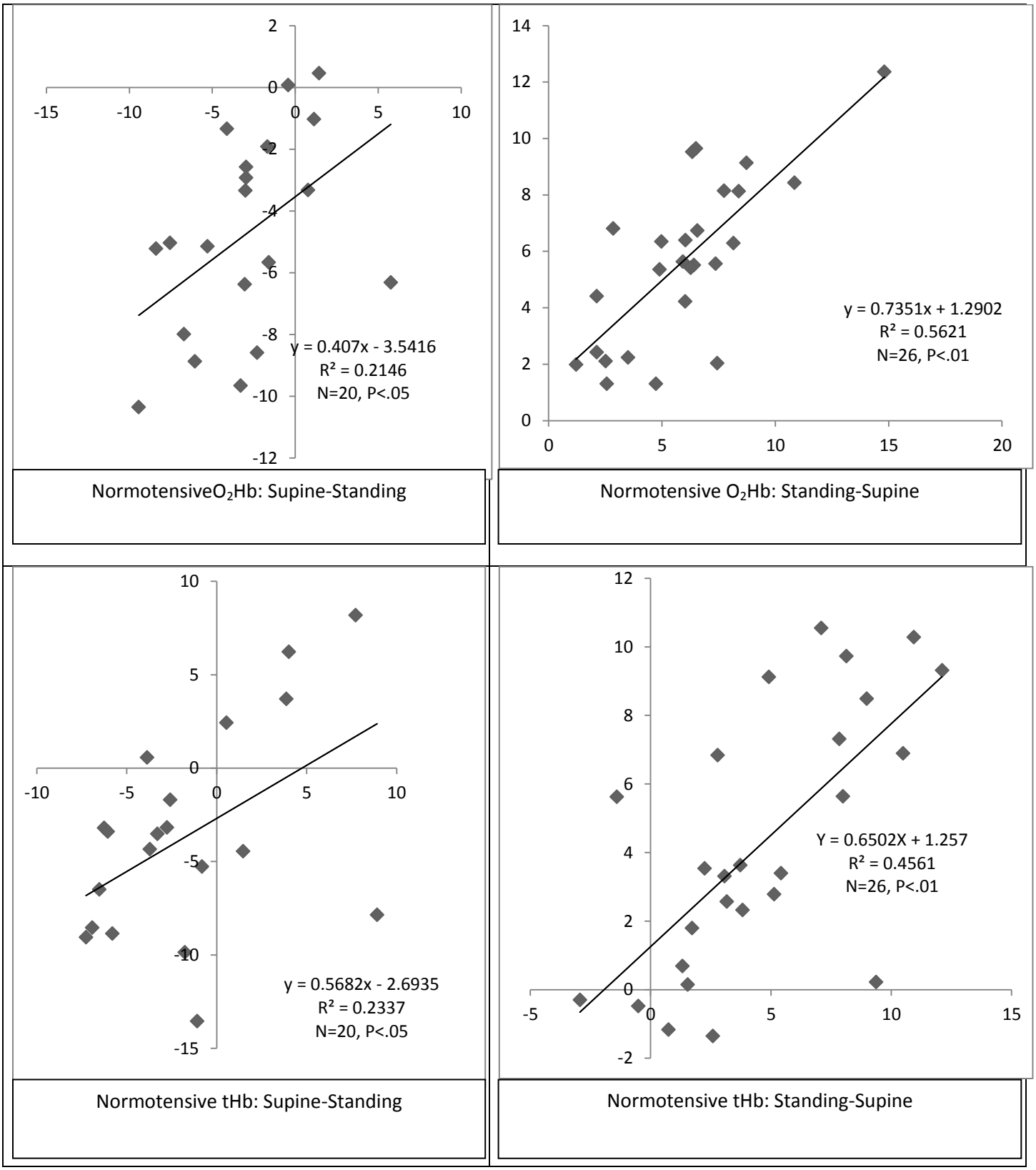

Figure 3.3A: Scatterplots of hemodynamic trial-retrial responses in normotensive participants with common variance and regression equation.

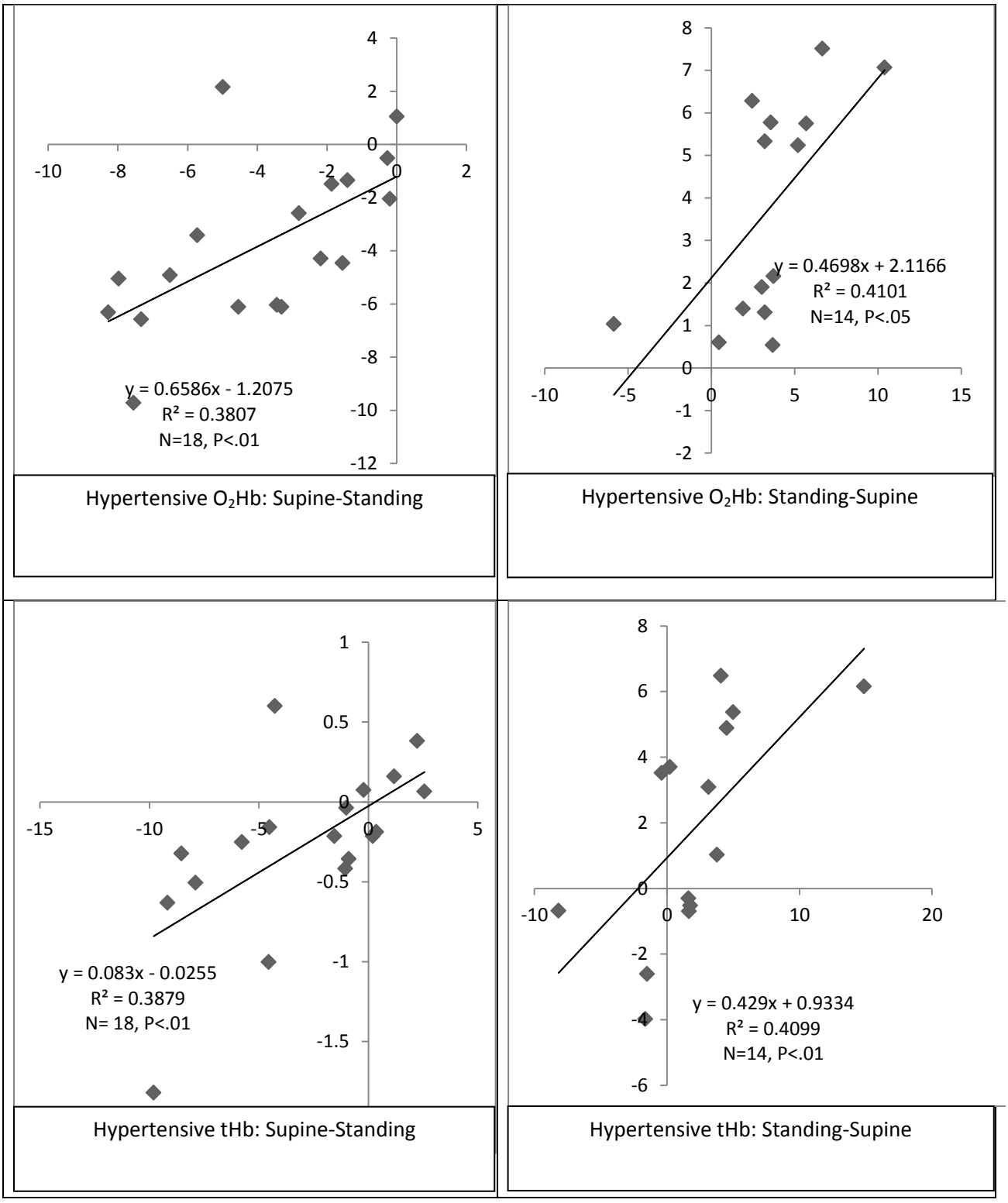

Figure 3.3B: Scatterplots of hemodynamic trial-retrial responses in hypertensive participants with common variance and regression equation.

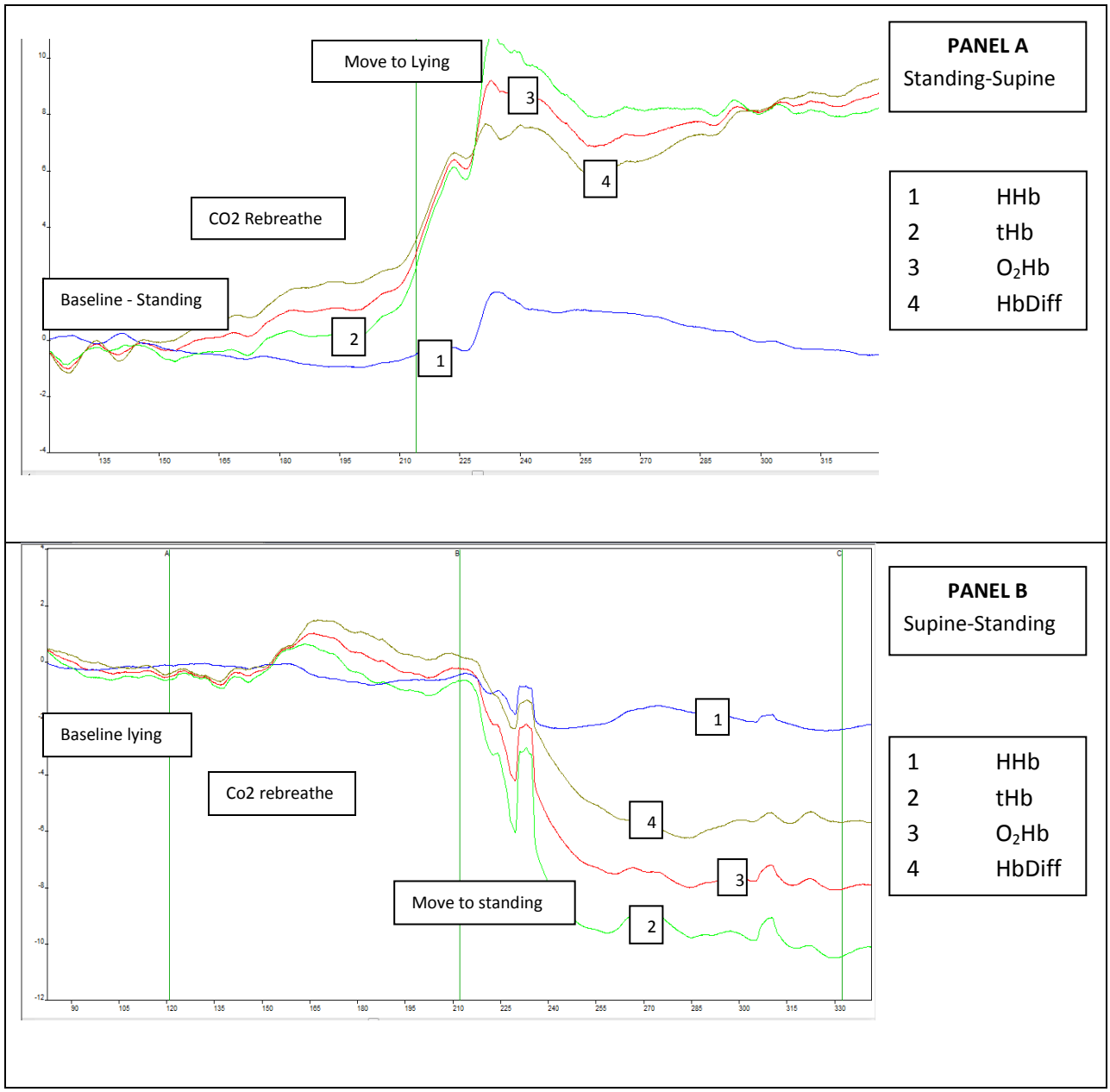

Figure 3.4: Representative traces during carbon dioxide rebreathing and postural change in a hypertensive participant.

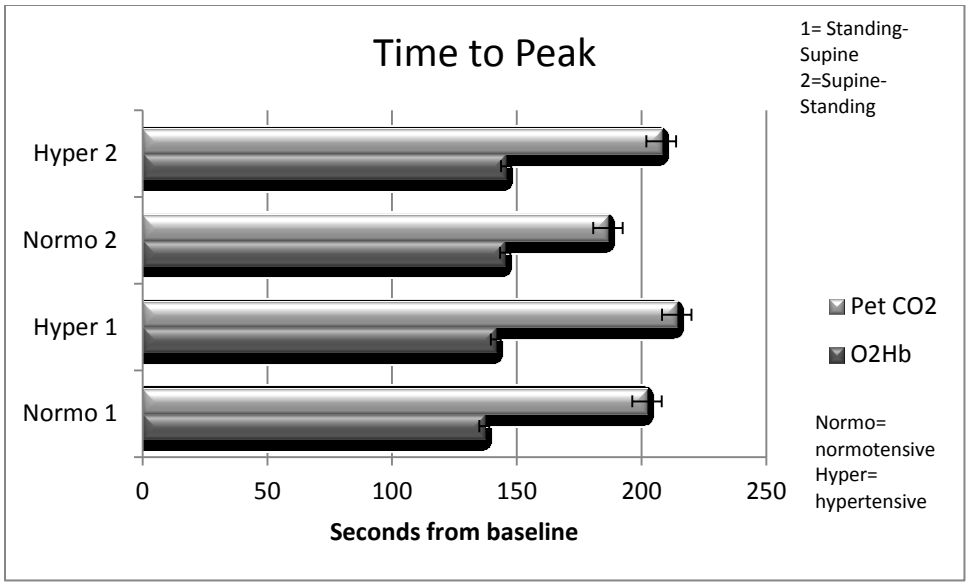

Figure 3.5: Time to peak end tidal CO_2 and O_2Hb in normotensive and hypertensive groups across trials.

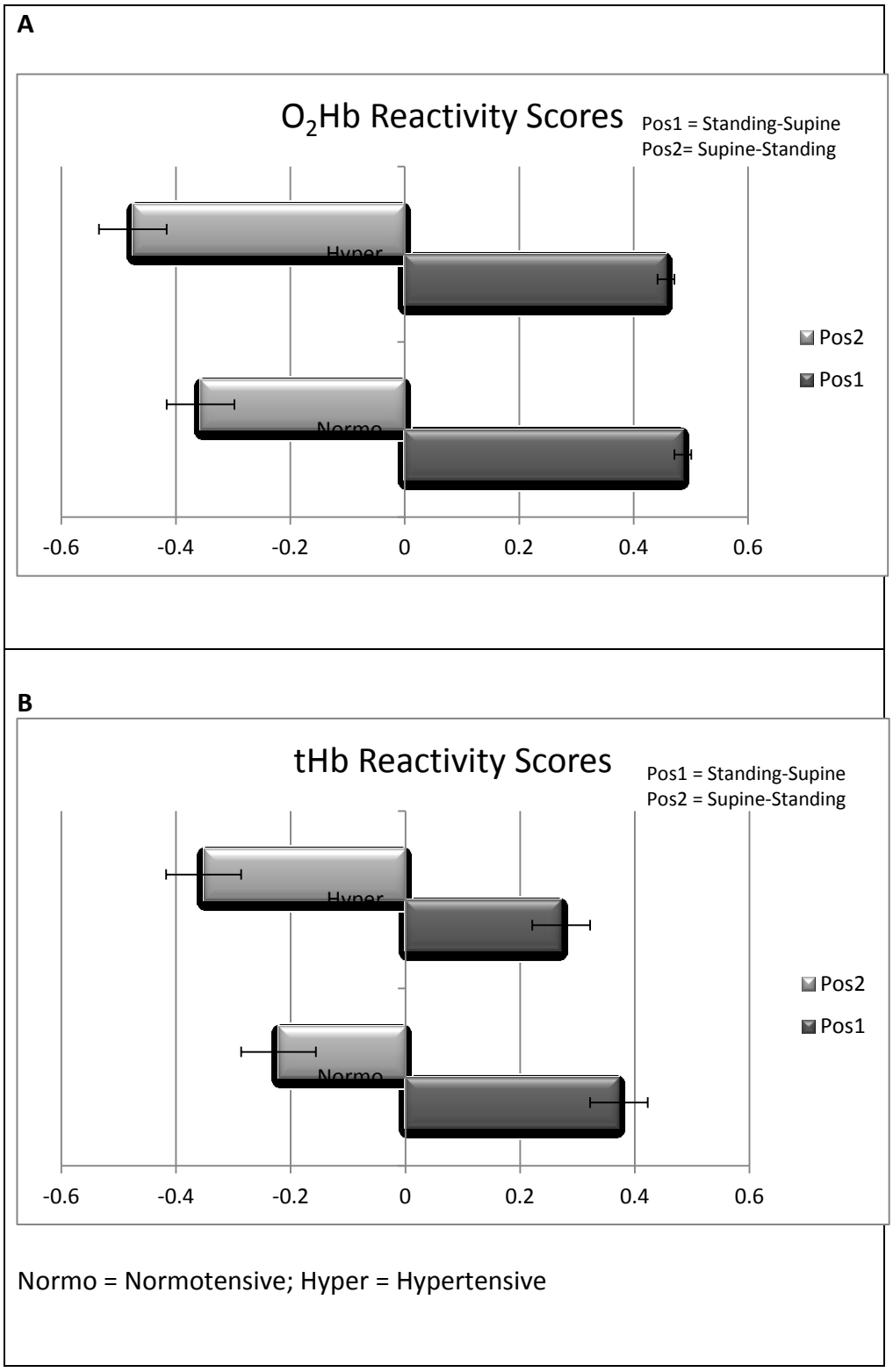

Figure 3.6A, B: Trends for O_2Hb and tHb reactivity scores in normotensive and hypertensive groups across trials.

Chapter 4

Hemodynamic Changes in the Prefrontal Cortex during Working Memory in Essential Hypertension

Introduction

As “the major player” in cerebrovascular disease, hypertension is the most important modifiable risk factor for brain dysfunction (Veglio et al., 2009). Even prior to the onset of complications, however, abnormally high blood pressure negatively affects the ability of the cerebrovascular system to distribute blood (Novak & Hajjar, 2010; Qiu, Winblad, & Fratiglioni, 2005). Generally, human cognition is accompanied by increased neuronal activity in the brain necessitating modulations in cerebral blood flow (Novak & Hajjar, 2010). For the most part, these changes, which are supported by neurovascular coupling, are commensurate with the needs of the particular task being performed (Bari et al., 2012). Such activity results in adjustments in cerebral hemodynamics to distribute nutrients in order to address the energy needs of active neurons. The efficiency in adjusting to these demands on human cognition is a measure of the vasodilatory reserve, that is, the ability within the cerebrovascular system to accommodate to blood flow needs (Fabiani et al., 2014). This reserve is a potential biomarker which can be expressed as a hemodynamic index. Such an index may highlight the relationship between hypertension-related microvascular changes and its impact on human cognition (Suhr & Chelberg, 2013).

In addition to its known complications, hypertension in middle age years is increasingly being correlated with later life cognitive impairment (Launer et al., 2010; Igase, Kohara, & Miki, 2012). Further, important clinical and epidemiological studies have identified otherwise

uncomplicated hypertension as an explanation for impaired performances on some cognitive tests regardless of age (Unverzagt et al., 2011; Elias, Goodell, & Dore, 2012). Such cognitive underperformance associated with hypertension may be caused by a reduction in the pertinent reserve of the cerebrovascular system. This is likely a direct result of the small vessel disease process, typical of the pathophysiology of hypertension (Grossman & Messerli, 1992; Schmeider, 2010). Such vascular manifestations of the disease are characterized by endothelial dysfunction and decreased perfusion to cortical tissue (Kitagawa et al., 2009). Hence, the energy demands of increased neuronal activity are deficient. To appropriately investigate the disease, the nexus between neurovascular changes in hypertension and cognitive function should be examined. Working memory presents such an opportunity.

Working Memory

Working memory is a functional measure of cerebral neuronal activity and is critical to all higher cognitive processes (Miller & Cohen, 2001; Buehner, Krumm, Ziegler, & Pluecken, 2006). It is the ability to keep specific information in mind while using that information to complete a task or manipulate a thought. This ability to resist distractions and avoid impulsive behavior is the foundation of "executive function", that is, our ability to plan ahead and effectively solve problems (Kupferman, Lande, Adams, & Pavlakis, 2013).

According to Baddeley (2003), basic working memory consists of several broad processes. These may include the so-called phonological loop, visuo-spatial sketchpad, and the central executive. The phonological loop, or phonological short term memory, is a rapidly decaying memory trace in which words and numbers can be maintained to help direct action or further a thought.

Evaluating this ability is an important part of the neuropsychological clinical workup (Gregory, 2011). The Wechsler Adult Intelligence Test (WAIS IV) (Pearson Education Inc., 2008) includes the digit span task as an important segment in the test of phonological working memory. The task consists of repeating and manipulating numbers spoken by an examiner in a prescribed ordered fashion. Several studies using Positron Emission Tomography (PET) (Gerton et al., 2004), Functional Magnetic Resonance Imaging (fMRI) (Sun et al., 2005) and more recently functional near infrared spectroscopy (fNIRS) (Kaneko et al., 2011) have demonstrated cortical activation of the prefrontal cortex (PFC) during the digit span task. Further, an increasing number of investigations using the digit span task have shown deficits in brain activation in conditions as varied as schizophrenia, Alzheimer's disease and Parkinson's disease (Twamley, Palmer, Jeste, Taylor, & Heaton, 2006; Conklin, Curtis, Katsanis, & Iacono, 2000; Tamura, Kikuchi, Otsuki, Kitagawa, & Tashiro, 2003). These activation patterns may be altered under increasing cognitive load (Fishburn, Norr, Medvedev, & Vaidya, 2014). However, to our knowledge, loading of the digit span task with other neuropsychological tests has not been used in testing working memory in uncomplicated hypertension.

Another neuropsychological test of phonological working memory is the Auditory Consonant Trigrams (CCC). Also known as the Brown-Peterson procedure, it is designed to evaluate working memory and divided attention capacity (Mertens, Gagnon, Coulombe, & Messier, 2006), which have been reported to be deficient in hypertension (Scullin et al., 2013). CCC involves having the examinee recall three consonants spoken by the examiner after counting backwards for a specific delay period. The test is designed to present a brief distraction while requiring retention of information (Spreen & Strauss, 1998), a necessity in normal daily activity.

Researchers, (Parkin & Walter, 1991; Kopelman & Stanhope, 1997), report that CCC is particularly sensitive to changes in the frontal lobe including deficits in information processing.

Furthermore, with respect to information processing and hypertension, Swan and colleagues (1998) have suggested that the disease might be more selective to specific cognitive domains in those yet unaffected by stroke or dementia. Additionally, there is also a suggestion that hypertension impairs mainly elemental memory processes (Kupferman et al., 2013). The prefrontal region has been noted to atrophy more readily in hypertensive patients, when compared to other regions of the brain, and to the brain of normotensives (Gianaros, Greer, Ryan, & Jennings, 2006; Raz, Rodrigue, & Acker, 2003). These morphological changes, supported by the growing body of information describing decreased executive function in the disease (Elias, Goodell, & Dore, 2012) demand closer scrutiny. In this regard, investigating perfusion changes likely to accompany the small vessel disease process of hypertension is timely. To our knowledge an assessment of PFC hemodynamic changes in hypertension while performing CCC has not been done. Furthermore, using this test and the digit span test in tandem has not been reported.

