Cerebrovascular Hemodynamics, Postural Stability, Gait Dynamics, and Falls in Older Adults

by

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I understand that my thesis may be made electronically available to the public.

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ABSTRACT

Injurious falls in community-living older adults are associated with standing up suggesting that cerebral hypoperfusion following a postural transition might be a contributing factor. A large population study has recently indicated that one fifth of older adults do not fully recover BP after standing from a supine posture. The purposes of this thesis were to provide a comprehensive assessment between posture-related cerebral hypoperfusion and impaired postural stability, altered gait and falls in older adults.

This thesis measured arterial blood pressure regulation and cerebral tissue oxygenation (tSO_2) during orthostatic stressors including 3 different transitions to standing in older adults (n=77, ages 69-100 years, average = 86.6±6.6 years) and 2 different transitions to walking in a sub-group of these older adults (n=27, ages 71-101 years, average = 86.8±5.3 years). Primary results included the finding that, like the altered blood pressure responses, 19.5% of older adults had low tSO_2 on standing, and they had poorer postural stability. It was also found that a brief 10-s sitting-pause time improved tSO_2 and postural stability when performing a supine-sit-stand. Prospective tracking of older adults for 6-months revealed a trend to an increased likelihood of a future fall in those who had the greatest drop in tSO_2 on standing. Older adults with low tSO_2 (≤60%) during walking had compromised gait dynamics (increased step-step variability). Although gait speed was not directly related to reduced tSO_2, the increased mean gait cycle time and stance time associated with changes in OxHb of the older adults with low tSO_2 were significantly associated with reduced gait speed. Increased vascular stiffness was associated with lower CBF and altered cerebrovascular hemodynamics while walking as well as lower gait speed. Collectively, the findings from these two investigations support a relationship between cerebral hypoperfusion induced by transitions from supine to upright posture and compromised standing and walking stability with consequences for increased fall risk.

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LIST OF ABBREVIATIONS

ABP	Arterial blood pressure
ACA	Anterior cerebral artery
AD	Alzheimer's Disease
AP	Anterior-posterior
Avg	Average
BOLD	Blood-oxygen-level-dependent
BP_{MCA}	Mean arterial blood pressure at the level of the middle cerebral artery
BSA	Body surface area
CA	Cerebral autoregulation (prefix: d-dynamic, s-static)
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
COM	Center of mass
CON	Control condition (supplementary study)
COP	Center of pressure
COP-V	Center of pressure vector
CO_2	Carbon dioxide
carotidPP	Carotid pulse pressure
cCC	Carotid compliance coefficient
cDC	Carotid distensibility coefficient
cPP	Central pulse pressure
CR_{CO2}	Cerebrovascular reactivity to carbon dioxide
CVR	Cerebrovascular resistance (MAP/flow)
CVRi	Cerebrovascular resistance index (MAP/flow velocity)
DBP	Diastolic blood pressure (prefix: c-central)
DeoxHb	Deoxygenated Hemoglobin content (relative measure)
EDV	End-diastolic velocity (also represents MV)
HF	Heart failure
ICA	Internal carotid artery
IMT	Intimal-media thickness
$P_{ET}CO_2$	End-tidal carbon dioxide
PSV	Peak-systolic velocity
MAP	Mean arterial blood pressure
MCA	Middle cerebral artery
MFV	Mean flow velocity
ML	Medial-lateral
MV	Minimum velocity (also represents EDV)
NIRS	Near infrared spectroscopy
NWBB	Nintendo Wii Balance Board
OA	Older adults
OH	Orthostatic hypotension

OxHb	Oxygenated hemoglobin content (relative measure)
PCO_2	Partial pressure of carbon dioxide (subscripts: ET-end-tidal, a-arterial)
PI	Pulsatility index
PWV	Pulse wave velocity (prefix: cf-carotid femoral, e-estimated by Mobil-O-Graph)
Qi	Cardiac output adjusted to body surface area
RI	Resistance index
RMS	Root mean square
SBP	Systolic blood pressure (prefix: c-central)
SD	Standard deviation (represents variability)
SIT	Sitting (position)
SUP	Supine (position)
SVi	Stroke volume adjusted to body surface area
TBW	Total body water
TC	Thigh cuff deflation condition (supplementary study)
TCD	Transcranial Doppler ultrasound
TC-Hyp	Thigh cuff deflation and hyperventilation condition (supplementary study)
TotHb	Total Hemoglobin content (relative measure)
TPL	Total path length
TPRi	Total peripheral resistance adjusted to body surface area
TSI	Tissue saturation index
tSO_2	Regional cerebral tissue saturation

CHAPTER 1. REVIEW OF LITURATURE

Preamble

The proportion adults, aged 65 years and older, is increasing worldwide. The aging demographic is attributed to a decline in fertility rates and increased longevity of the older adult population. Globally, the proportion of older adults relative to the total population will double over the next 50 years, with proportions expected to be as high as 37% in more developed countries (United Nations 2002). In Canada, one in every four people will be aged 65 years or older by the year 2051 (Statistics Canada 2011a).

It is estimated that a third of older adults fall each year (Tromp *et al.* 2001). Falls in older adults can have devastating impacts, accounting for 85% of all injury-related hospitalizations, 40% of nursing home admissions and approximately 20% of deaths due to injury (Statistics Canada 2011b). Falls also impact balance confidence and increase an individual's fear of falling. A fear of falling typically leads to limited involvement in activities which reduces strength and flexibility, placing the individual at an increased risk of falling and a lower quality of life (Cumming R.G. *et al.* 2000).

Canada is a developed country and is in an advanced stage of demographic transition, implying that interventions designed to identify and reduce fall risk may have major health benefits for thousands of Canadians. Although the causes of falls are multifactorial, the literature suggests a clear relationship between impaired blood pressure regulation, or reduced cerebral blood flow regulation and fall risk (Kario K. *et al.* 2001; Heitterachi E. *et al.* 2002; Quach L. *et al.* 2011; Sorond F.A. *et al.* 2011; Finucane C. *et al.* 2017; Gutkin M. & Stewart J.M. 2016; Mehagnoul-Schipper D.J. *et al.* 2000b). Orthostatic hypotension (OH) is defined as a sustained reduction of systolic blood pressure (SBP) equal to or greater than 20 mmHg or a reduction of diastolic blood pressure (DBP) equal to or

greater than 10 mmHg within three minutes of standing (Freeman *et al.* 2011). Initial OH is defined as a transient fall in SBP equal to or greater than 40 mmHg or DBP equal to or great than 20 mmHg within 15 seconds of standing (Freeman *et al.* 2011). Incidence rates of OH increase with age (Masaki K.H. *et al.* 1998; Gupta V. & Lipsitz L.A. 2007; Tilvis R.S. *et al.* 1996) and are shown to be a predictor of falls in older adults (Ooi *et al.* 2000; Gangavati A. *et al.* 2011).

Posture changes are known to be an orthostatic stressor, as they cause a redistribution of blood volume, which evokes a reduction in mean arterial pressure. Following a posture change, mean arterial pressure has been shown to account for half the reductions observed in cerebral blood flow (CBF) (Kim Y.S. *et al.* 2011). If cerebral perfusion is not maintained, light-headedness and dizziness may ensue, thus leading to a potential fall. Orthostaic hypotension and poor recovery of blood pressure (BP) are independent risk factors for future falls, unexplained falls and injurious falls (Finucane C. *et al.* 2017). Yet the relationships between cerebral blood flow and oxygenation, with postural control or fall history has not been investigated.

Cerebral Blood Flow

The human brain accounts for merely two percent of total body weight yet requires 12-15 percent of resting cardiac output and 15-20 percent of the resting metabolic rate (Rowell L.B. 1993))p.242). Evidently, the brain is a highly metabolic organ which requires a constant and stable delivery of blood flow to ensure an adequate supply of oxygen (O_2) and glucose, and the clearance of carbon dioxide (CO_2). When cerebral blood flow is unstable or inadequate, functional activity is reduced. A 50% reduction in cerebral perfusion below resting supine values marks the critical lower limit of cerebral perfusion where syncope develops (Njemanze P.C. 1992). Cerebral oxygenation is tightly linked to cerebral perfusion, even during events of pre-syncope (Madsen *et al.* 1998). Thus

when syncope develops, following 5-7 seconds of neck occlusion (Rossen L.R. *et al.* 1943), both perfusion and oxygenation impact neuronal activity. The tight relationship between insufficient perfusion/oxygenation to syncope demonstrates the low metabolic reserve of cerebral tissue (van Dijk & Wieling 2013), and the gravity of a disrupted or insufficient amount of cerebral blood flow.

Regulation of Cerebral Blood Flow

The brain demonstrates low metabolic reserve which is tightly coupled to neuronal activity, suggesting hypoperfusion can cause functional decline (Njemanze P.C. 1992; Rossen L.R. *et al.* 1943) and eventually tissue damage if flow is not re-established. Since the brain is encapsulated by a rigid structure high levels of intracranial pressure can also cause severe cortical damage. Thus, tight regulation of cerebral blood flow is essential to avoid excessive hypo- and hyper-perfusion. Global cerebral blood flow is in part regulated by neurological regulation (sympathetic and parasympathetic components); however, it is the microcirculation (arterioles and capillaries) which regulates cerebrovascular resistance and greatly impacts cerebral blood flow (Equation 1-1). The myogenic response, neurological coupling and metabolic response, and chemical regulation (gas tension) are the local regulators of the microcirculation.

$$\text{Cerebral Blood Flow} = \frac{\text{Mean Arterial Pressure} - \text{Intracranial Pressure}}{\text{Resistance}}$$

Equation 1-1. Ohm's Law for Regulation of Cerebral Blood Flow

Neurological regulation

Sympathetic fibers of extra-cerebral blood vessels originate from the superior cervical ganglion, parasympathetic fibers originate in the sphenopalatine and otic ganglia, and sensory nerves

originate at the trigeminal ganglion (Hamel E. 2006). Both sympathetic and parasympathetic activities have been shown to regulate cerebral blood flow. A study by Mitchell et al. (2009) recorded the release rate of noradrenaline into the plasma, which is referred to as the 'noradrenaline spillover' (Mitchell D.A. *et al.* 2009; Seifert T. 2011). Noradrenaline is an indicator of cerebrovascular sympathetic nerve activity since it is the primary neurotransmitter of the sympathetic nerves (Mitchell D.A. *et al.* 2009). When postganglionic sympathetic nerve activity is reduced (via clonidine and trimethaphan) jugular noradrenaline spillover is significantly reduced, suggesting sympathetic nerves have a regulatory function for cerebral blood flow outside of the brain blood barrier (Mitchell D.A. *et al.* 2009). Animal models have also demonstrate sympathetic nerve activity to protect the cerebral circulation against increases in blood pressure while sleeping (Loos N. *et al.* 2005).

The parasympathetic nervous system acts on the pial and arteriolar vessels through the release of potent vasodilators, namely acetylcholine, vasoactive intestinal peptide, substance-P and calcitonin gene-related peptide (Branston N.M. 1995; Farkas E. & Luiten P.G.M. 2001). As mentioned above, the parasympathetic activity is derived from the sphenopalatine ganglion, where removal of the sphenopalatine ganglion in rats results in a reduction of cerebral blood flow while still maintaining blood pressure (Boysen *et al.* 2009). This demonstrates the vasodilatory capacity of parasympathetic activity on cerebral blood flow. Although parasympathetic activation can stimulate vasodilation, it does not appear to be a primary flow regulator in normal conditions, rather, its effects are predominately observed in pathological conditions (ischemia and migraines) (Hamel E. 2006). Arterioles and capillaries are not directly innervated by sympathetic and parasympathetic nerve fibers (Hamel E. 2006). The cerebral parenchyma loses the peripheral nerve supply and the neural input is then received by neurons located within the brain (termed intrinsic innervation). Hence, sympathetic and parasympathetic modulation of cerebral blood flow is isolated to large cerebral arteries on the

surface of the brain and the capacity of sympathetic and parasympathetic activity is to regulate cerebral blood flow is limited because vascular resistance is predominantly mediated by the microcirculation (Hamel E. 2006).

Myogenic Response

The myogenic response, also known as the 'Bayliss effect', is the smooth muscle reflex to a change in intravascular pressure (Bayliss N. 1902). The myogenic behaviour acts to protect downstream arterioles and capillaries form high levels of damaging perfusion by means of vasoconstriction in response to an increase in arterial pressure, and to ensure adequate tissue perfusion is maintained by means of vasodilation when arterial pressure decreases.