Assessing Hemodynamic Function in Hypertension

The neurological substrates that support the cerebral changes accompanying hypertension are likely to be complex. Nonhuman experimental data (Moore et al., 2002) and information from human neuroimaging correlational research propose that hypertension might influence the PFC earlier and/or more extensively than other regions of the brain (Raz et al., 2003). Strongly associated with activity in the PFC are information processing, attention and recall (Kopelman &

Stanhope, 1997). These are essential components of working memory which are tested by both the digit span task and the CCC.

The hemodynamic changes in the PFC accompanying these tests of working memory can be evaluated by fNIRS. fNIRS uses near infrared light (700 -1300nm) over the cranium to measure changes in concentration of cortical oxyhemoglobin (O_2Hb)and deoxyhemoglobin (HHb) that accompany the neuronal activity coinciding with the cognitive task(s) (Villringer & Chance, 1997; Kubo et al., 2008; Sumitani et al., 2006; Hoshi et al., 2003). The results of this optical technique have been demonstrated to be highly correlated with those of fMRI in assessing superficial cortical activity (R =0.98) (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006; Ferrari & Quaresima, 2012). fNIRS is known to have high temporal resolution (Lloyd-Fox, Blasi, & Elwell, 2010) and is amenable to a variety of test situations of mental function including the set-up of the digit span task (Kaneko et al., 2011), and likely the CCC.

Prefrontal activation studies using fNIRS during the digit span task have been successfully conducted in healthy populations (Hoshi et al., 2000; Kaneko et al., 2011). Hoshi et al. reported levels of right side PFC activation to be associated with performance on the digit span backward task. Additionally, Kaneko and colleagues (2011) reported greater concentration of O_2Hb in the prefrontal lobe in general (left and right side) accompanying the digit span backward task. These studies, notably in healthy populations, report both conflicting and inconsistent results. Using repetitive transcranial magnetic stimulation, Aleman and van't Wout (2008) also suggested the right PFC to be important in better performance on the digit span task. However a previous study using fMRI (Sun et al., 2005) reported greater activation in the left PFC on the

digit span backward task. Similar hemodynamic testing in hypertension groups has not been done and the unique microvascular changes of PFC oxygenation and laterality that might accompany the disease is unexplored. Moreover, no comparisons can be made between hypertensive and healthy populations from a standpoint of hemodynamic changes. Thus, the functional deficits associated with hypertension are poorly elaborated and the theoretical foundation for therapeutic intervention, where necessary, is not robust.

Much of the work in hypertension and its theoretical framework involves the elderly (Novak & Hajjar, 2010; Anson & Paran, 2005). Thus the emphasis on function and human performance/productivity is minimal. Such an issue drives two important considerations. First, there are questions that relate to behavioral performance in memory and correspondent hemodynamic changes in the brain of hypertensives. The mental processing capacity evaluated by working memory is potentially a useful marker of the reserve in cognitive function. Second, there are additional questions regarding changes in side to side activity in the hemispheres during working memory. In hypertension, such changes may be related to compensation or adjustment as a consequence of microvascular changes in the disease. To advance the discussion on brain hemodynamics and memory function, this study focuses on a hypertensive population in arguably their most active and productive years (55 years and younger).

Purpose and Hypotheses

The purposes of this study were to: (1) compare the behavioral performance between normotensive and hypertensive male participants (55 years and younger), on four tests of working memory, (2)evaluate the hemodynamic changes occurring in the PFC during these

working memory tests in the two groups; (3) investigate the issue of laterality of the hemodynamic responses in the PFC; and (4) examine the relationship between working memory performance and the hemodynamic changes in the normotensive and hypertensive groups. We hypothesized that: (1) performance on the working memory tests would be significantly impaired in the hypertensive compared to the normotensive participants, (2) the changes in PFC oxygenation (O_2Hb) and total hemoglobin (tHb) would be significantly higher in the hypertensive compared to the normotensive group, (3) there would be significant differences between the right and left PFC for blood volume changes (tHb) during the working memory tests in both groups, and (4) the changes in O_2Hb and tHb would be significantly correlated with working memory performance in both groups.

Methods and Procedures

Participant Recruitment

Recruitment for this study lasted approximately 15 months (January 2012 – April 2013), and included normotensive and hypertensive males between 19 and 55 years. Participants were recruited from the University of Alberta, health clinics and community organizations in the wider Edmonton community. Only males were recruited for this study to preclude issues regarding gender and cerebral hemodynamics (Tanida, Sakatani, Takano, & Tagai, 2004; Li, Luo, & Gong, 2010). Use of high blood pressure medication did not preclude participation in the study. The characteristics of participants who were eligible for the study along with exclusion criteria are reported in Table 4.1.

Sample Size and Participant Characteristics

The intended sample size of this study was 25 participants for each group which would correspond with estimated statistical power in excess of 0.93 (Portney & Watkins, 2008). Written informed consent (Appendix B.1, C.2) was obtained from 25 normotensive and 15 hypertensive males. There were eight hypertensives (of a total of 23) that agreed to participate but did not complete the test. Seven of the hypertensives were on medically prescribed angiotensin receptor blockers, five on calcium channel blockers, while the others were on a combination of angiotensin converting enzyme inhibitors and diuretics. See Table 4.2 for pertinent characteristics of the participants that completed the study. All participants were right hand dominant except for one in either group. They were fluent in the English language and had resided in the Edmonton region for at least two years. Both groups were composed of a cross-section of the ethnic subpopulations that comprise the local community. Levels of education ranged from 13 to 21 years of formal education across the two groups with representation of all major occupational categories based on skill type as per National Occupational Classification (Statistics Canada, 2011).

Tests and Procedures

Procedures of testing were approved by Health Research Ethics Board, University of Alberta (Appendix F.1, F.2). Volunteers who felt that they met the inclusion criteria contacted the laboratory by email or phone. At the time of contact, participants were informed of the purpose of the study and the eligibility criteria explained. If the volunteer was deemed eligible for the study, a mutually acceptable testing time was scheduled.

All participants were instructed to avoid a heavy meal for more than four hours prior to the test, and to refrain from caffeinated drinks for at least two hours before testing. Participants arrived approximately one hour before test time and were informed of the purposes and risks of the study. Each participant was encouraged to ask questions about the study and was also advised of his right to stop the test at any time without repercussions. It was made clear to the participant that he should immediately report any discomfort to the examiner during testing. Participants were also advised of a post-test interview and debriefing to answer questions about the procedure. Next, the participant's weight, height, cranial circumference, resting heart rate and blood pressure was measured (American College of Sports Medicine, 2010). The participant then completed the Beck Depression Inventory (BDI- II) (Beck, Steer & Brown, 1996) and if no contra-indications were identified, he was then oriented to the equipment by the examiner. The typical testing period lasted approximately 75 minutes.

The working memory tests consisted of the three part digit span task and the CCC which were randomly ordered / counterbalanced and conducted in sitting. Resting blood pressure was monitored using the auscultatory method at the left arm in a sitting position (ACSM, 2010). Heart rate was monitored throughout testing with a wireless monitor and chest strap (Polar Global 100, Finland). The examiner encouraged all participants to give their best effort. However, aside from confirming that test instructions were understood with a brief trial for each test, no attempt was made to coach participants on the use of memory or recall strategies.

(1)The Digit Span Task (Sattler, 2008)

The digit span task is comprised of three parts: the digit span forward task (DSF), the digit span backward task (DSB), and the digit span sequencing task (DSS). All parts of the test procedure, including stopping rules and scoring, were followed as per the test manual - (WAIS IV, Pearson Education Inc., 2008). In the DSF the examiner reads aloud a number of increasing digit span starting with two digits and comprising two numbers per sequence, up to a total of eight sequences. The number of digits in each sequence is progressively lengthened and concluding at the eighth sequence. The participant is asked each time to repeat aloud the numbers in exact order as told by the examiner. The stopping rule is that a participant will not continue with the DSF if he gives two incorrect answers in the same sequence, or if he completes all eight sequences. One point is issued per correct response given by the examinee for a potential total of 16 points. Similarly, the DSB consisted of eight sequences of two numbers of increasing digit span. In this task the participant is asked to respond with an exact reverse order of the digits spoken by the examiner. The stopping and scoring rules were the same as for the DSF. The DSS also included eight sequences of two numbers of progressively increasing digit span. The instructions were that the participant should reorder the digits spoken by the examiner starting with the lowest number and repeat the digits to the examiner starting with the lowest. The stopping and scoring rules were as for the other parts of the digit span task.

(2) The Auditory Consonant Trigrams (CCC) (Spreen & Strauss, 1998)

In the CCC the examiner spoke three random consonants to the participant. He was then asked to count aloud and backwards in three's from a specific number also given by the examiner. After 9, 18, or 36 seconds of counting backwards the participant was stopped and asked to repeat the consonants initially spoken by the examiner. The participant was issued a point for each correct consonant given, totaling 15 points for each time period (overall total of 45 points). There were no stopping rules for the CCC aside from full completion of the test with the participant attempting all levels of the test.

(3) fNIRS and Hemodynamic Measures

A continuous wave two channel dual wavelength (760nm, 850nm) fNIRS machine was used (Artinis Oxymon MK IV, Netherlands) to monitor hemodynamic measures (O_2Hb, HHb, HbDiff and tHb) over the left and right PFC. The fNIRS optodes were precisely positioned over the forehead immediately above the supraorbital ridges on either side of the midline (Appendix G.1) with the detector-emitter distance of 4.5cm for each side to minimize signal contamination from extracerebral circulation (Vermeij, van Beek, Olde Rikkert, Claassen, & Kessels, 2012; van Beek, Olde Rikkert, Zhang, & Classen, 2011). This resulted in an approximate penetration depth of 2.7cm (60% of 4.5cm) (Minati, Kress, Visani, Medford & Critchley, 2011; Cui, Bray, Bryant, Glover, & Reiss, 2011).The midpoints of the detector-emitter distance corresponded to Fp1 and Fp2 in the International 10-20 system (Jasper, 1957) which have been associated, in MRI studies, with better neuroimaging signals in mental testing (Okamoto et al., 2004; Tanida et al.,

2007). These locations have also been used with digit span and other cognitive testing (Kaneko et al., 2011; Hoshi et al., 2000).

fNIRS sampling rate was at 10Hz throughout testing and participants wore a black blindfold (Appendix G.3) during testing to prevent distraction as well as to reduce ambient light in the sampling period. After sitting quietly for two minutes to establish a baseline and regularize fNIRS signals, the participant was asked to repeat the vowels (***a; e; i; o; u***) over 30 seconds as the control condition (Kaneko et al., 2011). See Figure 4.1 for the test protocol. After the initial baseline and control condition, testing continued as per the randomly ordered and counterbalanced digit span task and CCC. There was a two minute period of quiet seated rest between each task to minimize fatigue. The participant was encouraged to restrict verbalizations to test responses only and also to minimize body movements during the entire test period.

(4) Post-test Interview and Debriefing

Upon completion of the final memory test, the blindfold and optodes were removed and the participant asked to rate the strenuousness of the testing on a scale of 0 - 5 (0 = no strain at all; 5 = extremely strenuous). This rating scale was a modification of a measure of mental effort as described by Bratfisch, Borg, and Dornic (1972). The participant was also asked to list the strategies that he employed during testing to aid his test performance. The post-test session was not included in the hemodynamic measures.

(5) fNIRS Analysis

The hemodynamic changes were calculated by the manufacturer-supplied software utilizing the modified Beer-Lambert Law (Colier, Vanhaaren, & Oeseburg, 1995). A moving average of five samples per second was used to smooth the traces and facilitate analysis of the trends in the hemodynamic variables. Predetermined events were inserted in the fNIRS output to allow calculation of delta values. A colleague, unfamiliar with the study objectives, identified peak values in the fNIRS trace. The hemodynamic variables were monitored in real time and averaged over five second intervals using the data acquisition software (Artinis Medical Systems Inc., Netherlands). Delta values were calculated (peak minus control) similar to the procedure of Kaneko et al. (2011). See Figure 4.2 for calculation of delta values in a representative trace of a participant. To address concerns about the volume of the frontal sinuses and scalp to cortex distance biasing fNIRS hemodynamic scores (Hauessinger et al., 2011), we introduced head circumference as a covariate in the statistical analysis as suggested by these authors.

A laterality ratio score, previously used to assess prefrontal asymmetry during EEG studies (Davidson & Fox, 1982), and in fNIRS research (Tanida et al., 2004) was calculated using the following equation*:*

[right – left side]/ [right +left side] for changes in O_2Hb and tHb

By convention positive laterality ratio scores would indicate larger increases in O_2Hb and tHb are occurring in the right side while negative scores indicate larger changes are occurring in the left side (Davidson & Fox, 1982; Tanida et al., 2004). To further clarify the differences between the groups on behavioral performance and hemodynamic changes, we reported efficiency

measures for PFC hemodynamic changes. The efficiency measures were a modification of those suggested by Paas and Van Merriënboer, (1993) and calculated as follows:

$$\textit{Hemodynamic Changes Efficiency} = \textit{Cognitive Test scores}/O_2Hb, tHB, HbDiff$$

Statistical Analysis

Normality of the data was initially examined using the Shapiro-Wilks test. Independent 't' tests were used to identify differences between normotensive and hypertensive groups for their age, BMI and years of education. Statistical analysis of all hemodynamic measures was performed using delta values which are consistent with methods used in continuous wave fNIRS measurements (Hoshi, 2003; Scholkmann et al., 2014). All comparisons were conducted after matching 15 normotensive participants with 15 hypertensives on age (Green & Salkind 2011). A two-way repeated measures analysis of covariance (ANCOVA) was used to identify differences in behavioral performance between the normotensive and hypertensive groups for the four cognitive performance tests.

Also, a three-way repeated measures ANCOVA was used to investigate differences between normotensive and hypertensive participants on their PFC hemodynamic responses during testing. In these analyses, Group (normotensive, hypertensive) was the between subjects factor and the four Tests (DSF, DSB, DSS, CCC), and Side (left and right) were the within subjects factors. Head circumference was used as a covariate. Mauchly's test of sphericity was performed for the effect of test in the ANCOVA and 'F' ratios were adjusted using the Greenhouse-Geisser procedure. The Bonferroni correction for $P<.05$ was applied to control for

Type 1 error in the above ANCOVA analyses. Significant 'F' ratios were analyzed using the Scheffé post hoc procedure.

Pearson product moment correlation coefficients were used to examine the relationship between the hemodynamic measures, behavioral test scores and mental effort in each group (Bratfisch, Borg, & Dornic, 1972) during the tests. The Statistical Package Social Sciences SPSS (IBM version 21) was used for all statistical analyses (SPSS Inc., Chicago, USA.)

Results

Interpretation of the Three-way Analysis of Covariance

The procedure described by Keppel and Wickens (2004) was used in interpreting the results of the three-way Analysis of Covariance (ANCOVA). First the three-way interaction (Group by Test by Side) was examined. *Since none of the three way interactions were significant for any of the variables,* the following two way interactions pertinent to the study objectives were examined: (a) *Group by Test* to examine the differences in cognitive hemodynamic changes (O_2Hb, HHb, tHb and HbDiff) between the normotensives and hypertensives when the two sides were pooled (objective 2). This resulted in 30 measurements for each group; and (b) *Group by Side* to examine the differences between the normotensives and hypertensives in the right and left prefrontal lobes when the four tests were pooled (objective 3). This resulted in 60 measurements per group. When the two-way interaction was not significant, then the main effect of the pertinent factor (Group or Test or Side) was examined. Head circumference as a covariate did not affect the significance of the results.

Comparison of Behavioral Performance

There were no significant differences between the normotensive and hypertensive groups for BMI, years of formal education, and age in the matched pairs (Table 4.2). The hypertensive group demonstrated impaired behavioral performance on the four cognitive tests when compared to the normotensive group (P=0.027; Observed Power=0.613) as illustrated in Figure 4.3. The main effect of Test was significant on the two-way repeated measures ANCOVA (P<0.01). Pairwise comparisons revealed CCC with a significantly higher mean score than the other three tests (P=0.000; Partial Eta Squared=0.887). Within the CCC, there was a significant decrease in performance between the 9 seconds and 36 seconds delay periods in conducting the test for the normotensive participants (P=0.014), and for the hypertensives (P=0.026). An additional test of perceived mental effort/strain (Bratfisch, Borg & Dornish, 1972) identified a consistent, but non-significant trend of higher mental effort in the hypertensive group.

Hemodynamic Changes during Cognitive Tests in Normotensive and Hypertensive Groups

A representative trend of the hemodynamic responses during the four cognitive tests is illustrated in Figure 4.2. In both groups of participants these trends were similar, but the magnitude of these changes was different across the groups. One should caution that comparing traces across groups might not be accurate in fNIRS analysis (Hoshi, 2003). At the start of the test O_2Hb, tHb and HbDiff demonstrated systematic increases with a concomitant decrease in HHb. Upon termination of the test, these variables reverted towards the baseline value and demonstrated a similar response when the next cognitive test was initiated.

Mean O_2Hb values noted for the hypertensive group were uniformly higher across the left and right PFC, but was not significantly different from the normotensives (P=0.201; Observed Power=0.244). In pairwise comparison of the tests across both groups, there was a significantly higher mean O_2Hb for CCC (P<0.001; Observed Power=0.998) in the left and right PFC.

Similarly, the overall trend was for higher tHb concentration in the left and right PFC in the hypertensive group compared to normotensives, but this also did not reach significance (P=0.239; observed power= 0.213). The effect of Test revealed that CCC was significantly greater than the other three tests (P<.05) on the tHb variable. On the main effect of Side, there was no significant difference between left and right PFC on the tHb and O_2Hb variables. However, descriptive plots of the variable means revealed a distinctly sharper increase in O_2Hb and tHb concentrations in the left side of the hypertensives.

The differences between O_2Hb and HHb (i.e. HbDiff) revealed a non-significant difference between the groups with higher changes noted in the hypertensive group. Similar to O_2Hb and tHb, the plot of HbDiff changes revealed a distinct trend for sharper rise in concentration changes in the left side of the hypertensive group. In pairwise comparisons of the tests on the variable HbDiff, CCC resulted in significantly greater changes than the other three tests (P<.001).

A descriptive charting of the calculated efficiency scores for O_2Hb, tHb and HbDiff across the groups demonstrated a consistent trend of lower efficiency in the hypertensive group. Figure 4.4 (Panels A, B and C) illustrates this pattern.

Laterality Testing

A trend for negative laterality scores is suggestive of greater left PFC changes (Tanida et al., 2004). Laterality scores for O_2Hb and tHb changes were not significant across the groups, however in the hypertensive group three out of the four tests resulted in negative laterality scores. Figure 4.5 illustrates PFC asymmetry in O_2Hb and tHb changes using laterality scores. In the hypertensive group the largest changes were in the left side for O_2Hb, tHb and HbDiff variables.

Correlations between Cognitive Tests and Hemodynamic Changes

There were no significant correlations in the normotensive group between behavioral performance and O_2Hb and tHb changes in the right and left PFC. However in the hypertensive group, significant correlations were observed between: (1) tHb in the left and right PFC during DSB; and (2) O_2Hb in both the left and right PFC during DSB. The scatterplots of the significant relationships are illustrated in Figure 4.6 (Panel A – D). Additionally, Figure 4.7A illustrates the trend between oxygenation and mental strain across both groups indicating statistical significance for the left and right PFC in the hypertensives during DSF ($P<.05$). Figure 4.7B illustrates the comparison of performance and mental strain across the groups.

Discussion

Modifications in cerebrovascular reserve as a consequence of small vessel disease in hypertension can be viewed through the interplay between behavioral performance, hemodynamic changes and the efficiency of PFC function in general. These modifications will be

compared to normotensives and discussed below from the following perspectives: (a) comparison of cognitive performance, (b) comparison of hemodynamic responses, (c) mental effort and cognitive adjustment, (d) PFC lateralization and functional compensation, and (e) relationship between behavioral performance and hemodynamic responses in the groups.

Comparison of Cognitive Performance between Normotensive and Hypertensive Participants

Our first hypothesis postulating that there would be a significantly impaired behavioral performance by the hypertensive group was supported. Additionally, a description of performance efficiency scores (O_2Hb, tHb, HbDiff) showed diminishing performance efficiency trends in the hypertensives (Figure 4.4: Panel A, B, C). To our knowledge, this study is the first to demonstrate a pattern of impaired cognitive performance in conjunction with trends of lowered hemodynamic efficiency in a hypertensive group. Importantly, our study participants (19 - 55 years) were still within their most occupationally productive years. This finding provides relevant information on the potential impact of the disease on human productivity. Previous studies that identify cognitive impairment in hypertensives have mostly focused on elderly and less active populations which necessarily provoke questions about “normal” aging and deconditioning as confounding variables (Anson & Paran, 2005; Jacobs et al., 2013). Our findings allow the debate on the hypertension-cognition relationship to surpass these basic queries and initiate questions on underlying mechanisms. Hemodynamic changes in the PFC are likely part of the neural mechanism mediating the cognitive performance in the disease.

Comparison of Hemodynamic Responses between Normotensive and Hypertensive Participants

As a second hypothesis, we postulated higher O_2Hb and tHb changes in the hypertensives. The trend for higher mean concentrations for both O_2Hb and tHb suggests support for our proposition, but the non-significant results may be the result of low statistical power. Increase in O_2Hb during all the tests were accompanied by a trend of decreasing or unchanged HHb (Figure 4.2), consistent with what is considered a typical pattern of neuronal activation in the PFC (Villringer & Chance, 1997; Hoshi, 2003; Perrey, 2008). We can thus infer that the hypertensive group was demonstrating increased neuronal activation in the PFC despite a relatively impaired behavioral performance. Increases in neuronal activation on cognitive tasks in healthy and pathological populations have been previously observed in fNIRS activation studies (Ehlis, Schneider, Dressler, & Fallgatter, 2014), as well as similar fMRI (Sato et al., 2013) and PET studies (Owen et al., 1999). However, in this study, the higher O_2Hb levels for the hypertensive group suggest the possibility of a higher neuronal activation-rate when compared to normotensives. A concurrent trend for higher HbDiff is indicative of attempts at greater oxygen extraction and workload (Ayaz et al., 2012; Derosière et al., 2013) in the hypertensive group. Léon-Carrion et al. (2008), reporting on healthy participants, stated that cognitive performance levels tended to parallel O_2Hb levels in the PFC. Results of our study, in addition to being consistent with these findings, also demonstrated an important comparative difference between a relatively young hypertensive group and normotensives. The trends for higher O_2Hb, tHb and HbDiff levels in the hypertensive group despite an impaired behavioral performance suggest diminished cognitive work efficiency. This is evidenced by the description of

hemodynamic efficiency measures previously mentioned. In addition to performance efficiency, mental effort is an important variable for consideration.

Mental Effort and Cognitive Adjustment

In the post-test interview, the hypertensives reported higher overall subjective mental strain during cognitive testing. Accompanying the pattern of higher strain in the hypertensives and overall higher oxygenation levels there was significantly impaired performance (Figure 4.7A, B). Hence there is evidence that the hypertensive group was striving for efficiency. The Compensation Related Utilization of Neural Circuits Hypothesis (CRUNCH) (Reuter-Lorenz & Cappell, 2008) indicates that given similar memory loads, individuals with poorer memory capacities tend to deploy more brain activation than those with higher abilities (Schneider-Garces et al., 2009). In this study, the trend for higher hemodynamic changes (O_2Hb, tHb and HbDiff) in the hypertensive group, coupled with objectively poorer performance, appear to support CRUNCH. The subjective reports of increased mental strain represent increased effort/ load associated with testing. It is possible that this scenario is attributable to a decreased memory span (Cowan, 2001), accompanying the physiological effects of hypertension.

Nyberg et al. (2009) demonstrated that a vital determinant of working memory span is the ability to adequately engage the frontal lobe while attending to the demands of a particular task. According to these researchers, this signifies the importance of "relative task difficulty" or the demanding nature of the memory task. The hypertensives in our study might be engaging the PFC more intensely in an effort to compensate for a "relatively" more difficult task than that experienced by the normotensive for the same test. O_2Hb changes that vary with mental

strain may provide a neurovascular index for the reported mental effort. To further explain performance and possible compensatory mechanisms accompanying hypertension, inter-hemispheric adjustments in brain oxygenation provide a fertile area of inquiry.

PFC Lateralization and Functional Compensation

Our third hypothesis that there would be significant changes in asymmetry in right and left side oxygenation and blood volume was not supported. However there was a distinct trend of increasing blood volume changes in the left side of the hypertensive group. This may provide a broader theoretical explanation of the possibility of compensatory effects of hypertension during cognitive testing.

There are known trends in neuronal compensation across the hemispheres to address performance deficits at the individual level (Schneider-Garces et al., 2009; Vermeij, van Beek, Olde Rikkert, Classen, & Kessels, 2012). Hence comparing hemodynamic changes in the left and right PFC during cognitive testing of hypertensives may inform on a similar compensatory phenomenon. The laterality ratio scores, designed to measure asymmetry in PFC activation patterns indicated that during the four tests the hypertensives had negative laterality scores for tHb. This suggests, by convention, that increases in the left PFC blood volume changes were larger than the right during testing (Tanida et al., 2004). Furthermore, the three variables O_2Hb, tHb and HbDiff all showed a trend of sharper increases in the left PFC of the hypertensives. Given the behavioral performance differences between the groups previously mentioned, it is possible that the left PFC became increasingly activated, additive to the right PFC, in an attempt to compensate for deficiency in performance. A similar compensatory phenomenon has been

reported in aging studies (Reuter-Lorenz & Cappell, 2008; Vermeij et al., 2012) bearing some resemblance to brain activation patterns in hypertension. The relationship between behavioral performance and hemodynamic responses may further inform on the possibility of compensation across the hemispheres in this disease.

Relationship between Behavioral Performance and Hemodynamic Responses in Normotensive and Hypertensive Participants

Our fourth hypothesis proposed a significant correlation between O_2Hb and tHb changes and behavioral performance in the groups. Significant correlations on these two variables were identified only in the hypertensive group. They occurred between these measures and DSB on both the left and right PFC. Interestingly, Kaneko et al. (2011) reported that DSB in a healthy population resulted in greater levels of PFC activation than the other digit span test (DSF). Given the striving for efficiency in the hypertensive group previously discussed, it is possible that higher activity during DSB testing resulted in a greater drive to compensate for behavioral deficiency in the hypertensive. This could have resulted in the significant correlation between performance and hemodynamic responses, as well as the increased activity in the left PFC. One should also note that of the four tests performed in our study, hypertensives underperformed on the DSB.

Hoshi et al. (2000) reported that digit span tests resulted in increased activation in the right PFC in healthy participants. Though no previous information exists for CCC or for hypertensives in this regard, our findings indicate that the pooled tests, digit span and CCC, trended towards more pronounced left PFC activation. The possibility exists that these changes are the result of

microvascular pathology typical of hypertensive disease, and are reminiscent of compensatory age-related changes. This assertion should be tempered with knowledge of the limitations of our experimental procedure.

Limitations of the Study

In interpreting the findings of this study, certain limitations should be considered. Notably, there is an issue of statistical power due to small sample size in the case of the hypertensives. The methodological restrictions of administering the digit span test and CCC with unique rules of test administration made testing cumbersome. Additionally, the use of fNIRS for hemodynamic evaluation with this particular test combination is unusual. However, in future analysis, an alternative method utilizing a better level of discrimination on cortical activation such as the "slope method" as advocated by Mandrick et al. (2013) would be appropriate.

As the main device in this study, continuous wave fNIRS was used to measure hemodynamic changes. It applies continuous near infrared light and measures the attenuation of the incident light to quantify concentration changes in hemoglobin. When hemodynamic concentration changes are localized, as in brain activation studies, the light differential path length factor through the tissues is assumed to be constant and this is likely to be inaccurate (Hoshi, 2003; Scholkmann et al., 2014). Hence delta values, not absolute concentrations, are used in calculating hemodynamic changes with brain activation. This was the case in our study and thus limits how the results can be generalized and utilized clinically.

Another limitation in fNIRS measurement of the brain is in accounting for the scalp to cortex distance. The variation in size of the frontal sinuses and scalp thickness affect light penetration

of the PFC and thus fNIRS recording. Given that the same emitter-detector distance was used in all cases, the degree of activated cortex measured would vary given individual differences in frontal sinus parameters (Hauessinger et al., 2011; Strangman & Li, 2014). Additionally, continuous wave fNIRS have shown that even under resting conditions hemoglobin oxygenation fluctuates (Hoshi, 2005). Systemic fluctuations such as arterial pulse oscillations and respiration result in fluctuating patterns of oxygenation. When one factors in known slower vasomotor oscillations from the pial arteries (Minati et al., 2011; Cheng, Shang, Hayes, Saba, & Yu (2012), we should be cautious in interpreting and applying these results without replication.

In our study, testing lasted up to 75 minutes over four cognitive tests which likely resulted in fatigue; this was not quantified. Both behavioral performance and hemodynamic values may be thus influenced with the stacked use of the tests. Though the four cognitive tests were counterbalanced, the control condition was administered at the beginning of testing. This could have a variable effect on calculated delta values for each test. Additionally, two participants reported discomfort with the blindfold used in testing and this could have hampered performance.

The characteristics of the participants also suggest a need for caution in interpreting these findings. The volunteers in this study were generally of a higher educational level and mostly employed in white collar occupations. Naturally, this would limit generalizability of our findings to other populations. Further, the time since diagnosis of hypertension ranged from one to 20 years; hence the small vessel disease and perfusion changes in the PFC would be quite variable in our sample. In addition, one hypertensive participant reported having a history of recent

diabetes mellitus not indicated prior to testing. Inclusion of ischemic scores such as the Hachinski Ischemic Index (Pantoni & Inzitari, 1993) would render the results more clinically pertinent to the implications of small vessel disease in hypertension.

Conclusions

Cerebrovascular vasodilatory reserve correlates with the physiological markers of hypertension such as endothelial dysfunction in brain microvasculature. Brain vascular reserve is likely to influence behavioral performance and individual functional capacity. Oxygenation and blood flow changes help to identify the efficiency of neurovascular coupling in the brain that supports this reserve. Efficiency in the features of cerebral neurovascular coupling is ultimately revealed in behavioral performance and hemodynamic adjustments accompanying the reduced cognitive function.

The alteration in cognitive performance as demonstrated in this study in a relatively young group of hypertensive males advocates the importance of addressing the disease earlier in its evolution. Most importantly, it emphasizes the study of hypertension through a prism of functional capability that utilizes its modifiable characteristic. The possible attempts at physiological compensation in the PFC and suggested trends of alteration of hemispheric asymmetry propose a premature aging inclination. Such a feature, should it be confirmed, is not unique in organ systems affected by hypertension. However, these findings and their potential impact on the executive function in the prime years of productive life, focuses clinical attention on important parameters of the disease well in advance of old age.

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Table 4.1: Inclusion and exclusion criteria for the normotensive and hypertensive participants

Group	Inclusion	Exclusion
Normotensive	• Males • Age 18 – 55 • No history of hypertension or cardiovascular disease • No history of neurological or psychiatric disorder	• Smoker • Regular use of prescription or non-prescription medication or illegal drugs • English language communication difficulty • Participating in similar study • Beck Depression Inventory (BDI II) score >13 (Beck, Steer & Brown, 1996).
Hypertensive	• Males • Age 18 – 55 • History of high blood pressure > 1 year (confirmed by a physician licensed in the province of Alberta) • No history of dementia, stroke, heart attack or kidney disease • No history of neurological or psychiatric disorder	• Smoker • English language communication difficulty • Participating in similar study • Hypertension beyond stage 1 (above 159/99mmHg) (Chobanian et al., 2003), or hypertension deemed not to be fully controlled • Beck Depression Inventory (BDI II) score >13 (Beck, Steer & Brown, 1996).

Table 4.2: Characteristics of matched normotensive and hypertensive participants (Mean±SD)

	Age	Body Mass Index	Code of Physical Activity	Years of Formal Education	Resting Systolic BP	Resting Diastolic BP
Normo (N=15)	38.47±8.03	27.75±3.38	4.64±2.12	16.60±2.64	117.08±11.96	80.43±7.24
Hyper (N=15)	42.2±10.95	29.47±4.56	4.67±2.32	17.47±2.59	130.54±11.07*	86.17±5.01∫

*significant at P=.006 (hypertensive with higher resting SBP)

∫significant at P=.03 (hypertensive with higher resting DBP)

Code for Physical Activity = /7 (as per Ross and Jackson, 1990).

Normo = normotensive; Hyper = hypertensive

Table 4.3: Summary of mean hemodynamic changes during the four cognitive tests in normotensive and hypertensive participants measured at the right and left prefrontal lobe (mean ± SE)

Group	Side	DSF	DSB	DSS	CCC
Oxyhemoglobin					
Normotensive	Right	2.728±.290	2.335±.385	2.627±.430	3.824±.558*
N = 15	Left	1.515±.505	1.722±.600	1.854±.544	3.124±.493*
Hypertensive	Right	2.481±.290	2.817±.385	2.939±.430	4.360±.558*
N = 15	Left	2.178±.505	2.489±.600	2.692±.544	4.687±.493*
Deoxyhemoglobin					
Normotensive	Right	-.236±.151	-.080±.228	-.372±.196	-.657±.185
N = 15	Left	-.677±.336	-.551±.403	-.919±.358	-.633±.329
Hypertensive	Right	-.270±.151	-.309±.228	-.558±.196	-.505±.185
N = 15	Left	-.115±.336	-.422±.403	-.601±.358	-.601±.329
Total Hemoglobin					
Normotensive	Right	2.481±.322	2.311±.497	2.315±.450	3.162±.539**
N = 15	Left	.809±.756	1.058±.918	.843±.755	2.389±.681**
Hypertensive	Right	2.225±.322	2.508±.497	2.381±.450	3.855±.539**
N = 15	Left	2.063±.756	2.067±.918	2.091±.755	4.086±.681**
Hemoglobin Difference					
Normotensive	Right	2.974±.335	2.358±.387	2.939±.489	4.487±.634∫
N = 15	Left	2.286±.394	2.387±.458	2.866±.529	3.860±.503∫
Hypertensive	Right	2.766±.335	3.128±.387	3.500±.489	4.870±.634∫
N = 15	Left	2.292±.394	2.912±.458	3.294±.529	5.288±.503∫

*Indicates significant mean difference P≤.004 (CCC > DSF, DSB, DSS in O_2Hb) for both groups

**Indicates significant mean difference P≤.017 (CCC> DSF, DSB, DSS in tHb) for both groups

∫Indicates significant mean difference P≤.002 (CCC > DSF, DSB, DSS in HbDiff) for both groups

Table 4.4: Correlations between hemodynamic responses and behavioral scores for normotensive and hypertensive participants

Group	Side	DSF	DSB	DSS	CCC
Oxyhemoglobin					
Normotensive	Right	.090	.248	.221	-.275
N=15	Left	.283	.410	.263	.191
Hypertensive	Right	.272	.613**	.103	.200
N=15	Left	.416	.732**	.166	.302
Deoxyhemoglobin					
Normotensive	Right	-.292	-.192	.111	.470*
N=15	Left	.170	.089	-.090	.429
Hypertensive	Right	.745**	.423	-.222	-.247
N=15	Left	.199	.446*	-.028	-.244
Total Hemoglobin					
Normotensive	Right	-.066	.082	.268	-.143
N=15	Left	.282	.297	.129	.342
Hypertensive	Right	.522*	.665**	.063	-.020
N=15	Left	.346	.680**	.163	.106
Hemoglobin Difference					
Normotensive	Right	.219	.416	.151	-.373
N=15	Left	.217	.449*	.325	-.282
Hypertensive	Right	-.066	.342	.171	.227
N=15	Left	.378	.645**	.194	.326

*Indicates significant correlation at P<.05

**Indicates significant correlation at P<.01

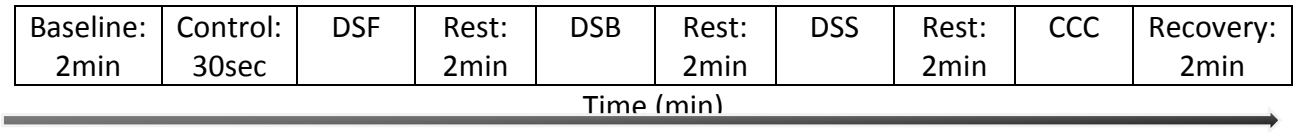


Figure 4.1: Cognitive testing procedure of normotensive and hypertensive participants during digit span and auditory consonant trigrams test.

Note: Tests were randomly ordered

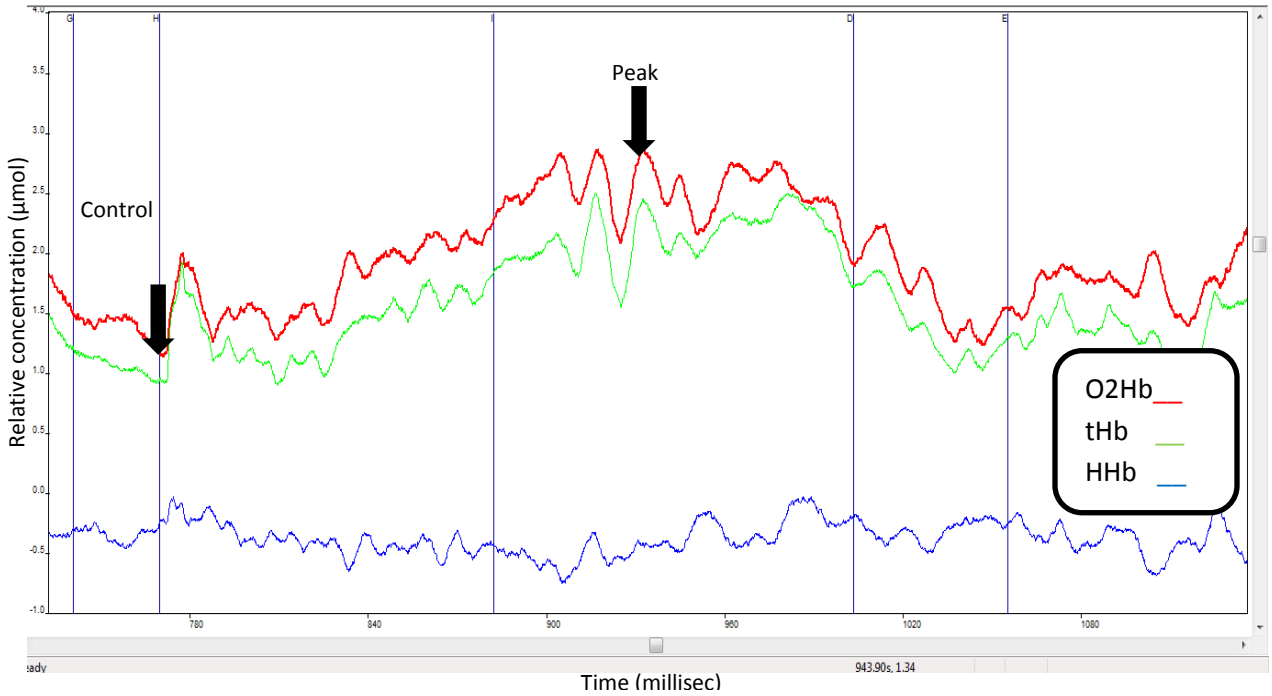


Figure 4.2: Hemodynamic concentration changes (µmol) during Auditory Consonant Trigrams test for a representative normotensive participant. Delta value = [Peak minus Control].

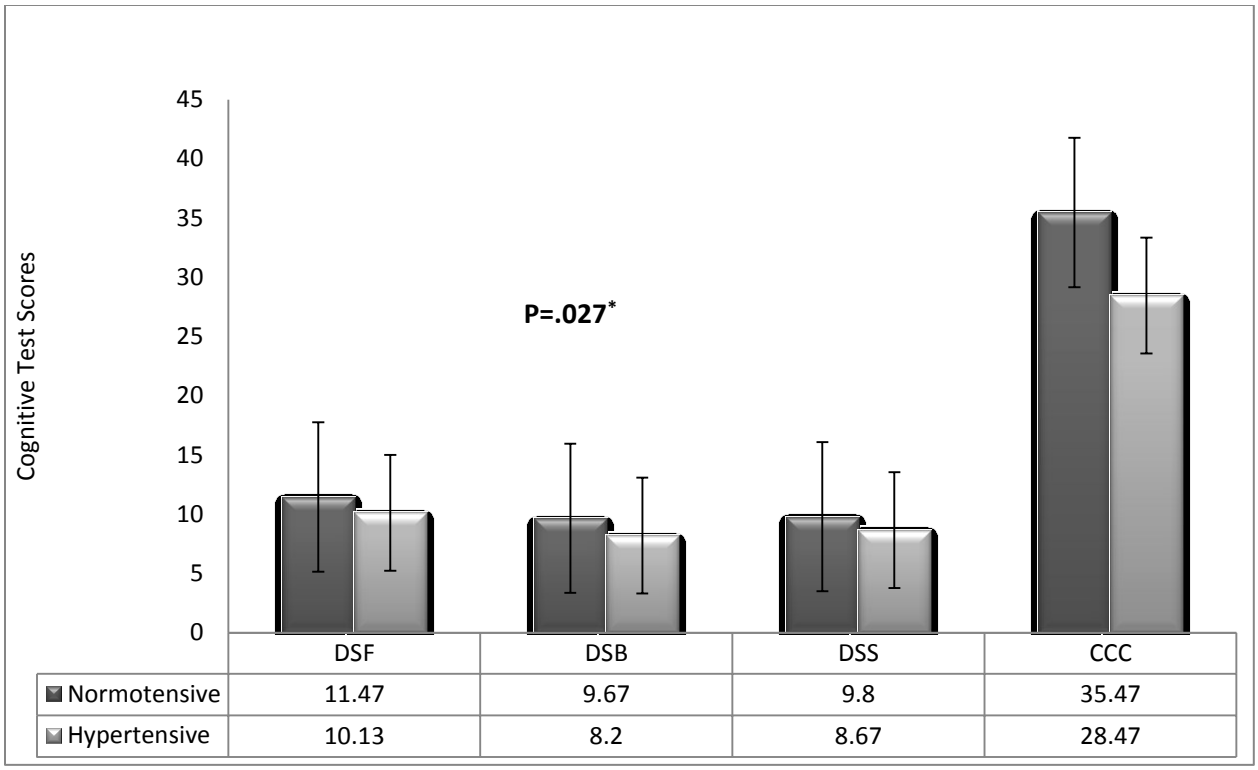


Figure 4.3: Behavioral performance scores during digit span and auditory consonant trigrams test for matched normotensive and hypertensive participants (DSF = /16; DSB = /16; DSS = /16; CCC = /45). *Performance significant, P=.027.

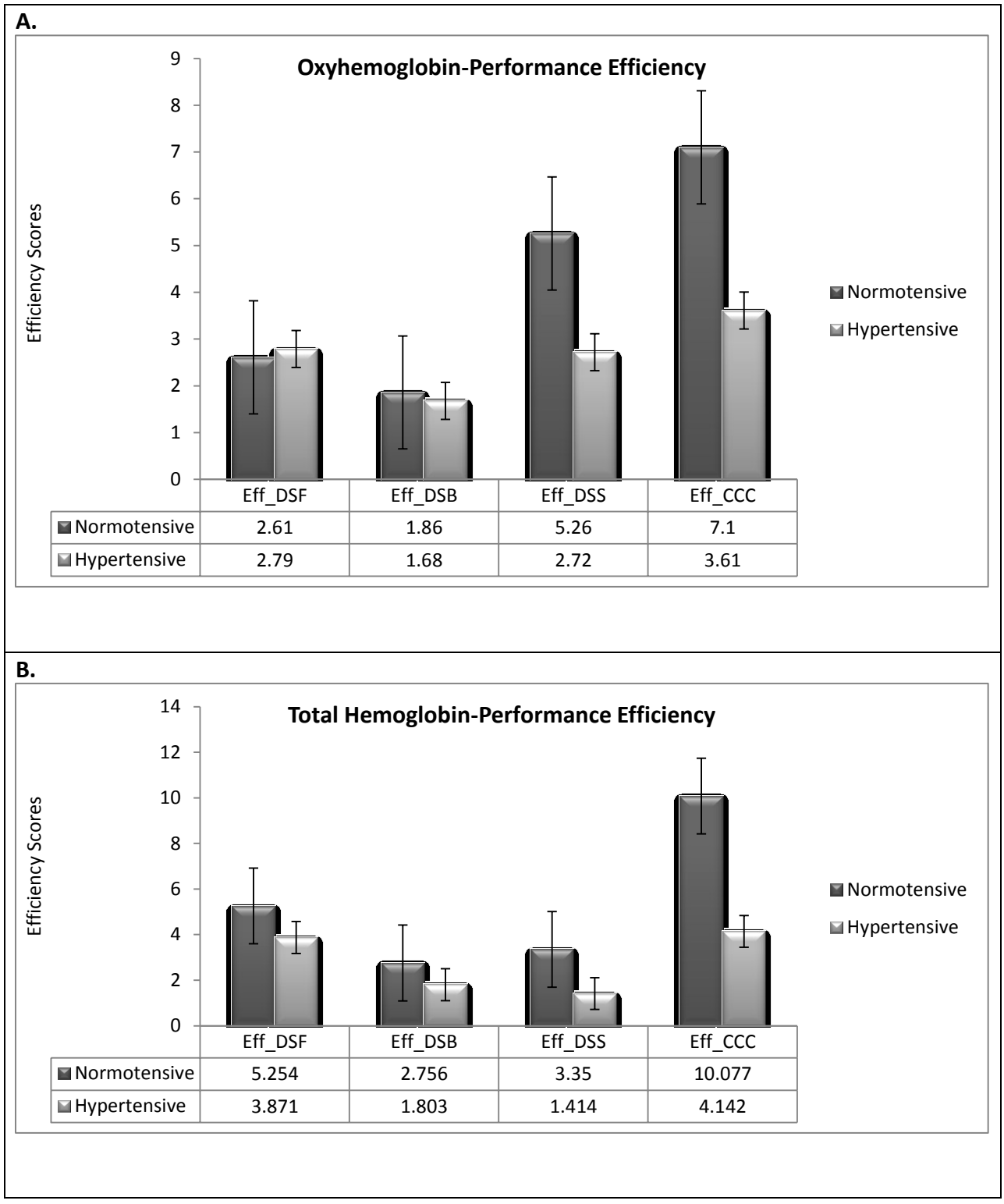


Figure 4.4 (Panel A, B): Performance efficiency (oxyhemoglobin, total hemoglobin) in normotensive and hypertensive participants during digit span and auditory consonant trigrams