Increases in transmural pressure cause depolarization of the muscle cell membrane and opening of the voltage-gated calcium channels (Jaggar J.H. 2001). With the release of calcium, vasoconstriction develops via increases in myosin light-chain phosphorylation (Jaggar J.H. 2001). In humans, the calcium mediated response of active tone is present from 20 mmHg to 90 mmHg in cerebral resistance arteries (Wallis S.J. *et al.* 1996). However, when calcium is abolished and intraluminal pressure is still raised, effective vascular constriction is no longer evident (Wallis S.J. *et al.* 1996). This suggests, the myogenic response is abolished by the deduction of extracellular calcium, making it a calcium dependent mechanism. Furthermore, the myogenic response is independent of the endothelium (Wallis S.J. *et al.* 1996). This is demonstrated by the removal of the endothelium (by passing an air bolus through the vessel) and exposing the vessel to a substance shown to elicit endothelial-dependent relaxation (Wallis S.J. *et al.* 1996). These findings are consistent with rat studies (McCarron J.G. *et al.* 1989; Smeda J.S. *et al.* 1989) but controversial in feline studies (Harder D.R. *et al.* 1989a; Harder D.R. *et al.* 1989b), suggesting endothelial-dependency may rely on vascular

size, or the methods used to remove the endothelium (Wallis S.J. *et al.* 1996). Despite the evidence from animal endothelial-dependent studies, the myogenic response in cerebral arteries is evident in humans (Wallis S.J. *et al.* 1996) (review by (Koller A. & Toth P. 2012)).

Neurovascular Coupling and Metabolic Regulation

Neurovascular coupling, often termed as functional hyperemia, describes the increase in blood flow to cerebral tissue in neutrally active regions (Atwell D. *et al.* 2010). Recent evidence supports a feed forward mechanism (neuronal activity → increase CBF → energy supplied) where neurotransmitter-mediated signaling, mainly the synaptic release of glutamate, controls cerebral blood flow through the activation of astrocytes (review by (Atwell D. *et al.* 2010)). Astrocytes physically link to neurons and cerebral vascular beds providing a structural connection. This position allows astrocytes to identify changes in synaptic activity and couple them with energy metabolism. Functionally, it is thought that low to moderate synaptic activity gives rise to signaling molecules known to stimulate vasodilation (glutamate, potassium and adenosine triphosphate (ATP)) (Paulson O.B. *et al.* 2010). When glutamate is released it acts through a receptor on the neuron which raises intracellular calcium concentration, causing nitric oxide synthase to release nitric oxide, which cause dilation in the smooth muscle arterioles (Atwell D. *et al.* 2010). Through various pathways of the astrocyte, the glutamate-signaling molecules mediate calcium release from the endoplasmic reticulum and also exchange intracellular sodium for extracellular calcium, which causes vasodilation (Paulson O.B. *et al.* 2010; Atwell D. *et al.* 2010). The astrocytes also produce arachadonic acid, epoxyeicosatrienoic acid (EET), potassium, and postaglandins which dilate the arterioles (Atwell D. *et al.* 2010). ATP is utilized by the signaling pathways which increases cerebral metabolic rate for glucose (Paulson O.B. *et al.* 2010). ATP is also hydrolyzed within the astrocyte and is converted to

adenosine which also causes vasodilation. Local oxygen concentration impacts the functionality of these molecules to increase or decrease blood flow (Atwell D. *et al.* 2010). The oxygen availability impacts the synthesis of the messenger molecules involved with neurovascular coupling (nitric oxide, and arachadonic acid), and it impacts the lactate and adenosine levels which modulate vasodilation of the arterioles (Atwell D. *et al.* 2010). There is a high energy cost for the astrocytes to process neural signaling to mediate blood flow. Thus, the high glucose consumption of the astrocytes is matched by increased cerebral blood flow in order to meet the needs of the cerebral tissue (review by (Paulson O.B. *et al.* 2010)).

The feed forward neurotransmitter-mediated signaling pathway mentioned above is supported by Gourine et al. (2005) who show increases in partial pressure of arterial carbon dioxide ($PaCO_2$) triggers the release of ATP from chemo-sensitive regions on the medulla oblongata pia matter in anaesthetized rats (Gourine A.V. *et al.* 2005). Although the exact mechanism responsible for ATP release in response to PaCO2 or hydrogen ion concentration ($[H^+]$) is unclear, it is evident that this ATP release precedes the venality responses of $PaCO_2$ (Gourine A.V. *et al.* 2005), supporting a feed forward response.

Chemical Regulation (Gas Tension)

The cerebral vasculature is highly sensitive to changes in $PaCO_2$ (Lennox WG & Gibbs EL 1932). Increases in $PaCO_2$, known as hypercapnia, result in cerebral vasodilation, which increases cerebral blood flow in an attempt to re-stabilize pH levels (Lennox WG & Gibbs EL 1932). Hypercapnic conditions are known to increase cerebral brain blood flow by 3-5% per mmHg rise in end-tidal carbon dioxide ($P_{ET}CO_2$) (Pandit J.J. *et al.* 2003; Clivati A. *et al.* 1992; Hida W. *et al.* 1996; Ainslie P.N. & Duffin J. 2009) and as much as a two-fold increase in brain blood flow (Levy M.N. & Pappano A.J. 2007).

Conversely, low levels of $PaCO_2$, known as hypocapnia, result in vasoconstriction which reduces cerebral blood flow (Kety S.S. & Schmidt C.F. 1941; Wasserman A.J. & Patterson J.L.Jr. 1961). Although the mechanisms of altering cerebral blood flow are still under debate, researchers do know that changes in $[H^+]$ are the drive to induce vessel dilation. It is perceived that hypercapnic conditions lower pH levels (acidosis) which actives potassium (K^+) channels, specifically ATP-sensitive K^+ and voltage-gated K^+ channels, which lie in the vascular smooth muscle. This generates an increase in K^+ efflux and hyperpolarization of the endothelial cells. A hyperpolarized current travels along the endothelium where voltage gated calcium channels are then closed, which reduces intracellular calcium and activates vascular relaxation (review by (Ainslie P.N. & Duffin J. 2009)).