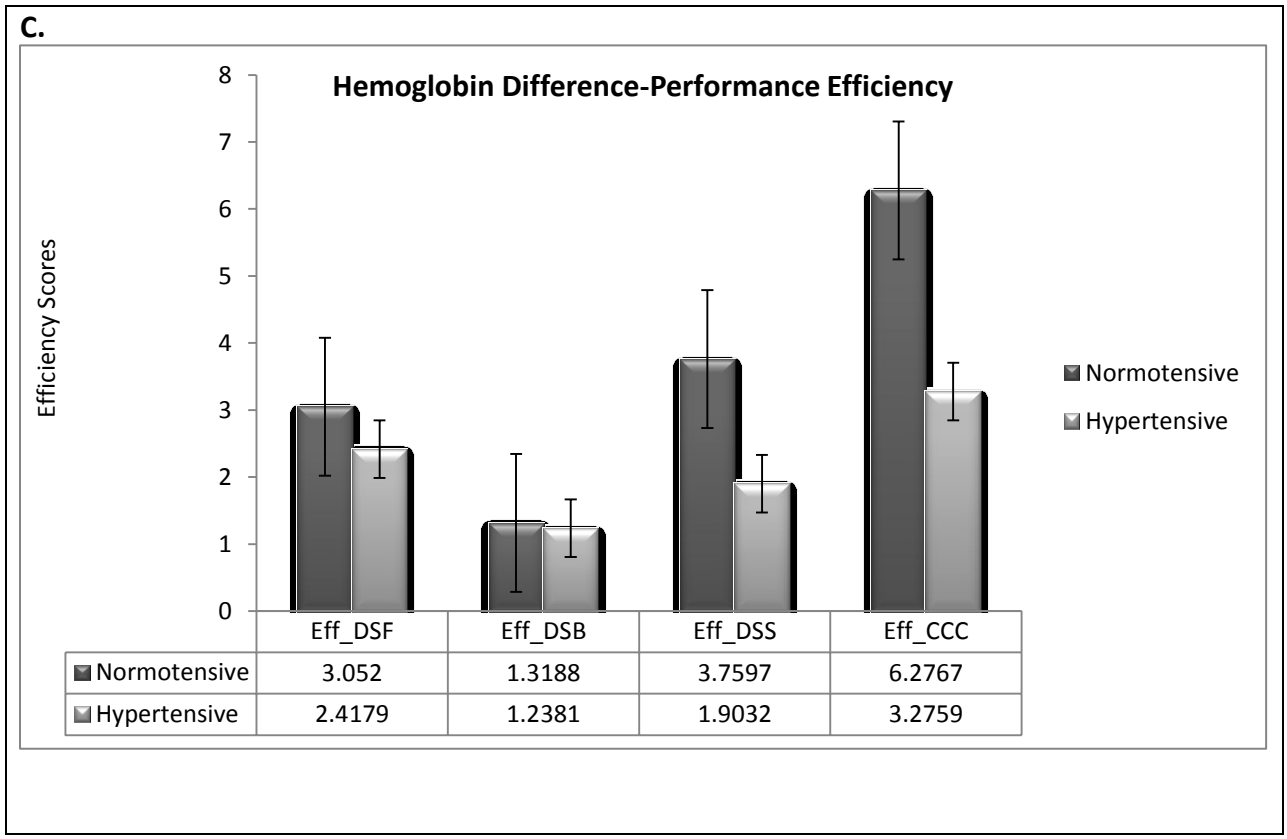


Figure 4.4 (Panel C): Performance efficiency (hemoglobin difference) in normotensive and hypertensive participants during digit span and auditory consonant trigrams

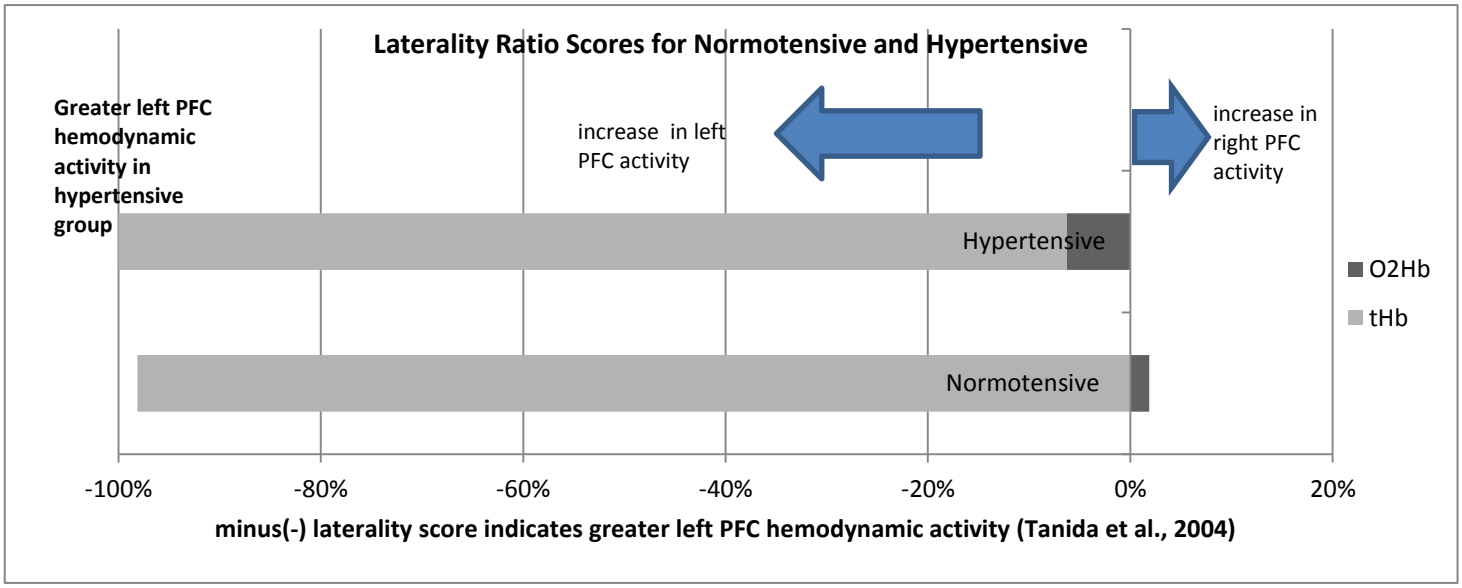


Figure 4.5: Prefrontal laterality ratio scores of normotensive and hypertensive participants during digit span and auditory consonant trigrams test

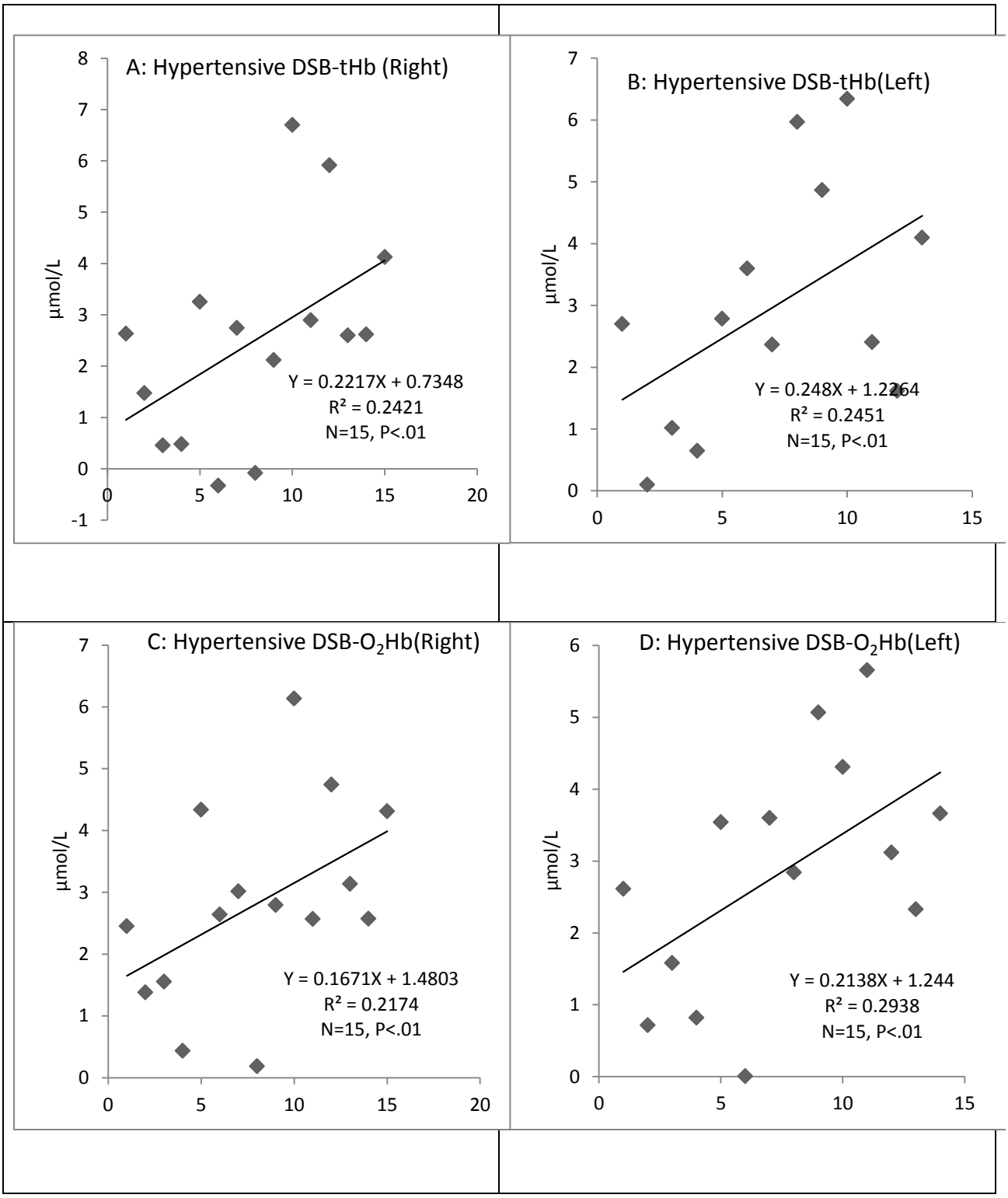
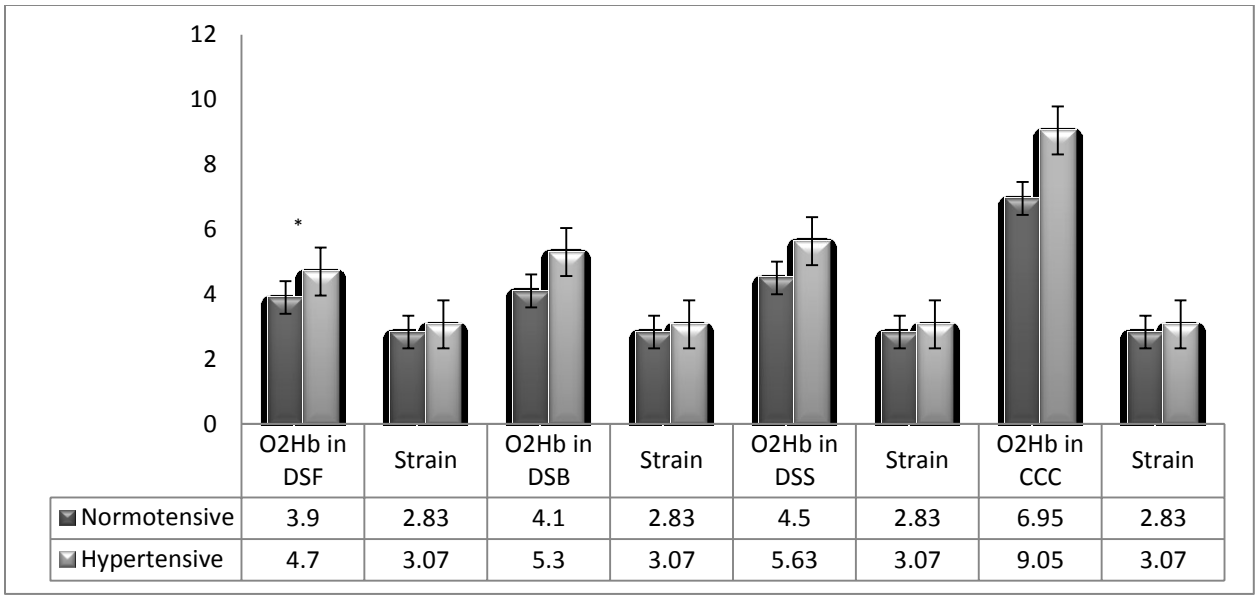


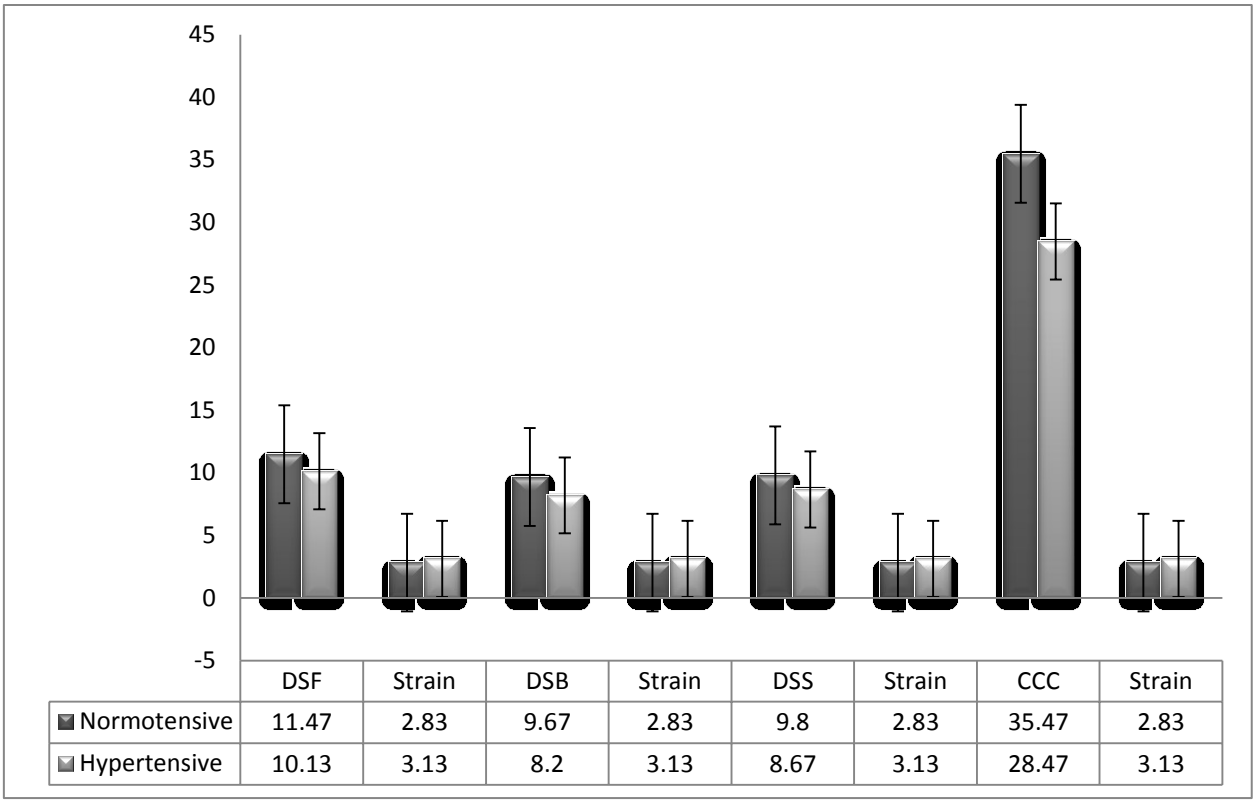
Figure 4.6: Panel A, B, C, D - Scatterplots of significant correlations between hemodynamic changes and digit span in hypertensive participants.



	O2Hb in DSF	Strain	O2Hb in DSB	Strain	O2Hb in DSS	Strain	O2Hb in CCC	Strain
Normotensive	3.9	2.83	4.1	2.83	4.5	2.83	6.95	2.83
Hypertensive	4.7	3.07	5.3	3.07	5.63	3.07	9.05	3.07

Figure 4.7A: Oxygenation and perceived mental effort in normotensive and hypertensive participants during digit span and auditory consonant trigrams test. (DSF = /16; DSB = /16; DSS = /16; CCC =/45; perceived mental strain = /5)

*Hypertensive demonstrated significantly greater strain during DSF (P<.05)



	DSF	Strain	DSB	Strain	DSS	Strain	CCC	Strain
Normotensive	11.47	2.83	9.67	2.83	9.8	2.83	35.47	2.83
Hypertensive	10.13	3.13	8.2	3.13	8.67	3.13	28.47	3.13

Figure 4.7B: Behavioral performance and perceived mental effort in normotensive and hypertensive participants during digit span and auditory consonant trigrams test. (DSF = /16; DSB = /16; DSS = /16; CCC = /45; perceived mental strain = /5)

Chapter 5

Hemodynamic Responses of the Prefrontal Cortex during Exercise-Enhanced Attentional Control in Essential Hypertension

Introduction

The ability of the vascular system to adequately perfuse the brain is the vital faculty connecting cognitive function to meaningful human activity (Novak & Hajjar, 2010). This critical intermediary, largely defined by the phenomenon of neurovascular coupling (Bari et al., 2012), can become diseased. One such disease is high blood pressure of unknown cause i.e. essential hypertension (Schmeider, 2010); and such an occurrence may theoretically impede cognitive and motor function thereby curtailing consequential human performance.

Apart from its known complications of stroke, heart and kidney disease, hypertension has been implicated in what is anticipated to be a twofold increase in cognitive impairment and dementia in the next decade (World Alzheimer Report, 2009). Within the past five years, death and disability due to hypertension has been estimated to result in annual loss of over 92 million disability-adjusted life years (Vasan, 2009).

Cognitive dysfunction as a consequence of hypertension is emerging as a distinct and major clinical entity (Elias, Goodell, & Dore, 2012; Staessen, Richart, & Birkenhager, 2007). The neural mechanisms that explain a hypertension-cognition interaction may be related to arterial stiffness and endothelial dysfunction that limit vessel reactivity, blood flow and thus brain perfusion (Novak & Hajjar, 2010; Schmeider, 2010). Accordingly, regional circulation is unable

to match the metabolic demands of increasing neuronal activity that accompany cognitive and motor function (Leff et al., 2011; Perrey, 2008; Girourd & Iadecolu, 2006). This inability to adjust to the increasing requirements of cognition, for example, results in functional changes that may be represented by decreased cognitive flexibility. The loss in efficiency of performance may be the result of a decrease in reserve dilatory capacity in the brain (Novak & Hajjar, 2010). Consistent with this analysis is the increasing association of uncomplicated hypertension with decreased cognitive performance (Elias et al., 2012; Kitagawa et al., 2009).

Notwithstanding, the literature linking the pathophysiological changes in hypertension to cognition is not straightforward. Research has demonstrated both a linear (Elias et al., 2012) and a non-linear relationship (Waldstein, Giggey, Thayer, & Zonderman, 2005) between hypertension and cognition. Other findings have shown both a negative and even a positive impact of the disease on cognitive function (see review by Anson and Paran, 2005). Most of these studies were done in the elderly with varied medication histories, length of disease exposure, and levels of blood pressure control (Anson & Paran, 2005). More importantly, they involved testing of multiple cognitive domains with differing emphases on brain substrates supporting the particular cognitive task. Working memory, psychomotor speed and executive function are three cognitive areas, along with the microstructure of the frontal lobe that have been shown to be affected by hypertension (Jacobs et al., 2013; Maillard et al., 2012).

An important deficiency in the hypertension-cognition literature, despite the findings of Maillard et al. (2012), is the absence of information on active young and middle-aged populations involving research questions predicated on performance and productivity.

Conceivably, the relationship between resting blood pressure and cognition may be a less sensitive measure of cerebrovascular reactivity and performance than blood pressure during physiologically challenging measures such as exercise (Anson & Paran, 2005). Combining exercise with a cognitive domain which is reportedly affected by hypertension, e.g. "executive function", will not only shed light on the changes due to hypertension under a physical challenge, but may uncover clinically relevant information on a physical stress-executive function-hypertension interaction. An important attribute of such coaction, and definitive to the cognitive domain of executive function, is the ability to actualize control over one's attention.

Attentional Control

Executive function implies information processing that drives goal directed behavior (Miller & Cohen, 2001; Kupferman, Lande, Adams, & Pavlakis, 2013) and in many ways it establishes human performance and productivity. Such behavior, most often associated with the prefrontal cortex (PFC), entails attending to and acting on relevant information while suppressing irrelevant responses (Golden & Freshwater, 2002).

Over most of the last century, objective measures of attentional control such as the Stroop effect have been used as a test of human executive function and cognitive flexibility (MacLeod, 1991). Participants are presented with conditions to test the Stroop effect (defined below) and asked to give timed responses to measure reaction time and "interference" which is considered an operationalized version of attentional control and cognitive flexibility (MacLeod, 1991). Impaired Stroop performance, seen as increased cognitive interference, is believed to represent

diminished capacity for attentional control and decreased frontal lobe function (Koechlin, Ody, & Kouneiher, 2003; Hyodo et al., 2012). The paradigm of the Stroop task is explained by the need to suppress a habitual response (reading word in black ink or like colored ink) to allow an unusual one (naming the color of the ink which is not the same as the printed word color) (MacLeod, 1991). As expected of concentrated cognitive activity, cerebral hemodynamic responses accompany Stroop performance (Hyodo et al., 2012).

Functional Near Infrared Spectroscopy and Prefrontal Cortex Function

Functional near infrared spectroscopy (fNIRS) measures hemodynamic responses at the microvascular level (arterioles, capillaries and venules) of activated tissue (Boas, Elwell, Ferrari, & Taga, 2014). Changes in these vessels are known to define the pathophysiological modifications accompanying hypertension (Veglio et al., 2009; Maillard et al., 2012), thus rendering fNIRS a suitable measurement technique for the microvascular responses accompanying this disease.

fNIRS uses near infrared light (700-1300nm) to measure regional changes in concentration of cortical oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) accompanying cognition (Chance, Zhuang, UnAh, Alter, & Lipton, 1993; Hoshi, 2003). It is an optical technique that has been validated with other established neuroimaging techniques (Alderliesten et al., 2014; Huppert, Hoge, Diamond, Franceschini, & Boas, 2006; Cui, Bray, Bryant, Glover, & Reiss, 2011), and remains an ecologically valid measure of hemodynamic changes in mental and motor testing (Derosière, Mandrick, Dray, Ward, & Perrey, 2013; Ferrari & Quaresima, 2012).