A second theory to alterations in cerebral blood flow from changes in $PaCO_2$ is the mediated release of nitric oxide (NO) from the endothelium and neurovascular coupling (neurovascular coupling described above) (Ainslie P.N. & Duffin J. 2009; Atwell D. *et al.* 2010). NO is an easily diffused molecule that has a half-life of approximately six seconds, causing rapid and easily attenuated responses (Sanders D.B. *et al.* 2000; Hobbs A.J. & Ignarro L.J. 1996). NO impairs calcium sensitivity and mediates smooth muscle relaxation (Sanders D.B. *et al.* 2000). Schmetterer et al. (1997) demonstrates hypercapnic increases in cerebral vasodilation in healthy young adults, and states this response is blunted by L-NMMA infusion, suggesting NO participates in hypercapnia-induced vasodilation (Schmetterer L. *et al.* 1997). Furthermore, Lavi et al (2006) measured brachial flow-mediated dilation (an NO derived endothelial marker of function/dysfunction) and respiratory induced changes of cerebral blood flow velocity during normocapnia, hyperventilation and hypercapnia (Lavi S. *et al.* 2006). They performed identical tests on individuals known to have endothelial dysfunction (hypertension and Diabetes mellitus) and healthy controls. A hyperemic response to increased $PaCO_2$ was significantly impaired in the hypertensive and Diabetic participants compared to the controls, but

had preserved pressure-dependent autoregulation (changes in cerebrovascular resistance with varying blood pressure challenges). This supports the hypothesis of NO involvement to cerebral blood flow regulation (Kleiger R.E. *et al.* 1987). In contrast, Ide et al (2007) suggests NO is not required for vasodilation in response to hypercapnia, based on the observation that L-NMMA did not alter cerebral blood flow velocity (Ide K. *et al.* 2007; Toda N. *et al.* 2009). Evidently the pathway of $PaCO_2$, and NO requires further investigation.

Changes in partial pressure of arterial oxygen (PaO_2) levels are also known to alter cerebral blood flow (Kety S.S & Schmidt C.F. 1948; harris A.D. *et al.* 2013). In an isocapnic hypoxic human condition (6.9% to 7.5% oxygen and CO_2 was added to inspired gas), cerebral blood flow increased from 45 to 77 ml/100g per minute (Cohen P.J. *et al.* 1967). Like increases in $PaCO_2$, decreases in PaO_2 mediate vasodilation via K^+ channel activation, increased intracellular calcium concentration and NO release (review on hypoxia by (Brugniaux J.V. *et al.* 200)). This mechanism may be of importance in hypoxic conditions (altitude or pulmonary disease) however in day-to-day activity low hypoxic conditions are not normally present.

Assessment of Cerebral Blood Flow

Cerebral blood flow can be measured by a variety of techniques, however, due to the non-invasive nature and portability of the transcranial Doppler ultrasound (TCD) and near infrared spectroscopy (NIRS), TCD and NIRS will be chosen for measuring cerebral blood flow over other means.

Transcranial Doppler Ultrasound

As first reported by Aaslid et al. (1982), TCD provides non-invasive evaluation of cerebral blood flow velocity in major intracranial vessels (middle, anterior and posterior cerebral arteries) (Aaslid R. *et al.* 1982). TCD uses an ultrasound pressure wave, typically 2MHz, to penetrate the skin and superficial tissue and reflect the traveling velocity of the red blood cells in a given vessel (Panerai R.B. 2009; Evans D.H. & McDicken W.N. 2000). This causes varying increases or decreases in frequency, known as the phase shift (Panerai R.B. 2009). By determining the phase shift and insonation angle, the velocity of red blood cells can be determined (Equation 1-2), and converted into an electronic signal used for further analysis (Panerai R.B. 2009). The use of TCD to measure relative cerebral blood flow velocity has been validated against single photon emissions tomography (SPECT) (Sorteberg W. *et al.* 1989), Xenon^{133} clearance technique (over a wide range of $PaCO_2$) (Clark J.M. *et al.* 1996), and functional magnetic resonance imaging (MRI) (high resolution match, r=0.95) (Deepe M. *et al.* 2000).

$$\text{Velocity of reflector (Red blood cells)} = \frac{f_d \cdot C}{2f_t \cdot \cos\vartheta}$$

f_d is the transmitted Doppler shift frequency, $Cos\ \vartheta$ is the correction factor based on the insonation angle, C is the speed of sound in soft tissue (in TCD it is constant at 1540 ms^{-1}), f_t is 2 MHz (for TCD) (Hoskins P.R. 1990). Thus, f_d and $cos\ \vartheta$ are the determinants of red blood cell velocity.

Equation 1-2. Doppler Frequency Shift Equation

TCD relies on a constant arterial diameter to assume brain blood flow (Equation 1-1). Previous work using MRI, did not observe a change in middle cerebral artery (MCA) diameter during moderate changes in end-tidal carbon dioxide ($ETCO_2$) or simulated orthostatic stress (lower body negative pressure) (Serrador J.M. *et al.* 2000; Valdueza J.M. *et al.* 1997). More recent studies using a higher

resolution MRI (3 Tesla versus 1.5 tesla) demonstrate an increased MCA cross sectional area of 16±7% during hypercapnia (+10mmHg) and a decrease of 8±6% during hypocapnia (-15mmHg) (Coverdale N.S. *et al.* 2014). The changes in diameter during hypo- and hypercapnia suggest an overall 0.4% change in MCA diameter for a given change in mmHg $ETCO_2$ (Coverdale N.S. *et al.* 2014). Similarly, studies evaluating internal carotid artery (ICA) diameters demonstrate a change in cross sectional area of 11.5±% during hypercapnia (50 to 65 mmHg $PaCO_2$), -6.6±2.9% during hypocapnia (15 to 30 mmHg) and 6.3±8.1% during hypoxia (35 mmHg PaO_2 matched with SaO_2 70%) (Willie *et al.* 2012). In consideration of these discrepancies findings, caution should be taken when forming conclusion around TCD measures as cerebral blood flow velocity values may be underestimated in the presence of manipulated arterial gas concentrations.

Another consideration when using TCD, is the ability to insonate the MCA through the transtemporal window. Successful window insonation is dependent on temporal bone thickness which in turn is affected by age, sex, and ethnicity (Halsey J.H. 1990). Studies have found failure to record an MCA waveform in 3% of Caucasian males, 11% of Caucasian females, 4% of Black males, and 42% of Black females (51 to 99 years) (Halsey J.H. 1990). In comparison, a study involving 597 Japanese volunteers (16 to 89 years old), demonstrate the inability to acquire bilateral MCA flow signals in 29% of the participants (Itoh T. *et al.* 1993). In this sample of Japanese participants, age progressed the failure rate, as did being female, where 83% of women aged 70 years and older did not demonstrate a feasible MCA signal (Itoh T. *et al.* 1993). In a group of European participants the failure rate was marked at 5% (Aaslid R. *et al.* 1982), suggesting those of Black or Asian ethnicity prove to have a lower success rate for insonating the MCA (Halsey J.H. 1990; Itoh T. *et al.* 1993).

$$\text{Flow} = \text{velocity} * \pi * \text{diameter}^2/4$$

Equation 1-3. Blood Flow

Near Infrared Spectroscopy (NIRS)