Attentional control is known to significantly alter the hemodynamic responses in the PFC (Tachibana et al., 2012). Léon-Carrion et al. (2008), using fNIRS, demonstrated that an increase in hemodynamic response over the PFC coincided with increased performance on the Stroop interference task. They hypothesized that increased cerebral metabolism from the enhanced attentional control likely resulted in improved performance on the Stroop task. Reasonably, given its known association with arterial stiffness and endothelial dysfunction (Maillard et al., 2012), hypertensive disease processes may alter metabolic activity in the brain and affect hemodynamic adjustments to functional activity. In theory, the Stroop task combined with the stress of physical exercise may amplify the adjustments in PFC hemodynamic responses similar to that reported on dual task experimental designs in healthy individuals (Mandrick et al., 2013; Holtzer et al., 2011).

Exercise, Cognitive Performance and Hypertension

The acute effects of exercise on PFC activity and oxygenation are widely appreciated (Rooks, Thom, McCully & Dishman, 2010; Perrey, 2008). Previously, Rasmussen et al. (2007) and Subudhi, Miramon, Granger, & Roach, (2009) used fNIRS to demonstrate a significant positive correlation between motor performance and increased O_2Hb in the PFC. Their explanation, not dissimilar to that offered for cognitive activity (Léon-Carrion et al., 2008; Hoshi et al., 2003; Chance et al., 1993), was that the increased metabolism required for the exercise necessitated increased brain oxygenation. Rooks et al. (2010) in a systematic review reported a quadratic relationship between exercise intensity and cerebral oxygenation. The main finding was that moderate to high intensity exercise resulted in the highest levels of PFC oxygenation. In most

cases, this preceded the respiratory compensation threshold, and at intensities beyond this point, there was a systematic decline in O_2Hb until termination of exercise (Rupp & Perrey, 2008). These findings suggest that maximal exercise capacity may be limited by decrease in neuronal activation, a finding which may be highly relevant in diseased populations with low aerobic capacity.

In further addressing the acute effects of exercise on cognitive function, Yanagisawa et al. (2010) demonstrated that an acute bout of moderate intensity exercise resulted in significant improvement in performance on the Stroop task administered shortly thereafter. Similar results using mild intensity exercises (30% VO_{2peak}) have been recently reported by Byun et al. (2014). Other researchers tested reaction time on the Eriksen flanker task during exercise and found significant improvement at 60%VO_{2peak} compared to rest (Ando, Kokubu, Yamada, & Kimura, 2011). Interestingly, according to these researchers, the improvements on the test were demonstrated to be independent of levels of PFC oxygenation. Coincidentally, the Eriksen flanker task presents similar demands on attentional control and cognitive flexibility to the Stroop task (Ando et al., 2011). However, the studies cited evaluated the responses in healthy participants, and the effects of simultaneous exercise on attentional control and oxygenation in a hypertensive population remain unknown.

Exercise induces physiological changes in multiple organ systems. Decreased cardiac output resulting from increased cardiac afterload in hypertension will contribute to decreased cerebral perfusion, exercise capacity and potentially cognitive performance (Koike et al., 2004). With regard to a hypertension-cognition interaction and its presentation, this scenario generates

several research questions. What is the impact of the integration of attentional control/ cognitive flexibility and exercise on functional capabilities in a hypertensive population? Furthermore, what is the impact of the physiological effects of hypertension on brain function under stress relevant to human performance and productivity in general? Loss in productivity, both a cognitive and a physical phenomenon, recently being ascribed to the effects of cardiometabolic risk including hypertension, is growing in concern as the disease incidence and subsequent complications escalate (Vasan, 2009; World Alzheimer Report, 2009; Sullivan, Ghushchyan, Wyatt, & Hill, 2007). As an elemental exploration of this debate, the present study investigated the hemodynamic changes of the PFC in relatively young male hypertensives (<56 years) during testing of attentional control enhanced by exercise.

Purpose and Hypothesis

The overall purpose of this study was to compare modified Stroop test performance and the changes in PFC hemodynamic responses between normotensive and hypertensive males (56 years and younger) at rest and at two different exercise intensities. An absolute and a relative exercise workload were chosen to minimize the effect on analysis of differing fitness levels among participants. The specific objectives were to compare the two groups on the following parameters: (1) attentional control performance; (2) changes in hemodynamic responses in the PFC; and (3) efficiency in hemodynamic performance. The secondary goal was to examine the relationship between attentional control performance and hemodynamic responses in both groups.

The following hypotheses were tested: (1) the hypertensive group will demonstrate significant impairment of attentional control as measured by performance on the exercise-enhanced incongruent Stroop task; (2) changes in PFC O_2Hb and tHb will be significantly reduced in the hypertensive group; (3) the hypertensive group will show significantly reduced efficiency in cognitive performance when assessed by the changes in O_2Hb, tHb and HbDiff during the Stroop performance at the three different intensities; and (4) changes in O_2Hb , tHb and HbDiff will be significantly correlated with incongruent Stroop performance in the two groups at all three intensities.

Methods and Procedures

Recruitment of Participants

Normotensive and hypertensive males (18 – 56 years of age) were recruited between the months of January 2012 and April 2013 for this study. Recruitment posters were placed at the University of Alberta campus, pharmacies and health care clinics around the city of Edmonton. In addition, information sessions about the study were presented to local community groups and organizations. Potential participants contacted the investigators by phone or email at which time the purpose of the study and eligibility were clarified. Recruitment was limited to males since questions on hemodynamic changes in the brain and gender under dual stress of exercise and cognitive load have not been discussed in the literature. Table 5.1 provides the inclusion and exclusion criteria for study participants.

Sample Characteristics

The calculated sample size based on the effect size of similar studies (Rooks et al., 2010) was 25 participants for each of the two groups which would have an estimated statistical power in excess of 0.72 (Portney & Watkins, 2008). The final sample size included 25 normotensives, and 23 hypertensives; however, only 15 of the hypertensive participants completed the testing protocol. All participants were fluent in the English language and included two left hand dominant normotensives and one left hand dominant hypertensive. The vision of all participants was normal or corrected normal. The hypertensive participants were on medically prescribed calcium channel blockers (five participants), angiotensin receptor blockers (seven participants) and angiotensin converting enzyme inhibitors with diuretics (three participants). A summary of relevant participant characteristics is provided in Table 5.2.

Tests and Procedures

Written informed consent was obtained from all eligible participants (Appendix B.1, C.3). Hypertensive participants provided details of medication use which, aside from prescribed beta blockers, did not preclude participation in this study (Appendix D.1, D.2). They were also instructed to have their physician complete and return a PARMedx form (CSEP, 2002). The Health Research Ethics Board – Health Panel of the University of Alberta approved all testing procedures (Appendix F.1, F.2).

Participants were instructed to avoid a heavy meal for four hours, or caffeinated drinks for two hours before testing. Heavy physical exercise was also to be avoided over the prior 24 hours. Participants arrived at least one hour before the scheduled test time to complete appropriate

forms and familiarize themselves with test equipment and procedures. They also completed the Physical Activity Questionnaire (PARQ), the Code for Physical Activity (Appendix E), and the Beck Depression Inventory (BDI II) (Beck, Steer, & Brown, 1996) prior to testing. Each participant was advised that he could stop the testing at any time without repercussions. After the examiner scored the BDI II and reviewed the PAR Q, given no contraindications were identified, formal testing was initiated. The examiner measured participant height, weight, head circumference, resting heart rate and blood pressure using standard procedures (ACSM, 2010). Testing period for this study was approximately 90 minutes.

Participant Preparation

The fNIRS optodes were attached bilaterally to the prefrontal region (Appendix G.1) prior to testing and remained in place for all three parts of the test. They were positioned on either side of the midline (2 – 3cm apart) just rostral to the supraorbital ridge (Vermeij, van Beek, Olde Rikkert, Claassen, & Kessels, 2012) (see fNIRS measurement below). Heart rate was monitored throughout testing with a wireless heart rate monitor (Polar Global CS 100, Finland). Initial resting blood pressure was taken at the left arm (auscultatory method) after five minutes of quiet sitting. The fNIRS machine was then turned on to start recording as the participant rested quietly for two minutes to establish baseline fNIRS signals.

The first part of testing was conducted with the participant sitting in a chair to preclude prolonged sitting on the cycle ergometer which could be uncomfortable and might have affected the control condition and testing at rest. For the control condition, the participant was instructed to repeat the vowels (***a, e, i, o, u)*** continuously for 30 seconds (Kaneko et al., 2011).

This was followed by the Stroop task which was preceded by the relevant instructions. A schematic representation of the test procedure is presented in Figure 5.1A.

Stroop Task

The standardized version of the Stroop task consists of three pages (8.5" x 11" sheet) with 100 items in five columns (20 items each). The first page involves the "neutral condition" with color words written in black ink. The second page contains color words in like colored ink (e.g. the word green in green ink), referred to as the "congruent condition". The final page or the "incongruent condition" contains color words written in different colored ink (e.g. the word green in red ink) (Golden & Freshwater, 2002). After the examiner completed the instructions, the participant was given the first page and asked to read the words aloud as quickly as possible for 45 seconds. The first page was taken away and the participant asked to read the second, then third pages in similar manner. The number of colors correctly read aloud in the 45 second period was recorded. The third page ("incongruent condition") was repeated at the designated cycling intensities. The results of the incongruent condition at rest and during both cycling intensities were used as the dependent variable for performance on the exercise-enhanced modified Stroop task.

Submaximal Cycle Trial

After completion of the modified Stroop task at rest, the participant was helped to the electronically braked cycle ergometer (Lode – Ergometrics 800, Sensormedics, CA), a process of 10 -15 seconds, and comfortably seated to begin the second part of testing (Appendix G.4). There was a two minute warm up at 0 Watts (50 – 60 rpm), which was followed by cycling for

six minutes at an absolute load of 50 Watts. In the sixth minute of this trial, the incongruent Stroop task was repeated. The blood pressure at the left arm was measured before gradually decreasing resistance and cycling cadence to cessation in 1 minute. Heart rate was monitored throughout the test which ended with a two minute rest period.

The third part of the study started after a brief period (10-15 seconds) to adjust the equipment and included a two minute warm up at a load of 0 Watts (50 – 60 rpm). Resistance was increased at a minimum of 10 Watts per minute to result in an RPE above 13, and up to 75% of age predicted $HR_{max.}$ Maximum heart rate was calculated as 220 minus age (yrs.) (ACSM, 2010). The incongruent condition of the Stroop task was repeated in the sixth minute of cycling at this relative load. Blood pressure and heart rate monitoring was as for the second part of testing. A cool down period of two minutes concluded this portion of the study with monitoring of blood pressure over the next 10 minutes to ensure return to within 10mmHg of resting levels. See Figure 5.1B for the cycle trial test procedure.

For all three parts of testing, the score on the "incongruent condition" was indicative of attentional control and cognitive flexibility; higher scores meaning lower interference and better attentional control and cognitive flexibility (Golden & Freshwater, 2002).

fNIRS Measurement and Hemodynamic Readings

A two channel dual wavelength (760nm, 850nm) fNIRS machine (Artinis Oxymon MKIV, Netherlands) was used to monitor hemodynamic changes bilaterally over the PFC throughout the three part test. Sampling was conducted at 10Hz throughout the experiment. The emitter-detector distance was 4.5cm, corresponding to approximately 2.7cm penetration depth (Minati,

Kress, Visani, Medford, & Critchley, 2011; Cui, Bray, Bryant, Glover, & Reiss, 2011), with the midpoint positioned at Fp1 and Fp2 of the international 10-20 system (Jasper, 1957). These points are designed to measure hemodynamic changes in the dorsolateral prefrontal cortex (Tanida et al., 2007; Okamoto et al., 2004).

fNIRS Data Analysis

For each of the three segments of the test protocol, delta values of O_2Hb, tHb, HHb, and HbDiff were calculated. The predetermined events were inserted during the test protocol to assist with calculation of delta values as follows: peak for each of the three parts of the procedure minus control at rest (Figure 5.2: Panels A, B, C, D, and E). The peak concentration values used were those occurring during the "incongruent" condition of the Stroop task for the three workloads. Identification of peak values was done by a colleague who was unfamiliar with the study objectives. The use of delta values for analysis is consistent with the operations of the continuous wave fNIRS device (Hoshi, 2003). These changes were calculated with the application of the modified Beer-Lambert Law (Colier, 1995) using the manufacturer supplied fNIRS software (Artinis Oxymon MKIV, Netherlands). To facilitate analysis, a moving average of five samples per second was applied to smooth the output traces. Head circumference was used as a covariate to address concerns about the varied size of the frontal sinus affecting fNIRS penetration and hemodynamic concentration changes (Hauessinger et al., 2011).

Hemodynamic efficiency measures were calculated for oxyhemoglobin, total blood volume and hemoglobin difference changes using the following formulae (a modification of Paas and Van Merriënboer, 1993):

Oxyhemoglobin Changes Efficiency = O_2Hb (mean of two sides)/Modified Stroop score

Blood Volume Changes Efficiency = tHb (mean of two sides)/Modified Stroop score

Hemoglobin Difference Efficiency = HbDiff (mean of two sides)/Modified Stroop Score

Statistical Analysis

Previous research has shown that blood pressure typically increases with age (Anson & Paran, 2005; Sairenchi et al., 2005). Therefore using age as a covariate to statistically control for the differences in performance during specific interventions between these two groups of participants is not recommended (Field, 2009). The initial sample indicated a significantly higher mean age of the hypertensive group. In order to minimize this age difference which could affect Stroop performance (Hyodo et al., 2012), the following age matching process was used. Both groups were divided into five age levels as recommended by Green and Salkind (2011) and the 15 hypertensives were matched with 15 normotensives on age levels for the remainder of the analysis. Head circumference was used as a covariate in all comparisons for the analysis.

To assess baseline group differences, unpaired t-tests were performed on participants' age, BMI, Code for Physical Activity and formal years of education. To identify difference in group performance on the modified Stroop task during the three workloads, a two-way repeated measures analysis of covariance (ANCOVA) (Group by Workload intensity) was conducted with workload as the within subject measure.

Normality of the data was initially examined using the Shapiro-Wilks test. A three-way analysis of covariance with repeated measures was performed to investigate the hemodynamic

responses. Group (normotensive, hypertensive) was the between subjects factor, while the three workloads and side (left, right) were the within subject factors. Mauchly's test of sphericity was used to examine the effect of workload in the ANCOVA, and 'F' ratios were adjusted using the Greenhouse Geisser procedure. The significant 'F' ratios were subjected to the Scheffé post hoc test. To control for Type 1 error in all analyses, Bonferroni correction for $P<.05$ was applied.

Hemodynamic efficiencies in the matched groups were compared by using a two-way repeated measures analysis of covariance (ANCOVA) (Group by Efficiency scores) for O_2Hb, tHb and HbDiff over the three workload intensities. Finally, to examine the relationship between attentional control (Stroop incongruent condition) and hemodynamic measures, we conducted Pearson Product Moment correlation coefficients between performance and the hemodynamic measures in each group. The Statistical Package Social Science Version 21 (SPSS Inc., Chicago, USA) was used for statistical analyses.

Results

Interpretation of the Three-way Analysis of Covariance

The results of the three-way ANCOVA were interpreted according to the procedure described by Keppel and Wickens (2004). Initially, the three way interaction (Group by Workload by Side) was examined. With no significant three-way interactions identified, the two way interaction (Group by Workload) was examined to compare the hemodynamic responses between the normotensive and hypertensive groups. When two way interactions were not significant the

pooled main effects of Group or Workload or Side (a total of 90 sample measurements each) were examined.

Characteristics of Participants

Some pertinent characteristics of the normotensive and hypertensive participants are summarized in Table 5.2 A, B. Despite the age matching procedure utilized, the hypertensive participants were older than the normotensives by eight years. However, there were no significant differences between the two groups on BMI, Code for Physical Activity and years of formal education. Resting systolic blood pressure was significantly higher in the hypertensive compared to normotensive participants.

Comparison of Attentional Control

There was no significant difference between the normotensive and hypertensive participants for the mean performance scores on the incongruent Stroop task across all three workload intensities (P=0.314; observed power=0.168). The main effect of workload intensity was significant (P=0.000) with the heavier workload (<75% of age predicted HR_{max}) resulting in the highest Stroop scores across both groups.

Hemodynamic Changes during Exercise-Enhanced Incongruent Stroop Task

Though a comparison of traces across groups is not entirely appropriate as per Hoshi (2003), the fNIRS trends were similar in both subject groups. A representative trace of O_2Hb and HHb hemodynamic responses over the three workloads is shown in Figure 5.2 (Panels A, B, C) as well as tHb and HbDiff responses in Panels D and E. O_2Hb, tHb and HbDiff hemodynamic responses

steadily increased with workload intensity, while HHb remained relatively unchanged during testing. During the rest period between bouts of cycling, hemodynamic responses trended towards baseline, and similarly during cool down and test termination. The two exercise conditions uniformly produced higher hemodynamic changes during the respective incongruent Stroop tasks. The changes for each hemodynamic variable are reported in Table 5.3.

For changes in O_2Hb, there were no significant differences between the two groups at rest and during the two workloads (P=0.098; Observed Power=0.379). For both groups, the main effect of workload was significantly higher during cycling up to 75% of age predicted HR_{max} (P=0.001; observed power = 0.938).

The tHb changes were statistically significant with higher changes occurring in the normotensives (P=.046; Observed Power=0.521). There was a significant main effect of workload, similar to O_2Hb, with the relative workload producing higher tHb responses across the groups (P=.002; observed power=0.925).

The HbDiff was not significantly different between the two groups (P=0.76). There was a significant main effect of workload intensity across the groups with the relative workload intensity resulting in the highest HbDiff (P=.000; observed power=0.993).

Efficiency Scores

For tHb efficiency, the normotensives were significantly higher across the three workloads (P=.036; Observed Power=0.565). HbDiff and O_2Hb efficiency scores were not significantly different between the groups. Note Figure 5.3 (Panels A, B, C) for comparison of group

efficiencies. Significantly higher efficiency scores were also noted at the higher exercise intensity for both groups on O_2Hb (P=.002), tHb (P=.005) and HbDiff (P=.000).

Correlations between Stroop Score and Hemodynamic Changes

The Pearson correlations between modified Stroop test performance and the PFC hemodynamic changes at rest and during exercise are summarized in Table 5.4. Significant correlations were observed between incongruent Stroop scores at rest and corresponding hemodynamic changes in both groups. In the hypertensive group significant positive correlations were observed as follows (1) O_2Hb and the modified Stroop scores in the right PFC $_{(\alpha 1=.05)}r_{(15)}$ =0.459; (2) HbDiff and modified Stroop scores in the right PFC $_{(\alpha 1=.05)}r_{(15)}$ =0.484; (3) HbDiff and modified Stroop scores in the left PFC $_{(\alpha 1=.05)}r_{(15)}$=0.419. For the normotensive group, significant negative correlations were noted as follows: (1) HbDiff and modified Stroop scores in the right PFC $_{(\alpha 1=.05)}$ $r_{(15)}$ =-0.579; and (2) HbDiff and modified Stroop scores in the left PFC $_{(\alpha 1=.05)}$ $r_{(15)}$ =-0.577. None of the correlations between Stroop scores and the changes in the hemodynamic responses during exercise at the two workloads were significant.

Additionally, regression analysis was performed to determine the total variance in hemodynamic changes explained by changes in mean arterial pressure (MAP) and heart rate during exercise enhanced modified Stroop performance. Coefficient of determination (R^2) was not significant for either group for O_2Hb, tHb or HbDiff changes when regressed on changes in MAP or heart rate.

Discussion

Hypertension-related small vessel disease may result in alteration of attentional control and cognitive flexibility performance when the individual is subjected to varying levels of physical stress. The results of these performance measures and accompanying hemodynamic changes will be compared with normotensives from the following standpoints: (1) exercise-enhanced attentional control performance; (2) the hemodynamic changes that accompany the performance; (3) the cognitive efficiency related to the performance; and (4) the relationship between the hemodynamic responses and performance.

Exercise-Enhanced Attentional Control Performance

Based on previous research (Raz & Rodrigue, 2003; Elias, Wolf, D'Agostino, Cobb, & White, 1993; Yanagisawa et al., 2010; Hyodo et al., 2012), it was hypothesized that the hypertensive group would demonstrate impaired performance on the incongruent Stroop task during different workload intensities. The current results did not support this hypothesis as there was no significant difference between the two groups on Stroop task performance at rest and during exercise. There was a tendency for the hypertensive group to demonstrate higher scores (12 – 15%), but these findings were not significant.

Unique to this study was testing of attentional control/cognitive flexibility (proxy for executive function) while simultaneously engaging in physical exercise of various intensities. It was anticipated that the cerebral blood flow and reactivity changes would highlight any cognitive flexibility differences between the groups on a dual activity. Possible explanations for the unexpected findings in performance pertain to hypertension-related issues and include:

(1) *Age* - This study had hypertensive participants 56 years old and younger, all relatively active physically and occupationally, similar to the normotensive group. Until recently, such a highly active group would be unusual for hypertensive studies (Anson & Paran, 2005). Previous research that has shown impaired cognitive function in hypertensives includes classical longitudinal studies with cognitive testing up to 20 years after the initial hypertension diagnosis. By then the patients were usually elderly and certainly beyond their most active years, (Elias et al., 1993; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998). This is important since the reason for such studies was primarily to establish a reported impact of hypertension on cognition, and not, as in this study, predicated on human performance and efficiency. Studies showing reduced cognitive performance in younger age groups generally utilize broad cognitive measures such as academic achievement tests (Kwak et al., 2009; Chaddock et al., 2012). Such tests, implicit by their design, examine multiple cognitive domains and are not typically administered during exercise. The present study departs from this customary approach with results that suggest a change in thought direction which emphasizes a more active paradigm to cognitive testing in the disease.

(2) *Evaluating Cognitive Function* – The cognitive measures generally used in assessing hypertension are numerous, and emphases on specific cognitive domains tend to be absent (Jacobs et al., 2013; Anson & Paran 2005) This adds to the confusion of what specific cognitive capabilities are impaired in hypertension, not to mention the added dimension of "normal" age related changes to cognition. Research has demonstrated that elderly hypertensives (65 – 79 yrs.) can perform as well as normotensives on

cognitive tests of accuracy, cognitive flexibility and cognitive speed (Kivipelto et al., 2001). The East Boston Epidemiological Study of the Elderly (Glynn et al., 1999) demonstrated that prospectively there was little evidence that blood pressure was related to cognitive decline in the elderly. This is also consistent with the SHEP Study that demonstrated levels of cognitive performance to be similar in controls and hypertensives (treated and untreated) over 60 yrs. The regularly cited Framingham Heart Study showed an inverse relationship between blood pressure and cognitive performance on only 4 out of 8 cognitive subscales (Elias et al., 1993). In that study there was a 12 – 14 year window between blood pressure measurement and assessment of cognitive function. These reports suggest that hypertension impairs some cognitive domains, but interestingly may improve other domains (Anson & Paran, 2005). Further, none of these studies evaluated cognitive function under varying degrees of physical stress which would be more representative of daily function. More recently, Maillard et al. (2012) reported cognitive decline at younger ages (40s) in hypertensives than previously identified. This finding suggests that a more active approach to assessment of cognitive function in hypertension would be appropriate.

(3) *The Exercise Dimension* - It is a generally accepted that acute exercise affects information processing in the CNS (Kamijo et al., 2004). Moderate intensity exercise, as utilized in this study, has a positive impact on CNS activity including performance on the Stroop task (Endo, Matsukawa, Liang, Nakatsuka, & Okamura, 2013), as well as P300 amplitude, an event related potential (ERP) component (Kamijo et al., 2004). The P300 is considered an index of cerebral activity during working memory and decision making

(Donchin & Coles, 1988) with increased amplitude denoting higher brain activity. Magnié et al. (2000), recently supported by Byun et al. (2014), suggested that these effects of exercise on the CNS are related to arousal with its widely described inverted U-shaped function (Yerkes & Dodson, 1908). In this study arousal was not explicitly measured. However it is possible that awareness of their hypertension diagnosis combined with knowledge of the value of exercise in the care of cardiovascular diseases like hypertension, resulted in enhanced arousal in the hypertensive group. Awareness of hypertensive status has been demonstrated to induce a significant increase in circulating catecholamines and general arousal on mental tests (Rostrup & Ekeberg, 1992; Rostrup, Kjeldsen, & Elde, 1990; Hamer, Batty, Stamatakis, & Kivimaki, 2010; Hamer, Taylor, & Steptoe, 2006).

The hypertensive group in this study was highly educated, and expressed being health-conscious and highly inquisitive about their condition to the examiner. Twelve of the fifteen hypertensives were white collar professionals who reported high participation levels in exercise and expressed awareness of its potential in hypertension control. The significant and consistent increase in modified Stroop performance with exercise intensity as shown in this study might be explained by increased arousal levels in both groups. However, in this particular sample of hypertensives, whose blood pressure was medically well controlled, there appears to be a positive effect on performance likely mediated by arousal. Competition for blood flow between the peripheral muscles and the PFC during cycling can potentially offer some explanation for the unexpected results between the groups. In addition, Hyodo et al. (2012) suggested that exercise improved

performance on the Stroop test in older participants (64 – 74yrs). These researchers also postulated that there was a hemodynamic compensatory involvement of the hemispheres as measured by fNIRS. In the present study two different intensities of exercise – an absolute and a relative load – demonstrated the higher intensity relative load resulted in better performance on the cognitive task. However, the relative intensity exercise was performed after the lighter absolute load (non-randomized) and a practice effect known to occur on the modified Stroop task (MacLeod, 1991), might have influenced the results. Comparing prior research findings with the present study suggests we might be very early on a line of research that investigates the effects of exercise in a hypertensive brain that may have a degree of hemodynamic compromise.

(4) *Hypertension Treatment Status* – The search for the potential association between hypertension and altered cognitive function has led not only to greater hypertension research in the elderly, but until recently, a tendency to recruit untreated hypertensives in clinical trials (Anson & Paran, 2005). Hence it could be argued that findings of impaired cognition in such populations might not be applicable to one of relatively active non-depressed young men with well controlled blood pressure as was the case in the present study. A curvilinear relationship between blood pressure and cognitive performance, as reported in the East Boston Study, suggests low and high blood pressure may result in cognitive impairment many years later while moderate hypertension may enhance cognitive functioning (Glynn et al., 1999). Kivipelto et al. (2001) reported that the odds of the mild hypertensive developing cognitive impairment were equal to or less than that of the normotensive. These are findings of not too recent

studies with conflicting information, clearly at odds with results of Maillard et al., (2012), neither of which explains the performance in an acute situation as in this study. Reviewing the hemodynamic changes in hypertensive populations may help explicate this complex relationship between hypertension and cognitive performance.

Hemodynamic Changes and the Exercise-Enhanced Stroop Performance

The normotensive group demonstrated significantly higher tHb than the hypertensives, but not higher O_2Hb or HbDiff over the three exercise intensities, thus offering partial support for the second hypothesis. The lack of a significant difference in O_2Hb between the two groups is consistent with the findings of Ando et al. (2011). They used the Eriksen flanker task (similar to the Stroop task) during submaximal exercise and found that the improved performance was independent of oxygenation changes in the PFC. In this study, the higher exercise intensity consistently resulted in significantly higher PFC hemodynamic changes and performance in both groups, but did not explain the lack of the anticipated difference in performance between the groups.

Although the hypertension literature is largely silent on hemodynamic changes in cognitive performance, the debate on age differences in cognitive activation studies in general may present thought trends that offer explanations for findings of enhanced (or non-impaired) performance in younger hypertensives. Laguë-Beauvais et al. (2013) reported that the interference effect of the Stroop task produced little activation in the PFC in healthy young adults while activation of both right and left PFC was noted in healthy older participants. This suggests that brain activation levels tended to be more readily observed when functioning

under sub-optimal conditions which may occur with aging, and relevant to this study, possibly in hypertension. Such differences, especially with respect to efficiency and performance, may be at play in the normotensive-hypertensive hemodynamic question; and the compensatory effect in cortical activation as suggested by Hyodo et al. (2012) may be more apparent with exercise of moderate intensity.

Cognitive Efficiency and Incongruent Stroop Performance

The normotensive group showed significantly higher efficiency than the hypertensives when tHb changes were used as a function of Stroop performance (Figure 5.3). Although the normotensive group was more efficient, the hypertensive group appeared to perform equally on the incongruent Stroop task. This suggests that the efficiency measures calculated using hemodynamic scores may not be relevant to hypertensives at least in this age group. Further, it supports the results of Ando et al. (2011) that attentional control tests such as the Stroop and Eriksen flanker task produce increased performance during exercise independent of oxygenation levels in the PFC. In healthy populations, several neuroimaging studies have demonstrated that higher efficiency does not necessarily mean better behavioral performance (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). These authors suggested that better performance may be indicative of the repertoire of compensatory strategies used by the individual or group. Such behavioral repertoire in the high performing, well-educated, relatively young hypertensives may be indicative of educational awareness of the disease and general healthy lifestyle to combat the disease. It is also conceivable that arousal levels in the hypertensives facilitate increased use of these and other compensatory strategies thereby

optimizing performance more readily than the more efficient normotensive. Correlational analysis between performance and hemodynamic responses present another dimension to explaining these findings.

Correlations between Hemodynamic Responses and Attentional Control

The current findings indicate significant correlations between modified Stroop performance and the changes in O_2Hb as well as HbDiff in both groups only at rest (Table 5.4). This partially supports the hypothesis postulated and suggests that the hemodynamic changes during exercise alter this relationship in yet unexplained ways. In the case of normotensives, significant negative correlations between HbDiff and attentional control were noted. These findings are similar to those of previous work done in our lab with young healthy male participants (being submitted for publication). The differing relationship between hemodynamic responses in exercise-enhanced attentional control versus rest may be related to the physiological mechanisms in arousal accompanying exercise (Kamijo et al., 2004). Increase in circulating catecholamines accompanying exercise and the positive effects of moderate intensity exercise on cognitive activity (Nakamura et al., 1999; Hyodo et al., 2012; Yanagisawa et al., 2010) are possible mechanisms explaining the impact of exercise on attentional control. The degree of arousal in the two groups and each group's proximity to optimal arousal level may have influenced behavioral performance on the modified Stroop task. Future research is required to explain this hypertension-exercise-cognition interaction and overcome challenges of exercise/cognition type study designs.

Limitations

The current findings should be interpreted in light of the following:

(1) *Hypertension awareness and sample size*: The sample of 15 hypertensives was comprised of highly educated, physically active individuals who expressed knowledge of the value of an active lifestyle in treating hypertension. This would limit the generalizability of the findings to other hypertensives. In addition, group differences on oxygenation were not significant with low statistical power. This study should be replicated with a larger sample as the trends with the present small sample suggest important findings on cognition and hypertension are imminent.

(2) *Degree of hypertension*: This study, like the majority of hypertension studies, utilized a dichotomy of hypertensive versus normotensive (Anson & Paran, 2005). The cut-off between the two states of health is arbitrary and has been changing over the years as more information is revealed on complications of higher blood pressure. Blood pressure is a continuous scale and it is difficult to say that the present cut-off point used to establish the diagnosis of hypertension has more negative pathophysiological changes than pressures a few points lower. In a poorly charted area of study, the cut-off points for hypertension using a dichotomous scale, might be causing loss of information on the real relationship between cognitive performance and blood pressure levels (Jacobs et al., 2013).

(3) *Time since diagnosis of hypertension*: In this study, the time since the initial hypertension diagnosis ranged from 1 to 20 years and therefore the likely

pathophysiological changes would be highly varied. Thus the vascular responses supporting the change in cognitive performance attributable to hypertension could not be accurately quantified. Details of ischemic changes evident from Functional Magnetic Resonance Imaging (fMRI) would be helpful in establishing the relationship between hemodynamic changes and performance in the disease.

(4) *Pharmacological control of hypertension*: In this study, blood pressure in the hypertensive group was well controlled in most cases with medication. These medications have differing mechanisms of action in lowering blood pressure. There is limited information about their impact on cognitive function at rest, not to mention cognitive function during exercise.

(5) *Nature of the cognitive test*: The modified Stroop task used in this study tended to narrow the cognitive domain studied which may be useful in isolating the sources of variation involved in the cognition-hypertension interaction. Further testing of discrete cognitive domains, meaningfully defined, will more likely advance the hypertension-cognition debate. In addition, the modified Stroop task was performed at three different workload intensities which were not randomized, with Stroop at rest and during the absolute load exercise preceding the higher intensity relative load exercise. Practice effect on the Stroop task and its intersection with different workload intensities was not clearly apportioned in this study. Further, given the length of the testing procedure and the effects of two bouts of exercise, mental and or physical fatigue could have impacted the results.

a. *Use of continuous wave near infrared spectroscopy*: Continuous wave fNIRS does not indicate absolute values of the hemodynamic changes during performance. The use of delta values therefore limits the application of these results and generalizability of the findings. Another important measurement issue is the potential impact of systemic physiological fluctuations on fNIRS measured hemodynamic changes, particularly with exercise. Though post-study regression analysis revealed no significant explanation of the total variance in hemodynamic responses by changes in mean arterial pressure or heart rate, replication of this study with a greater number of fNIRS channels and better physiological controls is warranted. One such control may be as advocated by Gagnon et al. (2012) to reduce superficial contamination with short optode separation measurements. Additionally, only the amplitude measure was used in the analysis of fNIRS traces. Comparison of these results with other approaches such as "area under the curve" would be appropriate.

(6) *Age:* Despite matching on age levels, the eight year age difference between the groups will provoke questions on the confounding effects of age on cognitive findings in a hypertensive population. A larger sample with tighter age matching is appropriate to help clarify the relationship between the subject groups.

Conclusions

In the present study, relatively young stage 1 male hypertensives demonstrated no significant impairment in performance on the exercise-enhanced modified Stroop task when compared to age-level matched normotensives. Cognitive performance appeared to be independent of oxygenation changes, and as expected, the normotensive group was significantly better on tHb efficiency. The apparent independence of performance from oxygenation and performance from superior hemodynamic efficiency are new findings in the area of hypertension research. The enhancement of the Stroop task with moderate intensity exercise might have brought the group of relatively young hypertensives closer to optimum arousal in the test situation. It is hoped that this exercise-based approach to cognition and hypertension will be pursued in the interest of a rehabilitation-type paradigm in hypertension therapy.

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Table 5.1: Inclusion and exclusion criteria for the normotensive and hypertensive participants

Group	Inclusion	Exclusion
Normotensive	• Males • Age 18 – 56 • No history of hypertension or cardiovascular disease • No history of neurological or psychiatric disorder	• Smoker • Regular use of prescription or non-prescription medication or illegal drugs • English language communication difficulty • Participating in similar study • Beck Depression Inventory (BDI II) score >13 (Beck, Steer & Brown, 1996). • +ve PARQ
Hypertensive	• Males • Age 18 – 56 • History of high blood pressure > 1 year (confirmed by a physician licensed in the province of Alberta) • No history of dementia, stroke, heart attack or kidney disease • No history of neurological or psychiatric disorder	• Smoker • English language communication difficulty • Participating in similar study • Hypertension beyond stage 1 (above 159/99mmHg) (Chobanian et al., 2003), hypertension deemed not to be fully controlled or on beta blockers • Beck Depression Inventory (BDI II) score >13 (Beck, Steer & Brown, 1996). • +ve PARQ

Table 5.2A: Participant characteristics for normotensive and hypertensive males (mean±SD) at rest

Group	Age	BMI	Code for Physical Activity	Yrs of Formal Education	Resting Systolic BP (mmHg)	Resting Diastolic BP (mmHg)
Normo (N=25)	34.47±8.79	27.56±3.37	4.53±2.13	16.40±2.38	117.27±11.27	81.80±5.73
Hyper (N=15)	42.86±11.51*	28.40±4.00	4.67±2.19	17.40±2.77	130.47±12.73ʃ	85.67±5.00

Table 5.2B: Participant characteristics for normotensive and hypertensive males (mean±SD) during cycling

Group	Mean Arterial Pressure Change (Rest-Peak Exercise)	Change in Heart Rate (Rest-Peak Exercise)	Mean RPE at Peak Exercise	Mean Power (Watts) at Peak Exercise
Normo (N=25)	4.55±5.91	46.73±7.70	14.3±1.55	101.33±22.71
Hyper (N=15)	6.20±5.50	43.13±5.41	14.6±1.58	93.57±22.48

*P=.03 (hypertensive group - older)

ʃ P=.000 (hypertensive group - higher systolic BP)

Code for Physical Activity = /7 (Ross & Jackson, 1990)

Normo = normotensive; Hyper = hypertensive

Table 5.3: Summary of matched modified Stroop performance and mean hemodynamic changes at three workloads for normotensive and hypertensive participants (mean ± SE)

Variable/Group		Rest	50W	75% HRmax
Stroop Performance				
Normotensive N=15		38.533±3.473	43.267±3.644	46.00±3.728*
Hypertensive N=15		42.333±3.473	48.267±3.644	52.333±3.728*
Oxyhemoglobin				
Normotensive	Right	2.146±.449	3.133±.707	5.090±.892
N = 15	Left	2.883±.604	2.876±.634	5.039±.892
Hypertensive	Right	2.345±.449	1.723±.707	2.989±.897
N = 15	Left	1.806±.604	1.799±.634	3.388±.892
Deoxyhemoglobin				
Normotensive	Right	.394±.361	.824±.458	1.515±.502
N= 15	Left	.888±.477	.433±.306	.828±.511
Hypertensive	Right	-.638±.361	-.322±.458	.504±.502
N = 15	Left	-.394±.477	-.026±.306	.476±.511
Total Hemoglobin				
Normotensive **	Right	2.470±.673	3.906±.998	6.480±1.153∫
N =15	Left	3.907±.934	3.752±.951	6.070±1.157∫
Hypertensive	Right	1.747±.673	1.493±.998	3.507±1.153∫
N = 15	Left	1.414±.934	1.771±.951	3.828±1.157∫
Hemoglobin diff				
Normotensive	Right	1.821±.460	2.359±.642	3.899±.881∫
N =15	Left	1.859±.535	1.653±.663	4.060±.862∫
Hypertensive	Right	2.943±.460	1.952±.642	2.482±.881∫
N = 15	Left	2.200±.535	1.802±.663	2.947±.862∫

∫ Relative load (<75%HR_{max}) produced higher responses than other intensities for O_2Hb, tHb, HbDiff (P<.005)

*Stroop performance score significantly increase with both higher workloads (P<.000)

** Normotensives produce higher overall tHb responses than hypertensive (P=.046)

Table 5.4: Pearson product moment correlations between matched modified Stroop performance scores and hemodynamic measures in normotensive and hypertensive groups

Variable/Group		Rest	50W	75% HRmax
Oxyhemoglobin				
Normotensive	Right	-.148	.272	.423
N=15	Left	-.423*	.261	.407
Hypertensive	Right	.459*	.084	.132
N=15	Left	.154	-.155	-.154
Deoxyhemoglobin				
Normotensive	Right	.364	.124	.266
N=15	Left	-.005	-.438*	-.032
Hypertensive	Right	-.381	.209	.291
N=15	Left	-.408	.259	.374
Total Hemoglobin				
Normotensive	Right	.102	.228	.419
N=15	Left	-.231	.169	.335
Hypertensive	Right	.396	.183	.229
N=15	Left	-.074	.016	-.041
Hemoglobin Difference				
Normotensive	Right	-.579*	.259	.365
N=15	Left	-.557*	.300	.399
Hypertensive	Right	.484*	-.034	-.017
N=15	Left	.419*	-.262	-.236

***Correlation significant P<.05**

Three parts of the Stroop Task at rest

Baseline 2 min	Part 1: Control condition	Instructions	Neutral Stroop 45 sec	Congruent Stroop 45 sec	Incongruent Stroop 45 sec

Time (min)

Figure 5.1A: Test procedure during the modified Stroop Task in normotensive and hypertensive participants at rest

Baseline: 2min	Cycling warm-up 2min at 0Watts	Part 2: Cycling at 50 Watts for 6 min Part 3: Cycling at <75% HR_{max} for 6 min	Incongruent Stroop Task - 45 sec	Cool-down for 2min

Time (min)

Figure 5.1B: Test procedure during the modified Stroop Task in normotensive and hypertensive participants during exercise.

Note: During the two exercise phases only the incongruent part of the Stroop task was used in the protocol.

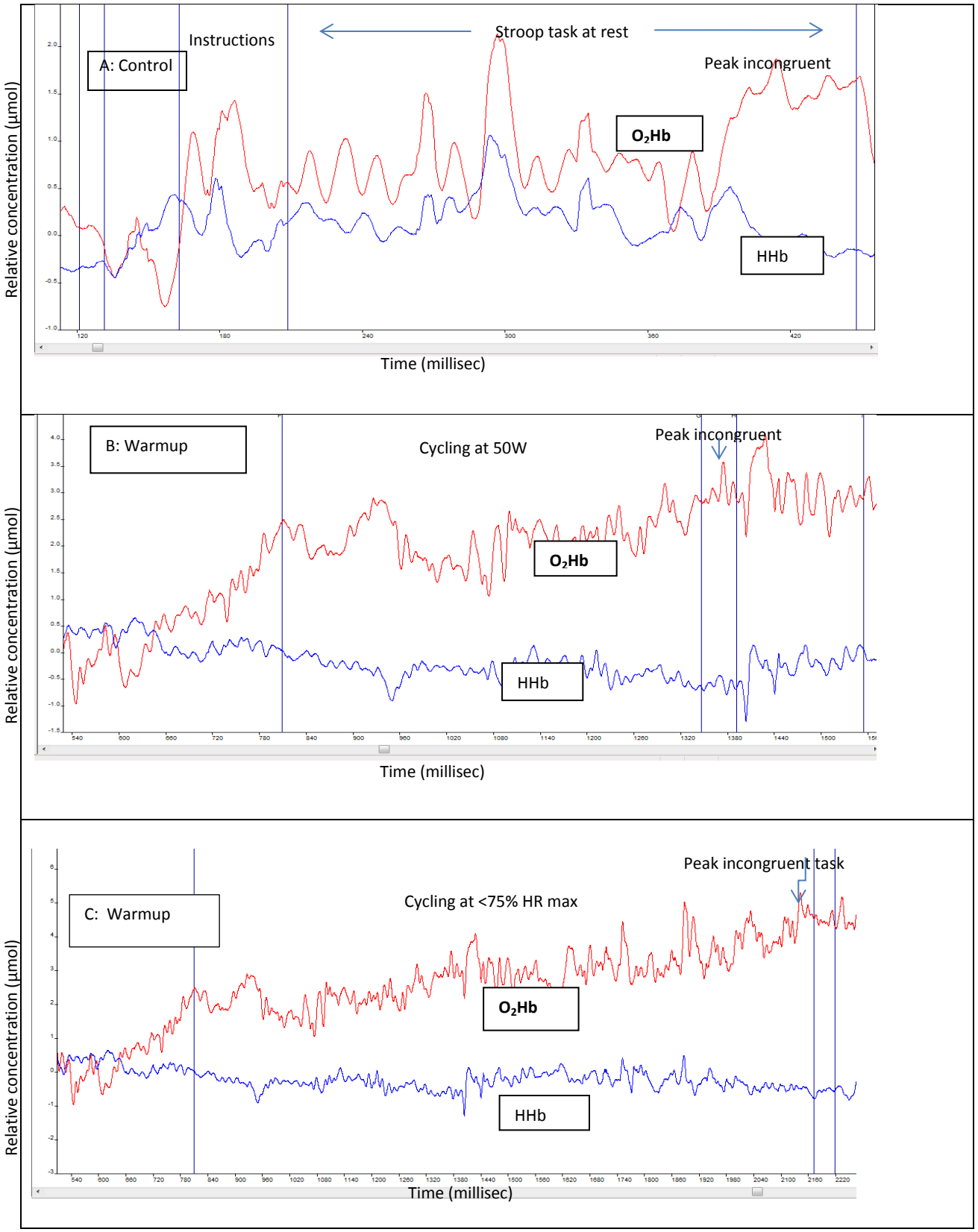


Figure 5.2: Panel A, B, C – Representative trace of three workload intensities of a hypertensive participant for O_2Hb and HHb.