Near infrared spectroscopy (NIRS) is a non-invasive device used to monitor relative changes in hemodynamic and metabolic activity of the brain. Near infrared light (700-1300 nm wavelength) is relatively transparent in biological tissues, making it possible for photons to reflect, scatter, and become absorbed into a tissue medium (Jobsis F.F. 1977). NIRS is used to evaluate cerebrovascular hemodynamics in the 650-950 nm wavelength range (Perrey S. 2008). The development of NIRS is based on the Beer-Lambert law which marks the relationship between absorption of light photons and the concentration of emitting photons through a coloured substance, known as chromophores (Perrey S. 2008). Chromophores are a construct of the heme molecule which absorb energy from visible light causing colouration. They have an absorption spectrum where the extinction coefficient is extracted as a specific wavelength which attenuates light, and is referred to as optical density (NIRS review by (Pellicer A. & Bravo M.C. 2011)). Optical density, or the attenuation of light due to absorption, can be calculated using the Beer-Lambert law (Equation 1-2) (Perrey S. 2008; Pellicer A. & Bravo M.C. 2011).

$$A = \log(I0/I) = \varepsilon * c * d \qquad \text{OR}$$

$$\text{Optical density (Absorption of light)} = \log\left(\frac{\text{incidence of light}}{\text{transmitted light}}\right) = \left(\begin{matrix}\text{extinction}\\ \text{coefficient}\end{matrix}\right)\left(\begin{matrix}\text{chromophore}\\ \text{concentration}\end{matrix}\right)\left(\begin{matrix}\text{optical pathlength}\\ \text{(thickness of solution)}\end{matrix}\right)$$

Equation 1-4a. Beer-Lambert Law

Photons used in tissue spectroscopy travel in an arc or elliptical trajectory rather than the traditional straight line (Perrey S. 2008; Okada E. *et al.* 1997; van der Zee P. *et al.* 1990). The arc trajectory is in part attributed to the photons traveling through various tissue mediums at different depths causing photon reflection of varying degrees (Perrey S. 2008). To account for inhomogeneous tissues a differential pathlength (DPF) factor is added to the Beer-Lambert law which accurately accounts for tissue differences (Equation 1-4b) (Hiraoka M. *et al.* 1993; Delpy D.T. *et al.* 1988; Patterson M.S. *et al.* 1989). DPF calculations are based on age and range from 4-6.5 in cerebral tissue (Pellicer A. & Bravo M.C. 2011; Duncan A. *et al.* 1995).

$$A = \log (I0/I) = \varepsilon * c * d * DPF + G$$

Equation 1-4b. Beer-Lambert Law

In addition to DPF, light attenuation rate is impacted by the source to detector spacing, where a greater distance results in a deeper site for sampling (Pellicer A. & Bravo M.C. 2011; Patterson M.S. *et al.* 1989). A short source-detector distance would result in a shallow arc trajectory which would largely sample superficial tissue (scalp and skull). By increasing the source-detector spacing, the relative contribution of surface tissue and extra-cerebral blood flow to the NIRS signal decreases (Hiraoka M. *et al.* 1993). Thus, source-detector differences less than 2.5 to 3 cm are not recommended (Pellicer A. & Bravo M.C. 2011).

NIRS use for cerebral tissue was first published by Jobsis (1977) who monitored relative OxHb, deoxygenated hemoglobin (DeoxHb), and total hemoglobin (TotHb) concentrations (Equation 1-5) in the human brain (Jobsis F.F. 1977).NIRS devices also calculate an estimate of regional tissue saturation

(tSO_2) termed tissue saturation index (TSI) (Artinis 2011). TSI is measured as the percentage of OxHb relative to TotHb(Equation 1-6) and will be referred to as tSO_2 (Artinis 2011).

TotHb = Oxygenated Hemoglobin + Deoxygenated Hemoglobin

DiffHb = Oxygenated Hemoglobin – Deoxygenated Hemoglobin

Equation 1-5. Total Hemoglobin and Hemoglobin Difference (NIRS)

$$tSO_2 = \left(\frac{\text{Oxygenated Hemoglobin}}{\text{Deoxygenated Hemoglobin + Oxygenated Hemoglobin}} \right) \text{x } 100\%$$

Equation 1-6. Cerebral oxygenation (tSO_2)

NIRS is used as an index of cerebral blood flow as it demonstrates very similar hemodynamic responses to TCD during motor tasks, exercise and hypo- and hypercapnic exposure (Hirth C. *et al.* 1997; Ide K. & Secher N.H. 2000; Smielewski P. *et al.* 1995). NIRS has also been significantly correlated to 133Xenon clearance changes in cerebral flow (Skov L. *et al.* 1991). However, NIRS is a local (at the arteriole and capillary level) not a global measure of cerebrovascular hemodynamics. Anatomically 70% to 80% of the cerebral blood is located in the venous system (~5% in capillaries, ~20% in arterioles, and the rest lies in post-cellular vessels) suggesting most of the detected hemoglobin is found in post-cellular vessels (Ide K. & Secher N.H. 2000; Ogoh S. & Ainslie P.N. 2009). Blood-oxygen-level-dependent functional MRI maps neuronal activity by imaging concentration changes of paramagnetic deoxHb (magnetic field differs if oxygen is bound or unbound to the heme molecule) (Sakatani K. *et al.* 2007). NIRS is significantly correlated to blood-oxygen-level-dependent functional MRI during neuronal activation of both motor and cognitive tasks (Sakatani K. *et al.* 2007; Toronov V.

et al. 2001; Strangman *et al.* 2002; Huppert *et al.* 2006), and has been significantly correlated to position emission tomography (PET, requires radioactive isotope) during a verbal fluency task (Hock C. *et al.* 1997). Thus, NIRS is a viable tool for measuring local neurovascular coupling and metabolic demand.

During neuronal activation, neurovascular coupling changes local OxHb, DeoxHb and TotHb, where OxHb typically increases and DeoxHb decreases (Kono T. *et al.* 2007; Sakatani K. *et al.* 2007; Schroeter M.L. *et al.* 2002; Moghimi S. *et al.* 2012). An increase in OxHb or a decrease in DeoxHb would result from either an increase in blood flow or a decrease of oxygen extraction (Schroeter M.L. *et al.* 2002). Although this is the typical response to neurovascular coupling, some studies report an increase in OxHb without any reductions in DeoxHb, or a decrease in OxHb (Quaresima V. *et al.* 2012). A decrease in OxHb and an increase in DeoxHb would be the consequence of a decrease in blood flow or an increase in oxygen extraction/consumption (Sakatani K. *et al.* 2007; Smielewski P. *et al.* 1995). In such a case, it is speculated that the tissue site is negatively activated and blood flow is reallocated to the area of cognitive processing (Quaresima V. *et al.* 2012; Boorman L. *et al.* 2010; Lague-Beauvais M. *et al.* 2013).

Brain function is tightly coupled with brain metabolism and brain blood flow, even during resting conditions (Li Z *et al.* 2012). It is widely accepted that during wakeful resting conditions the human brain is highly active (review by (Binder JR 2012)). The brain spontaneously activates when not engaged in a goal directed task (Safonova *et al.* 2004; Obrig H. *et al.* 2000), such as a cognitive or motor task, making it difficult to establish a baseline condition for neural function (review by (Binder JR 2012)). Baselines or control conditions are essential in scientific experimentation as they provide a foundation for all comparisons. At present there are no established procedures to determine a baseline or control condition for the NIRS device. Specifically, it is unknown what the influence of the

resting levels are to subsequent tasks, and if a goal directed task can minimize baseline variability in the NIRS signals (see Chapter 3 for more details).

Cerebral Autoregulation

According to Ohm's law, alterations in perfusion are accommodated by changes in cerebrovascular resistance (Equation 1-1) (van Beek A. *et al.* 2008). Cerebrovascular resistance index (Equation 1-7) can be used as a measurement of cerebral blood flow resistance (Hughson R.L. *et al.* 2001). Cerebral autoregulation (CA) is the cerebral vasculature's ability to modulate resistance in order to maintain steady blood flow despite alterations in arterial blood pressure (Paulson O.B. *et al.* 1990; Lassen N.A. 1964). This relationship ensures relatively constant cerebral blood flow from 60 mmHg to 150 mmHg of mean arterial pressure (Paulson O.B. *et al.* 1990). Outside of the 60 mmHg to 150 mmHg range cerebral blood flow becomes passive to alterations in blood pressure. There are two ways to evaluate cerebral autoregulation: static and dynamic.

$$CVRi = \frac{\text{mean arterial pressure} - (\text{distance} * 0.78)}{\text{mean cerebral blood flow velocity}}$$

distance = length in cm from the heart to the middle cerebral artery

Equation 1-7. Cerebrovascular Resistance index (CVRi) mmHg/cm/s

Static cerebral autoregulation measures the overall efficiency of the cerebrovascular resistance response. It can be tested by comparing cerebral blood flow at two steady states, one after an isolated change in mean arterial pressure. If cerebral blood flow is maintained after blood pressure

manipulation, then cerebral autoregulation is intact. Conversely, if cerebral blood flow is significantly changed then cerebral autoregulation is impaired (Tiecks F.P. *et al.* 1995).

Dynamic cerebral autoregulation adapts to abrupt changes in arterial blood pressure, providing a rapid response (within a few seconds) to cerebral blood flow regulation (Zhang R. *et al.* 2002; Ainslie P.N. & Duffin J. 2009). TCD has a high temporal resolution for monitoring human cerebral blood flow, and when simultaneously combined with a noninvasive blood pressure recording device (finger-cuff plethysmography), dynamic cerebral autoregulation can be easily evaluated. It is important to note the significant impact $PaCO_2$ has on cerebral blood flow velocity and cerebral autoregulation (Edwards M.R. *et al.* 2004; Lennox WG & Gibbs EL 1932; Aaslid R. *et al.* 1989; Panerai R.B. *et al.* 1999). It is paramount to have estimates of $ETCO_2$ (infrared capnography), particularly during protocols involving postural transitions, mental activation, or physical activity, which are known to alter $PaCO_2$ (Panerai P.B. 2009). Dynamic cerebral autoregulation can be evaluated at rest (transfer function analysis) (Zhang R. *et al.* 2000; Zhang R. *et al.* 2002), or with manipulation of blood pressure by utility of a posture change (Kim Y.S. *et al.* 2008), thigh cuff release (Tiecks F.P. *et al.* 1995), head-up tilt (Carey B.J. *et al.* 2003), or lower body negative pressure (Guo H. *et al.* 2006).

Static and dynamic autoregulation measurements are significantly correlated for both intact and pharmacologically impaired autoregulation ($r=.93$, $P<.0001$) (Tiecks F.P. *et al.* 1995). Although the protocols result in the same outcome, dynamic measures of autoregulation are preferred as they expose the time in which cerebrovascular resistance is achieved (response time or latency) (Tiecks F.P. *et al.* 1995), and closely mimics a physiological stimulus experienced during activities of daily living. For a review on TCD use in dynamic cerebral autoregulation see (Panerai P.B. 2009).

Cerebrovascular Reactivity

Cerebral blood flow critically relies on the ability of the cerebrovascular beds to respond to changes in $PaCO_2$ (Lennox WG & Gibbs EL 1932). The quantitative change of cerebral blood flow for a given change in $PaCO_2$ marks an index of cerebrovascular function, termed 'cerebrovascular CO_2 reactivity' (CR_{CO2}) (Ainslie P.N. & Duffin J. 2009). Generally, to quantify CR_{CO2} cerebral blood flow is monitored at rest in a normocapnic condition and during inhalation of a 5% CO2 gas mixture or intravenous administration of acetazolamide (Bishop *et al.* 1986; Zhang R. *et al.* 2000). The stimulus driven response results in an increase in cerebral blood flow, and thus, the ability of the vascular bed to dilate represents an index of vasomotor function (Bishop *et al.* 1986). CR_{CO2} is also characterized as a marker of cerebral vasomotor reserve. Cerebral vasomotor reserve is the capability of the cerebral vessels to alter resistance in response to a stimulus, such as hypercapnia. For example, when carotid stenosis is present, cerebral perfusion pressure is reduced, causing the cerebral vasculature to maximally dilate in order to ensure adequate cerebral blood flow. The dilated vasculature yields a reduced vasodilatory reserve and this is demonstrated by an impaired response to inhalation of a hypercapnic gas (Markus H. & Cullinane M. 2001). A low reserve would suggest a greater risk for hypoperfusion during transient drops in CBF (posture change). CR_{CO2} is impaired in individuals known to have endothelial dysfunction (hypertension or diabetes mellitus), suggesting CR_{CO2} may serve as an indicator of endothelial function (Lavi S. *et al.* 2006). Numerous methods have been utilized to assess CR_{CO2} including blood oxygen level depend MRI (Hare H.V. *et al.* 2013), positron emission tomography (Herold S. *et al.* 1988), TCD (Piepgras A. *et al.* 1990) and NIRS (Smielewski P. *et al.* 1995; Totaro R. *et al.* 1998). Various pathological conditions such as Alzheimer's disease (den Ableelen As M.V. *et al.* 2013), hypertension (Maeda H. *et al.* 1994), Diabetes mellitus (Fulesdi B. *et al.* 1999), and stroke (Markus H. & Cullinane M. 2001) have impaired CR_{CO2} mediated responses. The cerebral