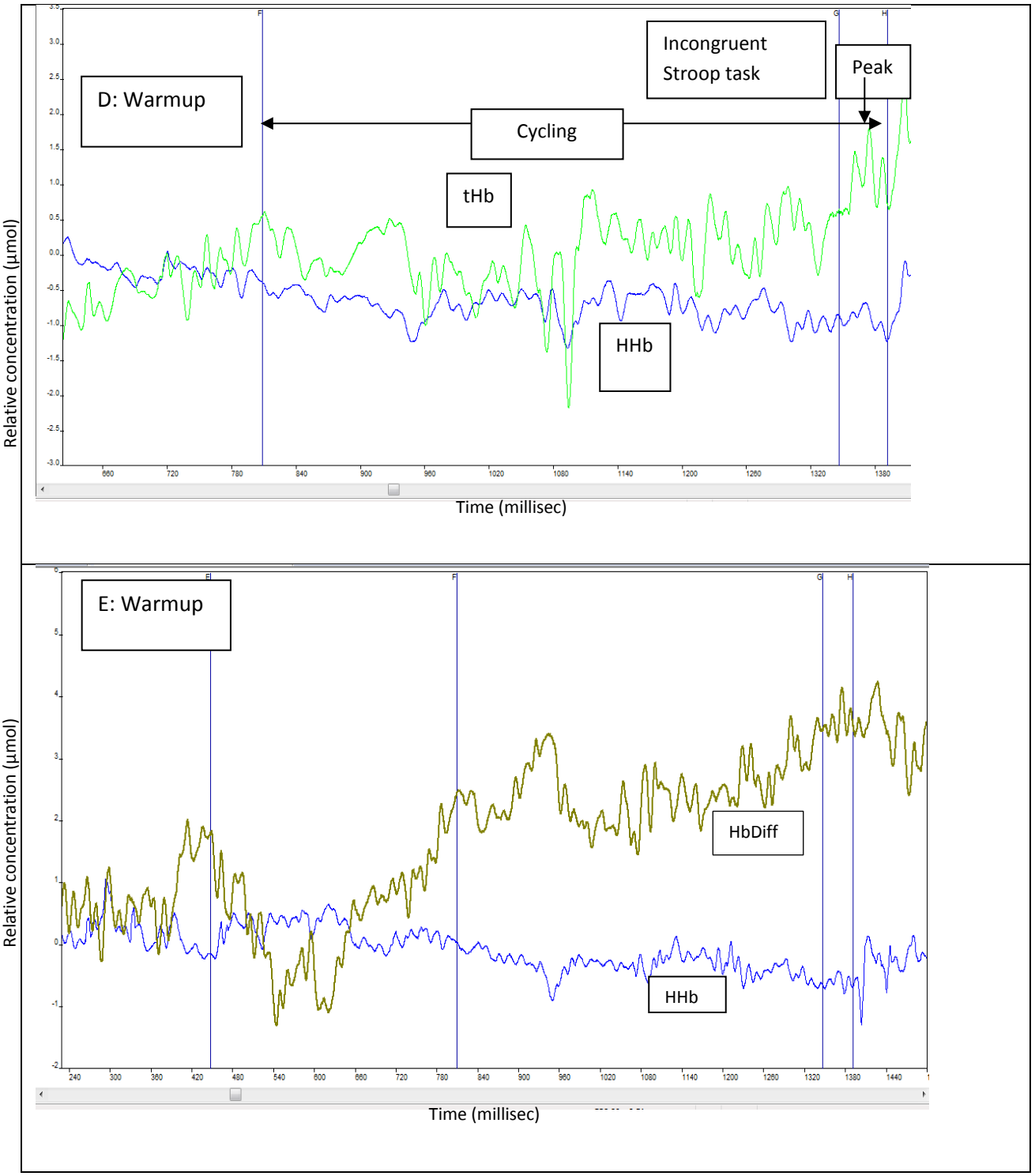
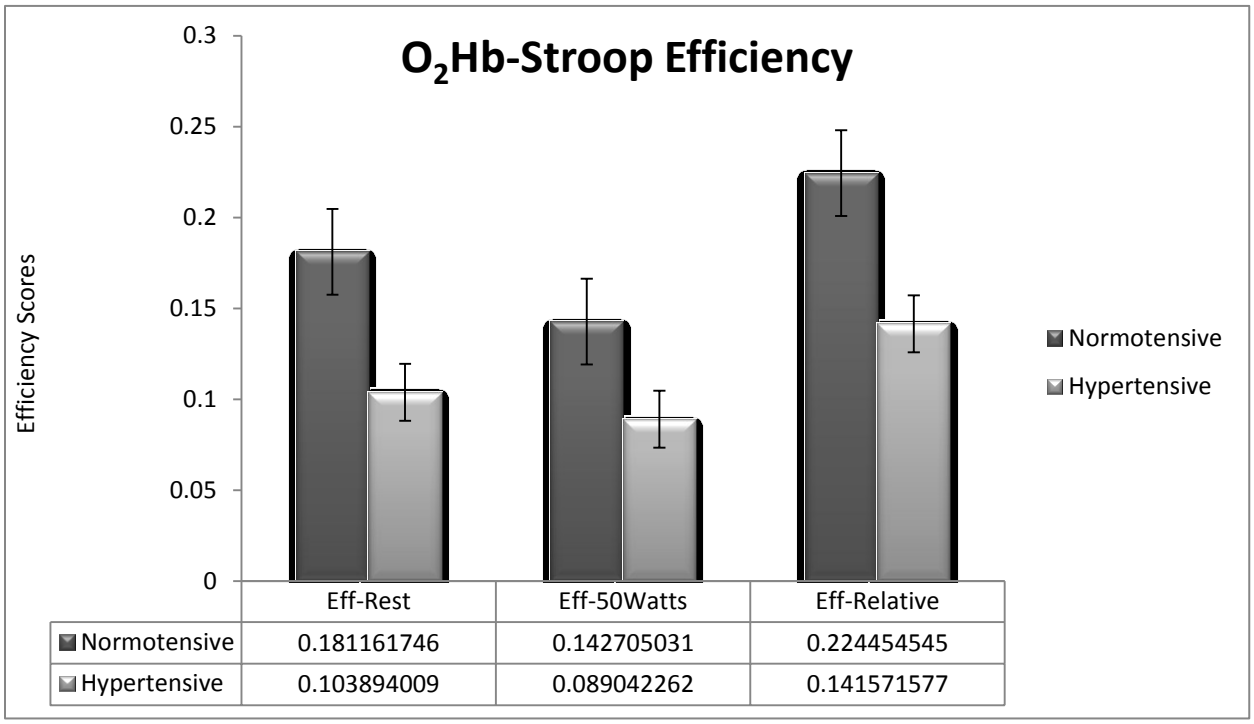


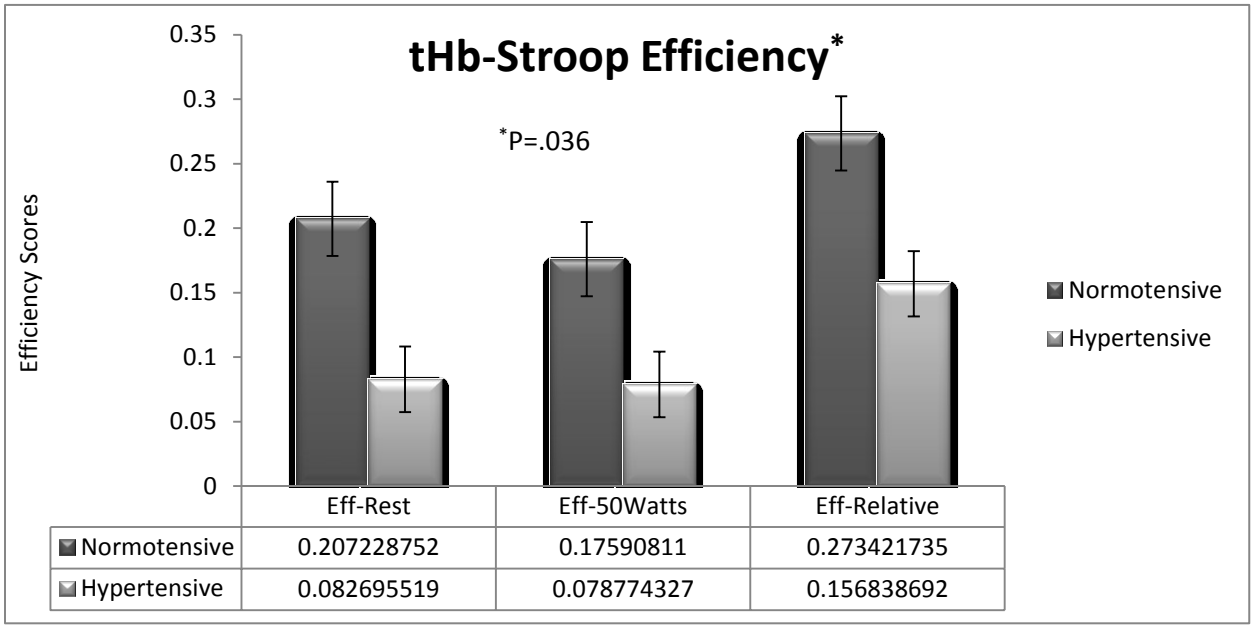
Figure 5.2: Panel D, E - Representative trace pattern for tHb and HbDiff in hypertensive participant.

A.



	Eff-Rest	Eff-50Watts	Eff-Relative
Normotensive	0.181161746	0.142705031	0.224454545
Hypertensive	0.103894009	0.089042262	0.141571577

B.



	Eff-Rest	Eff-50Watts	Eff-Relative
Normotensive	0.207228752	0.17590811	0.273421735
Hypertensive	0.082695519	0.078774327	0.156838692

Figure 5.3(Panel A, B): Efficiency scores for oxyhemoglobin and total blood volume changes during modified Stroop at rest and cycling for normotensive and hypertensive participants.

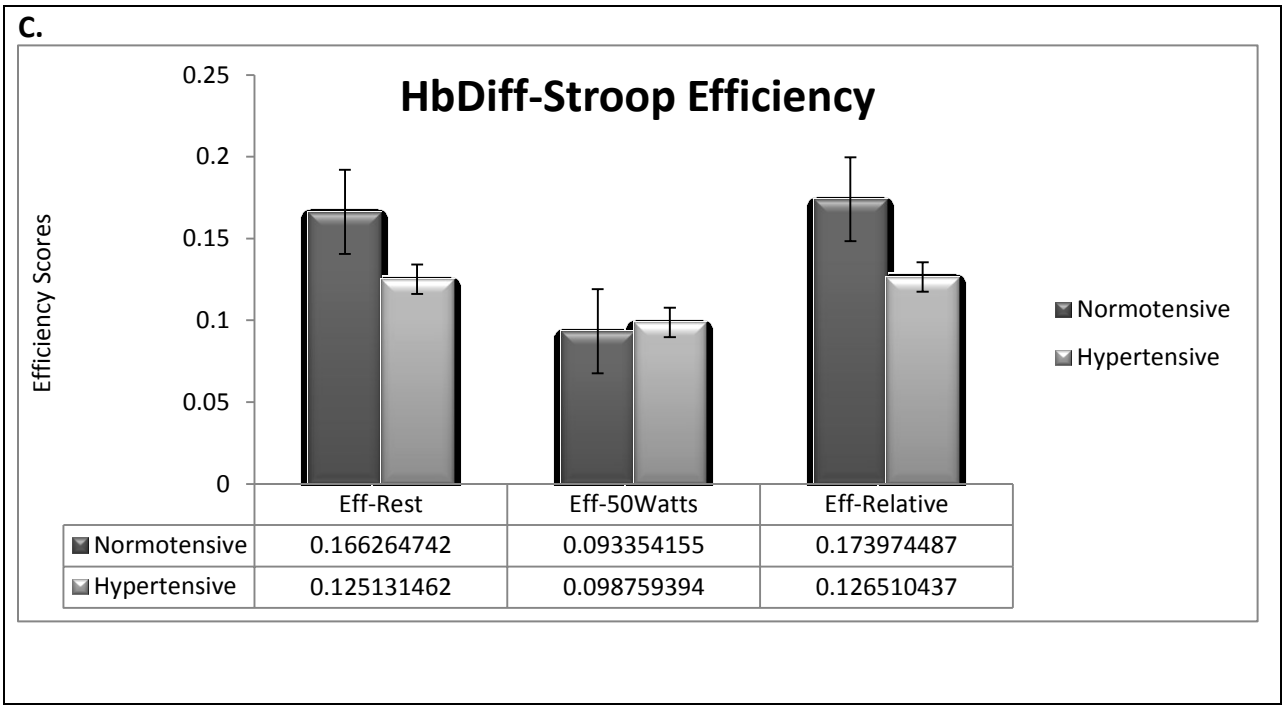


Figure 5.3(Panel C): Efficiency scores for hemoglobin difference changes during modified Stroop at rest and cycling for normotensive and hypertensive participants.

Chapter 6

General Discussion and Conclusions

Over the past 70 years, definitions of optimal health have evolved from a mere absence of disease and impairment to levels of performance and functional status (Bornman, 2004; Bruyere & Van Looy, 2005). Consistent with the more recent definition, rehabilitation science focuses on functional performance and maximizing physiological reserve (University of Alberta, 2013). This approach is compatible with evolving trends in cognition and hypertension research that emphasize structural and functional change in preference to identifying a global impact of the disease on the brain (Elias, Goodell, & Dore, 2012). Congruent with this model and in the context of functional performance and efficiency, the present project compared performance and the accompanying hemodynamic responses in the prefrontal cortex (PFC) during tests of cognition between normotensive and hypertensive using a variety of interventions.

Reliability of Functional Near Infrared Spectroscopy in Hypertension

Functional near infrared spectroscopy (fNIRS) (Artinis MKIV, Netherlands) was used to measure real-time microvascular hemodynamic changes in normotensive and stage 1 hypertensive males within the age range of 19 to 56 years. The first study demonstrated moderate to high levels of reliability of fNIRS-measured hemodynamic responses during hypercapnia followed by postural change in both groups. It also identified moderate reliability in fNIRS-measured CO_2 reactivity over the PFC of both normotensive and hypertensive participants. This is a new development and can serve as a foundation in informing treatment approaches based on hemodynamic adjustment in the disease.

There was a tendency for CO_2 reactivity to be impaired in the hypertensives compared to the normotensive which was consistent with previous hypertension studies (Hajjar, Zhao, Alsop, & Novak, 2010; Ficzere et al., 1997).The postural stress (post hypercapnia) during testing utilized the positions that are typically used in the clinical evaluation of postural hypotension (Naschitz & Rosner, 2007), thus offering a somewhat standard approach to testing reactivity in hypertension. In this disease, it is generally accepted that the cerebral autoregulatory curve is shifted to the right (Grossman & Messerli, 1992). Consequently, cerebral hypoperfusion (and syncope) can result from sudden or prolonged upright positioning at perfusion pressures that are higher than in the normotensive. This is clinically relevant in surgical positioning with general anesthesia (Lovell, Marshall, Elwell, Smith, & Goldstone, 2000) and in cerebrovascular accidents during periods of impaired cerebrovascular reactivity (Atkinson, Jones, & Ainslie, 2010). Application of these study findings can facilitate appropriate intervention in related circumstances which in turn may affect quality of life issues affiliated with cognition.

Cognitive Performance and Hypertension

Findings of the second study indicated significant impairment in working memory performance of the hypertensives. Consequently, executive function and human productivity that hinges on elemental working memory may also be compromised in this population (Elias et al., 2012; Rabbitt, 1998). These findings are consistent with a growing body of research on cognition and hypertension (Elias et al., 2012; Kotchen, 2011). Impaired hypertensive performance on working memory was accompanied by a trend of higher O_2Hb, tHb and HbDiff as well as decreasing efficiency scores. This suggests greater hemodynamic output albeit for a relatively

impaired performance in the hypertensives. Such a decrease in efficiency may be relevant to learning patterns in the hypertensive and may be useful for psychotherapeutic intervention.

Altered functional asymmetry across the prefrontal lobes in the hypertensive group was suggested by sharper increases in the left hemodynamic responses during working memory testing. Issues of inter-hemispheric changes as part of a compensatory strategy by the hypertensive brain are widely known in aging studies. The findings of this study, should they be confirmed, would for the first time identify a compensatory mechanism in the hypertensive brain that resembles a premature aging phenomenon (Reuter-Lorenz & Cappell, 2008; Jacobs et al., 2013). Coaction of working memory testing with other interventions, for example simultaneous exercise, may facilitate this compensation and may suggest therapeutic strategies. However, to our knowledge, the issue has not been examined which motivated our final study.

Exercise-Enhanced Attentional Control in Hypertension

The final study examined the hemodynamic responses in the PFC during a cognitive flexibility task during cycling at absolute (50W) and relative workloads. This dual approach evaluated attentional control during rest and various cycling workloads which may resemble the taxing of physiological reserves accompanying many functional tasks (Holtzer et al., 2011). Behavioral performance, as examined by the modified Stroop task, indicated no significant difference between the normotensive and hypertensive groups at different workloads. However there was a significant increase in tHb accompanied by an increase in efficiency (tHb/modified Stroop performance) in the normotensive group. This was an expected finding (Suhr & Chelberg,

2013), but was consistent with hypertensive trends of decreased reactivity in study 1 and significant working memory impairment in study 2.

Within each group, significant correlations were demonstrated between behavioral performance and the O_2Hb and HbDiff variables only at rest. This significance was not evident during exercise, possibly due to the arousal changes that accompany active exercise (Kamijo et al., 2004; Byun et al., 2014). The altered relationship as a result of different exercise intensities may indicate an avenue for therapeutic intervention as suggested by Hamer, Jones and Boutcher (2006) for the offspring of hypertensives, and is indirectly supported in healthy populations as noted by Endo et al. (2013). Further, these findings among young well educated and reasonably active hypertensives may be identifying a non-linear relationship between cognitive behavioral performance and hemodynamic responses previously noted in older hypertensives (Anson & Paran, 2005; Waldstein, Giggey, Thayer, & Zonderman, 2005). This highlights the less than straightforward relationship between cognitive performance and hypertension which likely will continue to have significant implications on health and productivity.

Implications for Clinical Practice

The impact of hypertension as measured by disability adjusted life years (Campbell, McAllister, & Quom, 2012; Vasan, 2009) entreats new therapeutic approaches which are predicated on issues of human performance. Understanding the microvascular modifications of the disease on cognitive function will help to craft strategies which may eventually ameliorate the related disability. The robustness of fNIRS measures of cerebrovascular reserve in this project offers

physiologically specific monitoring within the PFC which should be used as a building block for therapeutic intervention.

The present project focussed on men who were 56 years and younger, apparently in their most productive years. This is also the demographic least likely to be aware of their hypertension status and thus least likely to be treated (Campbell et al., 2012). Developing a greater awareness in this group as well as among the wider scientific community of how the so-called "silent killer" alters brain function at the microvascular level will help to foster improved adherence to treatment.

Therapeutic approaches, often used in Rehabilitation Medicine, are under-researched and under-utilized, but may in the future become highly relevant to young hypertensives. The imminent surge in cognitive impairment, a major part of which is hypertension-related, necessitates the urgent development of strategies and techniques that fit the thrust of improvement in functional performance. The 80 million prescriptions which were written in Canada for antihypertensive drugs in 2010 (IMS Health, 2011) indicate an unbalanced therapeutic strategy. It is anticipated that the current findings using a real-time non-invasive technique will stimulate further research to develop a new therapeutic paradigm around hypertension.

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Appendix A

Modified Lambert-Beer Law

The technique of fNIRS is based on the modified Lambert-Beer Law (See Colier 1995 for a review) given by

OD = acLB+G

OD = absorption of light expressed as the optical density

a = extinction coefficient of chromophore for the wavelength in uM-1cm-1

c = chromophore concentration in uM (Hb and HHb in this case)

L = distance between point of light entry and exit as per optode spacing on the tested skin surface in cm

B = differential path length factor (path length factor of light in the tissue accounting for issue of scattering) – assumed constant using continuous wave NIRS

G = correction factor for geometry of the tissue and optode positioning

The Lambert-Beer law was intended for a clear medium with non-scattering of light. When the law is applied to biological tissue (a highly scattering medium) a pathlength correction factor "B" must be applied, also called differential path length factor, to account for the increased optical path length associated with scattering (1988, Colier, 1995)

Appendix B.1

Consent Form

Part 1 (to be completed by the Principal Investigator):

Title: Hemodynamic Changes of the Prefrontal Cortex during Functional Activation in Essential Hypertension measured by Near Infrared Spectroscopy

Principal Investigator(s): Dr. Yagesh Bhambhani and Hercules Grant

Part 2 (to be completed by the research subject):

Do you understand that you have been asked to be in a research study? Yes No

Have you read and received a copy of the attached information sheet? Yes No

Do you understand the benefits and risks involved in taking part in this research study? Yes No

Have you had an opportunity to ask questions and discuss this study? Yes No

Do you understand that you are free to refuse to participate or withdraw from this study at any time? You do not have to give a reason and it will not affect your care. Yes No

Has the issue of confidentiality been explained to you? Do you understand who will have access to your records? Yes No

Do you want the investigator(s) to inform your family doctor that you are Participating in this research study? If so, please provide your doctor's name: Yes No

_____

This study was explained to me by:_____

I agree to take part in this study.

_____ _____ _____

Signature of Participant Date Witness

_____ _____

Printed Name Printed Name

I believe that the person signing this form understands what is involved in the study and voluntary agrees to participate.

_____ _____

Signature of Investigator or Designee Date

Appendix B.2

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

→ **DELAY BECOMING MUCH MORE ACTIVE:**

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Appendix B.3-PARMedX (Part 1 of 4)

Physical Activity Readiness Medical Examination (revised 2002)

PARmed-X PHYSICAL ACTIVITY READINESS MEDICAL EXAMINATION

The PARmed-X is a physical activity-specific checklist to be used by a physician with patients who have had positive responses to the Physical Activity Readiness Questionnaire (PAR-Q). In addition, the Conveyance/Referral Form in the PARmed-X can be used to convey clearance for physical activity participation, or to make a referral to a medically-supervised exercise program.

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. The PAR-Q by itself provides adequate screening for the majority of people. However, some individuals may require a medical evaluation and specific advice (exercise prescription) due to one or more positive responses to the PAR-Q.

Following the participant's evaluation by a physician, a physical activity plan should be devised in consultation with a physical activity professional (CSEP Certified Exercise Physiologist®. To assist in this, the following instructions are provided:

PAGE 1: • Sections A, B, C, and D should be completed by the participant BEFORE the examination by the physician. The bottom section is to be completed by the examining physician.

PAGES 2 & 3: • A checklist of medical conditions requiring special consideration and management.

PAGE 4: • Physical Activity & Lifestyle Advice for people who do not require specific instructions or prescribed exercise.

• Physical Activity Readiness Conveyance/Referral Form - an optional tear-off tab for the physician to convey clearance for physical activity participation, or to make a referral to a medically-supervised exercise program.

This section to be completed by the participant

A PERSONAL INFORMATION:

NAME _____

ADDRESS _____

_____

TELEPHONE _____

BIRTHDATE _____ GENDER _____

MEDICAL NO. _____

B PAR-Q: Please indicate the PAR-Q questions to which you answered YES

- ❑ Q 1 Heart condition
- ❑ Q 2 Chest pain during activity
- ❑ Q 3 Chest pain at rest
- ❑ Q 4 Loss of balance, dizziness
- ❑ Q 5 Bone or joint problem
- ❑ Q 6 Blood pressure or heart drugs
- ❑ Q 7 Other reason:

_____

C RISK FACTORS FOR CARDIOVASCULAR DISEASE:
Check all that apply

- ❑ Less than 30 minutes of moderate physical activity most days of the week.
- ❑ Currently smoker (tobacco smoking 1 or more times per week).
- ❑ High blood pressure reported by physician after repeated measurements.
- ❑ High cholesterol level reported by physician.
- ❑ Excessive accumulation of fat around waist.
- ❑ Family history of heart disease.

Please note: Many of these risk factors are modifiable. Please refer to page 4 and discuss with your physician.

D PHYSICAL ACTIVITY INTENTIONS:

What physical activity do you intend to do?

_____

_____

_____

This section to be completed by the examining physician

Physical Exam:

Ht	Wt	BP I) /
		BP II) /

Conditions limiting physical activity:

- ❑ Cardiovascular
- ❑ Musculoskeletal
- ❑ Respiratory
- ❑ Abdominal
- ❑ Other

Tests required:

- ❑ ECG
- ❑ Blood
- ❑ Exercise Test
- ❑ Urinalysis
- ❑ X-Ray
- ❑ Other

Physical Activity Readiness Conveyance/Referral:

Based upon a current review of health status, I recommend:

Further information:
- ❑ Attached
- ❑ To be forwarded
- ❑ Available on request

- ❑ No physical activity
- ❑ Only a medically-supervised exercise program until further medical clearance
- ❑ Progressive physical activity:
  - ❑ with avoidance of: _____
  - ❑ with inclusion of: _____
  - ❑ under the supervision of a CSEP Certified Exercise Physiologist®
- ❑ Unrestricted physical activity–start slowly and build up gradually

Supported by: Health Canada Santé Canada

1

Appendix C.1

Information Sheet

Study #1

Study Title: Cerebrovascular Reactivity with Carbon Dioxide in Essential Hypertension

Investigators: Hercules Grant (PhD Student, Rehabilitation Sciences)

e-mail: hercules@ualberta.ca

Supervisor: Yagesh Bhambhani, Professor

Tel (780) 492-1626

Background Information

Research has shown that breathing of air mixture with low concentration carbon dioxide can increase blood flow (vasodilatation) to the brain in normal as well as different types of diseases. Such an increased blood flow may have beneficial effects in some conditions. This has not been clearly established in high blood pressure.

A safe and non-invasive technique using near infrared light will be used to examine changes in brain blood flow during this test.

Study Objectives

The objectives of this study are:

- To examine whether breathing an air mixture with low concentration carbon dioxide causes increased brain blood flow in high blood pressure as in a healthy population
- To determine that magnitude of change in blood flow compared to healthy individuals
- To determine the reproducibility of measures as determined by the machine (Near Infrared Spectroscopy) in measuring these changes in blood flow

Study Procedures

You will be required to complete the following testing at the Work Physiology Lab Room 1-94, Corbett Hall.

Before Testing

You will be asked to refrain from strenuous exercises, caffeine or alcohol intake or a heavy meal for two hours prior to testing. You will be asked to complete a consent form and Physical Activity Readiness Questionnaire before testing. You will also complete forms on medication and physical and leisure activity in general. You will be asked to have your physician complete a PAR MedX form if you have been diagnosed with high blood pressure.

Testing Procedure

Familiarization

A day prior to actual testing, you will become fully familiarized with test procedures by a demonstration of all machines involved in the study. You will also be asked to fit into a mask and you will be informed of the typical instructions given during actual testing.

Testing

You will be dressed in non-restricting clothing and comfortably seated. Prior to testing we will take a 3 blood pressure readings over 5 minutes. We will clean your left forehead and attach two light probes to the area above the left eye secured with a strap. These probes will measure blood flow and oxygen changes in the brain. We will also attach a two way mask to a calibrated breathing apparatus and machine and ask that you sit quietly for no less than two minutes to obtain baseline signals. You will then breathe the air mixture for 30 seconds, which will then be followed by 2 minutes recording of baseline recovery information. There will then be 3 more blood pressure readings over the next five minutes to end the testing session.

We will repeat this procedure up to 2 hours later and again within five days.

Risks

Though highly unlikely you may feel short term dizziness which should have no residual effects. Please inform the investigator of any change in feeling or sensation during testing.

Benefits

Volunteering for this study will offer information on how the individual's brain blood flow reacts to a mixture of carbon dioxide and air. This reactivity will give information on the potential changes with other activities such as low grade exercise and mental activities as well as strategies in the treatment of high blood pressure.

Confidentiality

Research data will not identify you by name but only by a coded number. In addition to the investigators, the Health Research Ethics Board may have access to the data for monitoring purposes. Any report published from this study will not identify you by name. All study data will be kept for at least five years after the study is completed in a secure area accessible only to the principal investigator(s). All personal records will be held in full confidence unless required by legislation and code of ethics.

Freedom to Withdraw

All participants are free to withdraw from the study at any time. You will be promptly informed during the study if knowledge gained from this or any other study becomes available which may influence your decision to continue as a participant.

Appendix C.2

Information Sheet

Study#2

Project Title: Hemodynamic Changes of the Prefrontal Cortex during Functional Activation in Essential Hypertension Measured by Near Infrared Spectroscopy

Study#2: **Hemodynamic responses of the Prefrontal Cortex during Exercise-Enhanced Attentional Control in Essential Hypertension**

Investigators: Yagesh Bhambhani, Professor (Supervisor)

Faculty of Rehabilitation Medicine

Rm.3-73 Corbett Hall, University of Alberta

Tel (780) 492-7248; e-mail: yagesh.bhambhani@ualberta.ca

Hercules Grant (PhD Student, Rehabilitation Science)

Faculty of Rehabilitation Medicine

Rm. 3-48 Corbett Hall, University of Alberta

Tel (780) 966-0853; e-mail: hercules@ualberta.ca

Background Information

Research has shown that low to moderate intensity exercise can increase oxygenation and blood flow to the brain in healthy individuals as well as in those with different types of diseases. Such an increased oxygenation and blood flow indicates increased activity in the brain and may have beneficial effects in some conditions. This increase has not been established in those with high blood pressure.

A safe and non-invasive technique using near infrared light will be used to examine changes in brain oxygenation and blood flow while performing a submaximal cycle test.

Purpose of the Study

The purpose of this study is to examine whether low to moderate intensity cycling causes increased oxygenation and blood flow to the brain in those with high blood pressure and to determine the magnitude of such change while performing a test of concentration.

Study Requirements

You will be required to complete the following testing at the Work Physiology Lab Room 1-94, Corbett Hall, University of Alberta, and Edmonton, Alberta. The testing session will be arranged at times convenient to you.

Pre-test

You will be asked to refrain from strenuous exercises, caffeine or alcohol intake for 24 hours, and to avoid a heavy meal for two hours prior to testing. You will be asked to complete a consent form and Physical Activity Readiness Questionnaire before testing. You will also complete forms on medication and physical and leisure activity in general.

Prior to actual testing, you will become fully familiarized with test procedures by a demonstration of all machines involved in the study. You should dress in attire comfortable for exercise. You will also be asked to fit into a headband attached to a machine and you will be informed of the typical instructions given during actual testing.

Testing

Prior to testing, we will take blood pressure readings over 5 minutes while comfortably seated. We will clean your forehead with alcohol swabs and attach four light probes to the area above the eyes with adhesive and secured with a strap. These probes will measure blood flow and oxygen changes in the brain. We will ask that you sit quietly on the cycle ergometer for no less than two minutes to obtain baseline signals. You will also be fitted with a heart rate monitor around the chest which will need to be dampened. You will be asked to perform a test of concentration lasting approximately 5 minutes. You will then be asked move to the cycle, rest for 2 minutes and then to start pedaling while we will increase the resistance to a comfortable level. Your heart rate and blood pressure will be recorded during the 6 -8 minutes of cycling. You will be asked to perform the distraction test at about the 6^{th} minute. After a cool down period this test with be repeated with some difference in tension in the cycle. At the end of the cycling test, there will then be additional blood pressure readings over the next five minutes to end the session.

Risks

Though highly unlikely you may feel short term dizziness which should have no residual effects. Typical discomfort associated with low intensity exercise can be expected. Please inform the investigator of any change in feeling or sensation during testing.

Benefits

Volunteering for this study will offer information on how the individual's brain oxygenation and blood flow reacts to a low to moderate level of exercise and concentration. These findings will give information on the potential changes with other activities as well as strategies in the treatment of high blood pressure.

Confidentiality

Research data will not identify you by name but only by a coded number. In addition to the investigators mentioned above, the Health Research Ethics Board may have access to the data for monitoring purposes. Any report published from this study will not identify you by name. All study data will be kept for at least five years after the study is completed in a secure area accessible only to the principal investigator(s). All personal records will be held in full confidence unless required by legislation and code of ethics. Electronic files will be stored on a password-protected computer and printed files will be locked in a filing cabinet in the investigator's office.

Freedom to Withdraw

All participants are free to withdraw from the study at any time. You will be promptly informed during the study if knowledge gained from this or any other study becomes available which may influence your decision to continue as a participant.

Additional Contact

If you have concerns about this study, you may also contact Dr. Joanne Olden, Associate Dean of Graduate Studies, Faculty of Rehabilitation Medicine; Tel: (780)492-0651; email: joanne.volden@ualberta.ca

Appendix C.3

Information Sheet

Study #3

Study Title: **Hemodynamic Changes in the Prefrontal Cerebral during Working Memory in Essential Hypertension**

Investigators: Hercules Grant (PhD Student, Rehabilitation Sciences)

e-mail: hercules@ualberta.ca

Supervisor: Yagesh Bhambhani, Professor

Tel (780) 492-1626

Background Information

Research has shown that cognitive activity affects the flow of blood to the brain in the healthy individual. It is also known that some diseases cause a change in this blood flow. This has not been clearly established in high blood pressure.

A safe and non-invasive technique using near infrared light will be used to examine changes in brain blood flow during this test.

Study Objectives

The objectives of this study are:

- To examine whether performing a cognitive test causes changes brain blood flow in high blood pressure as in a healthy population
- To determine that magnitude of change in blood flow compared to healthy participants

Study Procedures

You will be required to complete the following testing at the Work Physiology Lab Room 1-94, Corbett Hall.

Before Testing

You will be asked to refrain from strenuous exercises, caffeine or alcohol intake or a heavy meal for two hours prior to testing. You will be asked to complete a consent form. You will also complete forms on medication and physical and leisure activity in general.

Appendix C.3 cont'd

Testing Procedure

Familiarization

Prior to actual testing, you will become fully familiarized with test procedures by a demonstration of all machines and items involved in the study. You will be given a short practice test with items similar to the actual test.

Testing

We will clean your forehead and attach light probes to the area above the both eyebrows secured with a strap. The probes will measure blood flow and oxygen changes in the brain. The investigator will start the test which will last approximately 75 minutes. The eyes will be covered to avoid distraction.

Risks

Though highly unlikely uneasiness may arise from keeping the eyes covered. Please inform the investigator of any change in feeling or sensation during testing.

Benefits

Volunteering for this study will offer information on how the individual's brain blood flow reacts to cognitive testing. The information obtained on brain blood flow with such mental activities may offer strategies in the treatment of high blood pressure and its effect on the brain.

Confidentiality

Research data will not identify you by name but only by a coded number. In addition to the investigators, the Health Research Ethics Board may have access to the data for monitoring purposes. Any report published from this study will not identify you by name. All study data will be kept for at least five years after the study is completed in a secure area accessible only to the principal investigator(s). All personal records will be held in full confidence unless required by legislation and code of ethics.

Freedom to Withdraw

All participants are free to withdraw from the study at any time. You will be promptly informed during the study if knowledge gained from this or any other study becomes available which may influence your decision to continue as a participant.

Appendix D.1

Medication History Form

ID#: Date:

Sex: M/F DOB: Weight: Height:

Medication	**Reactions or Side Effect**

Social History: Tobacco use N/Y #of packs/day: or # of packs/wk:

Alcohol use N/Y # drinks/day: or # of drinks/wk:

Current Medical Conditions, Allergies and Health Concerns

1.
2.
3.
4.
5.
6.

Medications (Prescriptions, non-prescriptions (vitamins, herbs, other)

Prepared in collaboration with Sherlene H. Brown Pharm. D., Pharmacist, Edmonton, AB.

Appendix D.2

Prescribed Medication for Hypertensives

Subject #	Medication	Drug Class	Usual Time of Day Taken	Years (approx.) Since Diagnosis
002	Adalat xL 30mg	Calcium Channel Blocker (CCB)	Evening/bedtime	20
003	Diavan Novasc	Angiotensin II Receptor Blocker (ARB) CCB	Evening/bedtime	10
011	None – diet	N/A	N/A	3
012	Olmetec	ARB	morning	1
015	Adalat xL 30mg, apo-lisinopril 10mg	CCB	Morning	3
016	Amlodipine Besylate 5mg, Losartan 75mg	CCB ARB	Morning	1
025	Diavan	ARB	Evening/bedtime	3
027	Coversyl PusHD Indapamidine/ Penidopril Amlodipine	ACE inhibitor Diuretic CCB	Day Evening/bedtime	8

Subject #	Medication	Drug Class	Usual Time of Day Taken	Years (approx.) Since Diagnosis
029	Cozar 10mg	ARB	Morning	10
030	Altace HT	ACE inhibitor	Morning	10
032	None –diet	N/A	N/A	1
034	Atacand	ARB	Evening	10
036	Diet	N/A	N/A	1
043*	Diet	N/A	N/A	1
047	Remopril	ACE inhibitor	Evenings	1
050	Atacand 50mg	ARB	Evenings	15

*later identified as Type II diabetic

Appendix E

CODE for PHYSICAL ACTIVITY

Use the appropriate number **(0-7)** which best describes your general ACTIVITY LEVEL for the PREVIOUS MONTH.

DO NOT PARTICIPATE REGULARLY IN PROGRAMMED RECREATION SPORT OR HEAVY PHYSICAL ACTIVITY.

0 – Avoid walking or exertion, e.g., always use elevator, drive whenever possible instead of walking.

1 – Walk for pleasure, routinely use stairs, occasionally exercise sufficiently to cause heavy breathing or perspiration.

PARTICIPATE REGULARLY IN RECREATION OR WORK REQUIRING PHYSICAL ACTIVITY, SUCH AS GOLF, HORSEBACK RIDING, CALISTHENICS, GYMNASTICS, TABLE TENNIS, BOWLING, WEIGHTLIFTING, YARD WORK.

2- 10 – 60 minutes per week.

3- Over one hour per week.

PARTICIPATE REGULARLY IN HEAVY PHYSICAL EXERCISE SUCH AS RUNNING OR JOGGING, SWIMMING, CYCLING, ROWING, SKIPPING ROPE, RUNNING IN PLACE, OR ENGAGING IN VIGOROUS AEROBIC ACTIVITY TYPE EXERCISE SUCH AS TENNIS, BASKETBALL OR HANDBALL

4- Run less than one mile per week or spend less than 30 minutes per week in comparable physical activity.

5 - Run 1 to 5 miles per week or spend 30 to 60 minutes per week in comparable physical activity.

6 – Run 5 to 10 miles per week or spend 1 to 3 hours per week in comparable physical activity.

7 – Run over 10 miles per week or spend over 3 hours per week in comparable physical activity.

(Scale developed for use at NASA/Johnson Space Center – Scale for rating physical activity in non-exercise V02 test) Ross and Jackson (1990).

Ross, R. M., & Jackson, A. S. (1990). Exercise concepts calculation and computer applications. Indiana, USA: Benchmark Press Inc.

Appendix F.1

Ethics Approval

Date:	January 23, 2012
Study ID:	Pro00023967
Principal Investigator:	Yagesh Bhambhani
Study Title:	Hemodynamic changes of the Prefrontal Cortex during Functional Activation in Essential Hypertension measured by Near Infrared Spectroscopy
Approval Expiry Date:	January 21, 2013

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel. Your application, including revisions received January 22, 2012, has been reviewed and approved on behalf of the committee.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health Services approvals should be directed to (780) 407-6041. Enquiries regarding Covenant Health should be directed to (780) 735-2274.

Sincerely,

Doug Gross, Ph.D.
Associate Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Approval F.2

Notification of Approval (Renewal)

Date:	January 16, 2013
Amendment ID:	Pro00023967_REN1
Principal Investigator:	Yagesh Bhambhani
Study ID:	MS1_Pro00023967
Study Title:	Hemodynamic changes of the Prefrontal Cortex during Functional Activation in Essential Hypertension measured by Near Infrared Spectroscopy
Approval Expiry Date:	January 20, 2014

Thank you for submitting this renewal application. Your application has been reviewed and approved.

This re-approval is valid for another year. If your study continues past the expiration date as noted above, you will be required to complete another renewal request. Beginning at 30 days prior to the expiration date, you will receive notices that the study is about to expire. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

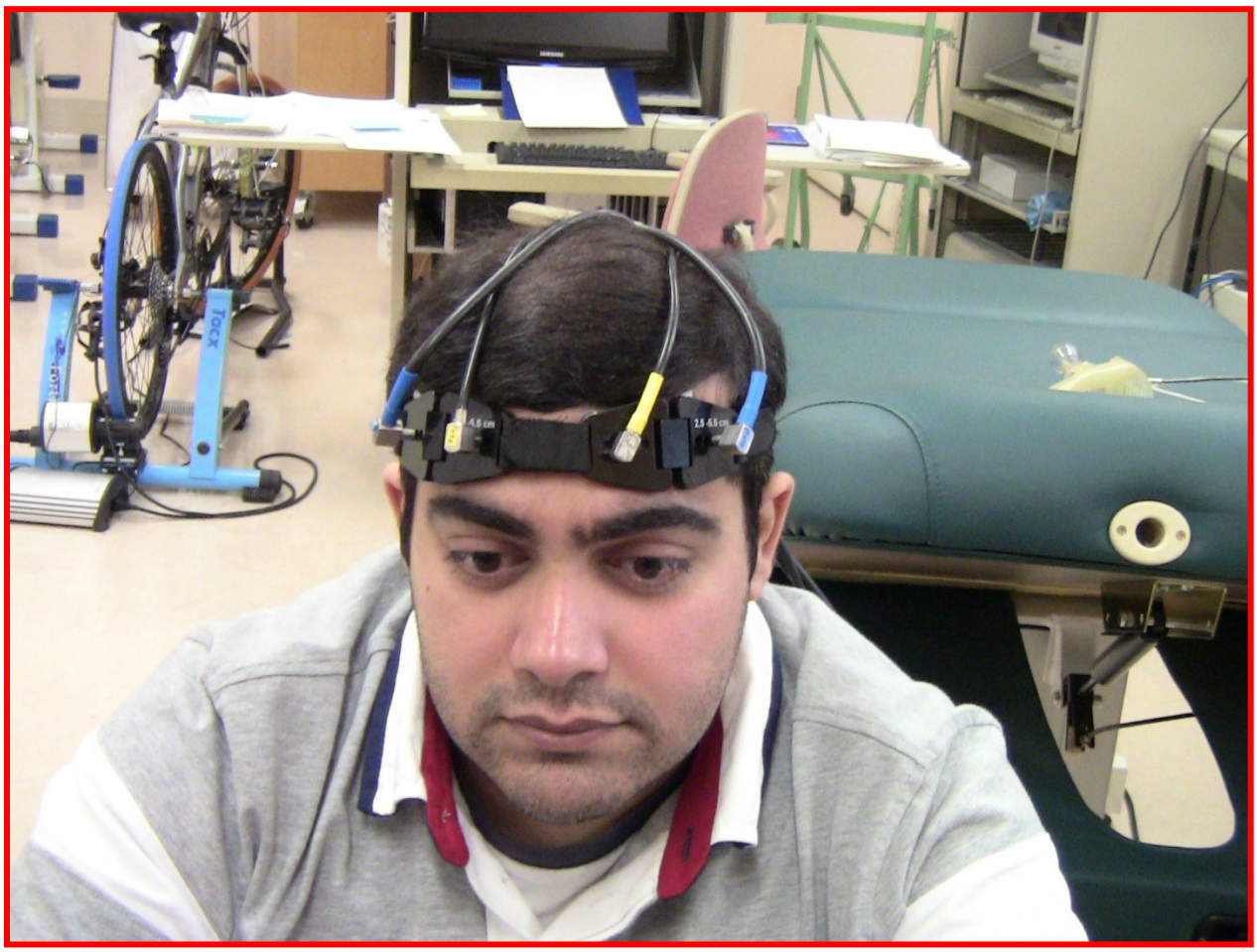
All study related documents should be retained so as to be available to the Health RIB upon request. They should be kept for the duration of the project and for at least 5 years following study completion.

Sincerely,

Dr. Glen J. Pearson, BSc, BScPhm, PharmD, FCSHP
Chair, Health Research Ethics Board - Health Panel

Appendix G.1

Location of fNIRS Probes on the Right and Left Prefrontal Lobes



Pairs of optodes were centred over FP1 and FP2 of the EEG International 10-20 System with fNIRS emitter-detector distance of 4.5cm

Note: Permission was granted by model for use of this picture

Appendix G.2

I. CO_2 Rebreathing in Supine Position

II. CO_2 Rebreathing in Standing Position

Gas mixture with 5%CO_2 was rebreathed for 30-90 sec via mask before participant moved to new position for 3 minutes; fNIRS recording was throughout procedure

Appendix G.3

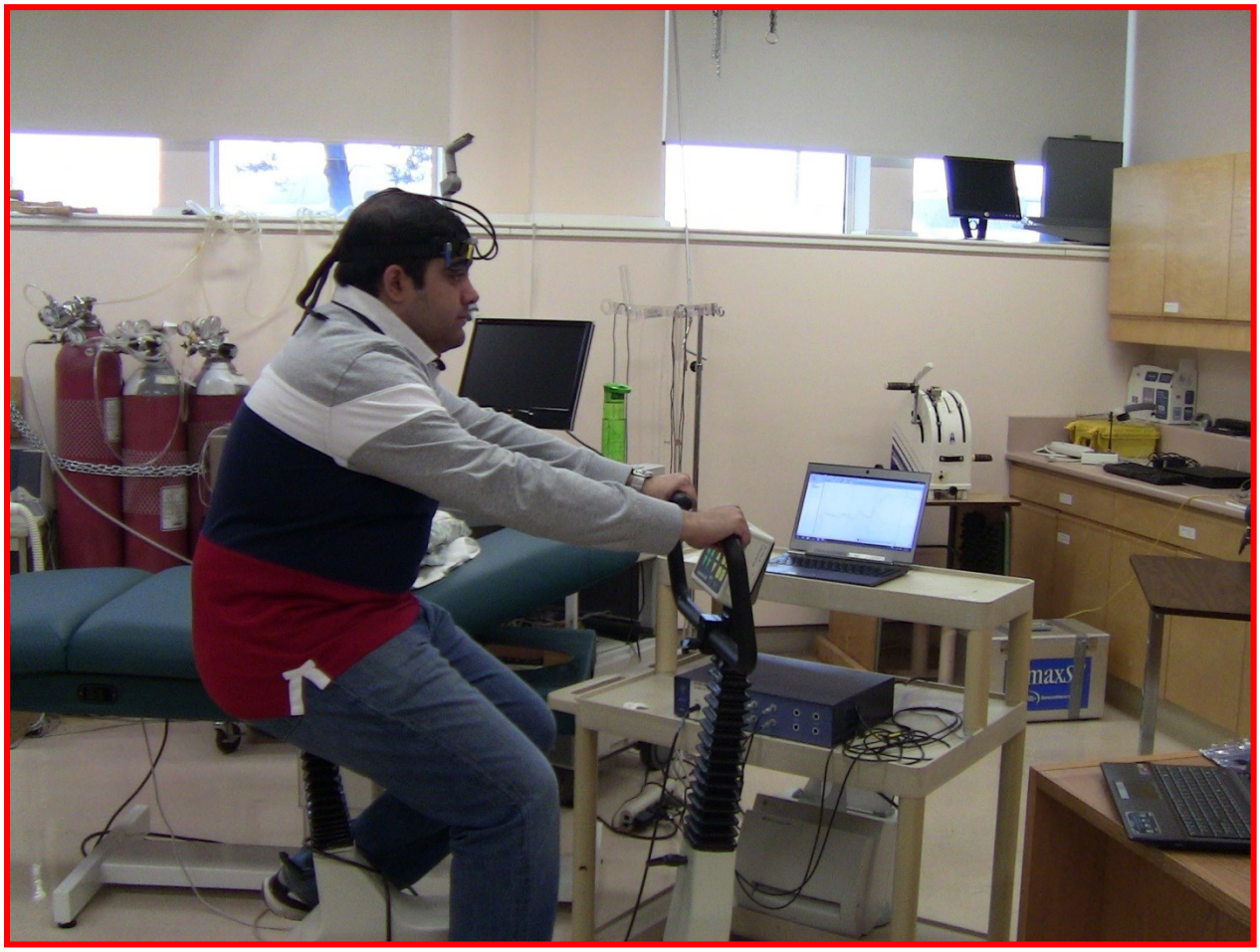
Cognitive Testing Position with Blindfold

This position was used for Digit Span and Auditory Consonant Trigrams testing with blindfold; fNIRS recording was throughout the procedure

Note: Permission was granted by model for use of this picture

Appendix G.4

Stroop Task during Cycle Trial



This position was used for modified Stroop task during cycling; fNIRS recording was throughout the procedure

Note: Permission was granted by model for use of this picture

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