vasodilator properties of $PaCO_2$ also appear to depreciate with age (Galvin S.D. *et al.* 2010), suggesting cerebrovascular health is reduced in older adult populations. It is important to note that CR_{CO2} is also influenced by wakefulness (review on CR_{CO2} by (Ainslie P.N. & Duffin J. 2009)). During sleep CR_{CO2} is reduced compared to wakeful hours, which contributes to lower levels of cerebral blood flow during sleep (Meadows G.E. *et al.* 2003). CR_{CO2} has a cut off value of 1.3%/mmHg which can be used as an indicator of poor cerebrovascular health (Kleiser B. & Widder B. 1992). Overall, CR_{CO2} has clinical importance (Markus H. & Cullinane M. 2001; Galvin S.D. *et al.* 2010; Maeda H. *et al.* 1994), and is an excellent means of evaluating cerebrovascular health.

Cerebral Blood Flow and Age

The relationship between reduced cerebral blood flow with increasing age is well established (Lipsitz L.A. 1985; Grolimund P. & Seiler R.W. 1988; Purkayastha S. & Sorond F. 2012; Kamper A.M. *et al.* 2004). Cerebral blood flow velocity, measured by TCD, decreases 0.3% to 0.5% per year from 20 to 70 years old (Leenders K.L. *et al.* 1990; Purkayastha S. & Sorond F. 2012; Vriens E.M. *et al.* 1989; Arnolds B.J. & von Reutern G.M. 1986; Grolimund P. & Seiler R.W. 1988). This results in a decrease of cerebral blood flow of 15% to 20% from 20 to 65 years of age (de la Torre 2012; Leenders K.L. *et al.* 1990; Chen Y. *et al.* 2011). Correspondingly, cerebrovascular resistance is higher in older adults (79±7 years) as compared to younger adults (25±7 years) (Kamper A.M. *et al.* 2004). The age related differences in cerebral blood flow can be attributed to age related changes in vessel geometry. In a patient population of adults (40-60 years, n=66) and older adults (60 years and older, n=34), ICA diameter (site 1: cavernous ICA, site 2: ICA terminus) and MCA diameter (site: M1 origin) significantly increased with age (Rai A.T. *et al.* 2013). Vessel structure (diameter and wall thickness) is largely driven by biomechanical and biochemical forces (wall and sheer stresses, and metabolic and

neurohumoral environment) which are known to change with age (Mitchell GF 2008). Sex differences of cerebral blood flow are noted between the ages 20 to 60 years (women have higher levels of blood flow velocity); however, these differences dissipate after 70 years of age, presumably due to menopause and lowering of hematocrit levels (Purkayastha S. & Sorond F. 2012; Vriens E.M. *et al.* 1989; Grolimund P. & Seiler R.W. 1988). The sex differences of cerebral blood flow correspond with sex differences in vessel geometry. In a patient population of 32 females and 17 males (14-86 year old, mean age 53), MCA diameter (site 1: M1 segment largest branch, site2: M1 segment smallest branch, site3: M1 segment parent vessel) and ICA diameter (site 1: terminal bifurcation largest branch, site2: terminal bifurcation smallest branch) were significantly larger in females compared to males (Lindekleiv H.M. *et al.* 2010). The female participants also had increased wall shear stress in both the MCA and ICA bifurcations as a result of smaller vessel diameters (Lindekleiv H.M. *et al.* 2010).

In addition to an age effect on cerebral blood flow velocity, OxHb and tSO_2 are lower in older adults (85±6 years) versus younger adults (28±4 years) (Hallacoglu B. *et al.* 2012). Hallacoglu et al. (2012) observed OxHb and tSO_2 decreases with increasing age and the authors suggest an age dependent impairment in cerebral metabolism and perfusion (Hallacoglu B. *et al.* 2012). The lower OxHb supply in older adults has also been associated with decreased neuronal activation and performance on cognitive tests (Hock C. *et al.* 1995; Herrmann M.J. *et al.* 2006; Hock C. *et al.* 1996).

Endothelial derived NO causes vasodilation, increases in flow, and acts to prevent atherosclerosis (Fisher J.P. *et al.* 2013). With age the capacity of the endothelium to produce NO declines (Toda N 2012) and the amount of reactive oxygen species, known to reduce NO bioavailability, increase (Donato A.J. *et al.* 2007; Ungvari Z. *et al.* 2010). These age related-changes in NO are thought to contribute to the lower resting cerebral blood seen with age (Thomas S.R. *et al.* 2008; Pialoux V. *et al.* 2009; Donato A.J. *et al.* 2007; Ungvari Z. *et al.* 2010). Okamoto et al. (2001)

and Kamper et al. (2004) have both demonstrated this impaired NO-mediated flow pathway in older adults. After 30 minutes of L-arginine infusion (which generates NO via NO synthase) in older (70 ±3 years) and younger (29±2 years) adults Okamoto et al. (2001) observed no between-group changes in blood pressure; however, cerebral blood flow velocity increased to a greater extent in the young adults, suggesting a diminished NO mediated cerebral blood flow response (Okamoto M. *et al.* 2001). Similarly, Kamper et al. (2004) administered L-NMMA (inhibits synthesis of NO by NOS) in young (25±3 years) and older (78±3 years) adults and found only the older adults had a significant decreased cerebral blood flow and increased cerebrovascular resistance; therefore, suggesting endothelial properties contribute to reduced cerebral blood flow with age (Kamper A.M. *et al.* 2004).

Several studies comparing cerebral autoregulation in young and older adults report an intact autoregulatory system with age (Carey B.J. *et al.* 2000; Carey B.J. *et al.* 2003; Lipsitz L.A. *et al.* 2000; Narayanan K. *et al.* 2001; Sorond F.A. *et al.* 2005; van Beek A.H. *et al.* 2008; Hernandez J.P. *et al.* 2010; Yam A.T. *et al.* 2005; Heckmann J.G. *et al.* 2003; Franke W.D. *et al.* 2006). Lipsitz et al. (2000) used a sit-stand posture change, as well as transfer function analysis during sitting and during standing to measure dynamic cerebral autoregulation in three adult groups (young adults: 24±1 year, older adults: 72±3 years, and older adults on antihypertensive medications: 72±2 years) (Lipsitz L.A. *et al.* 2000). In response to the transition, older adults on hypertensive medications were able to maintain cerebral autoregulation by reducing cerebral vascular resistance significantly more than the young adults or other older adult group. Moreover, transfer function analysis revealed no differences in gain between groups. In addition to measures of cerebral autoregulation, Lipsitz et al. measured cerebrovascular reactivity, and found the hyperemic response to CO_2 was significantly diminished in both older adult groups (Lipsitz L.A. *et al.* 2000). They concluded that although CO_2 reactivity was reduced in older adults their ability to retain cerebral autoregulation during a transition remains intact (Lipsitz L.A. *et*

al. 2000). As well as age, fitness level does not impact cerebral autoregulation (Franke W.D. *et al.* 2006). Franke et al. (2006) looked at cerebral blood flow velocity in response to lower body negative pressure in younger (23 years) and olderer (71 years) adults (Franke W.D. *et al.* 2006). The adults were grouped into either fit or unfit categories, and the researchers found no differences of cerebral autoregulation between groups (Franke W.D. *et al.* 2006).

When using NIRS to evaluate cerebrovascular hemodynamics, cerebral autoregulation of the prefrontal cortex is intact in older adult groups (Kim Y.S. *et al.* 2011; Edlow B.L. *et al.* 2010). Edlow et al. (2010) found a continuous effect of age (20-78 years) on the postural decreases in OxHb from a supine-stand transition (Edlow B.L. *et al.* 2010). It was determined that with increased age the magnitude of the postural decrease in OxHb was significantly less (Edlow B.L. *et al.* 2010). Additionally, a sex effect for the response to a change in posture was observed for all NIRS parameters (Edlow B.L. *et al.* 2010). As such, the supine-stand posture change would decrease OxHb in 30 year old males and females by −4.59 μmol L^{-1} and−3.75 μmol L^{-1}, respectively, and by −2.85 μmol L^{-1} and −2.01 μmol L^{-1}, in 60 year old male and female respectively (Edlow B.L. *et al.* 2010). The drop in OxHb was halved in older adults. Likewise, Kim et al. (2011) found smaller postural decreases in cerebral blood flow velocity and OxHb in older adults (52-65 years) compared to younger adults (27-33 years) (Kim Y.S. *et al.* 2011). The trending in cerebral blood flow velocity was significantly correlated to that of the mean arterial pressure at the level of the brain (Kim Y.S. *et al.* 2011). The OxHb signal was not correlated to the mean arterial pressure as it had a 3 second latency or delay from the cerebral blood flow trends (Kim Y.S. *et al.* 2011). The smaller postural decrease in OxHb with age has been attributed to either lower baseline cerebral blood flow measures or reduced capacity to redistribute cerebral blood flow to other areas in demand (Sorond F.A. *et al.* 2005; Edlow B.L. *et al.* 2010).

Structural and functional alterations of the vasculature contribute to altered cerebrovascular hemodynamics. With increasing age, vessels become stiffer. A stiffer vessel is less able to cushion arterial pulses, resulting in an augmented pressure wave form and a faster pulse wave velocity (PWV) (Mitchell GF 2008). With a stiff vessel and raised pulse pressure, the microcirculation (particularly the brain and kidneys) are threatened by encroaching excessive capillary pressures (Mitchell GF 2008). Arterial aging has been shown to influence cerebral hemodynamics in older adults (Robertson A.D. *et al.* 2010a). Robertson et al. (2010) found individuals (77±12 years) with higher ankle-brachial pulse wave velocity also have increased cerebrovascular resistance indexes which are significantly correlated to lower cerebral blood flow (r= -0.89) (Robertson A.D. *et al.* 2010a). Moreover, Tarumi et al. (2013) found lower central artery stiffness in middle aged endurance-trained (52±1 years) men, compared to sedentary men(54±1 years), which was significantly correlated to better neuropsychological scores (total composite memory and attention-executive function), carotid stiffness, and occipitoparietal perfusion by MRI (Tarumi T. *et al.* 2013). These findings indicate that lower arterial stiffness may attenuate or minimize the pathological process of reduced cerebral perfusion and cognitive decline in later life (Tarumi T. *et al.* 2013).

Although studies of healthy older adults indicate cerebral autoregulation is maintained with age (Carey B.J. *et al.* 2000; Carey B.J. *et al.* 2003; Lipsitz L.A. *et al.* 2000; Narayanan K. *et al.* 2001; Sorond F.A. *et al.* 2005; van Beek A.H. *et al.* 2008; Hernandez J.P. *et al.* 2010; Yam A.T. *et al.* 2005; Heckmann J.G. *et al.* 2003; Franke W.D. *et al.* 2006) some older adults who exhibit lower resting cerebral blood flow (Lipsitz L.A. 1985; Grolimund P. & Seiler R.W. 1988; Purkayastha S. & Sorond F. 2012; Kamper A.M. *et al.* 2004), tSO_2, OxHb (Hallacoglu B. *et al.* 2012), cerebrovascular reserve, as demonstrated by reduced CR_{CO2} (Galvin S.D. *et al.* 2010), and higher cerebrovascular resistance (Kamper A.M. *et al.* 2004; Robertson A.D. *et al.* 2010a) may demonstrate cerebral autoregulatory

impairment and have an increased risk of hypoperfusion during events of orthostatic stress, such as a posture change.

Orthostatic Hypotension

Orthostatic hypotension (OH) is defined as a sustained reduction of systolic blood pressure (SBP) equal to or great than 20 mmHg or a reduction of diastolic blood pressure (DBP) equal to or greater than 10 mmHg within three minutes of standing (The Concensus Committee of the American Autonomic Society and the American Academy of Neurology 1996). The first clinical reports of OH date back to 1864 when Liebermeister talks about syncopal episodes experienced after rising (Liebermeister C. 1864). OH can be asymptomatic, or it can be accompanied by numerous symptoms, such as lightheadedness, confusion, blurred vision, weakness, fatigue, and dizziness (Tilvis R.S. *et al.* 1996; The Concensus Committee of the American Autonomic Society and the American Academy of Neurology 1996). Although, the most significant symptoms are cerebral hypoperfusion and syncope (Stewart J.M. 2002) (reviews by (Meadow M.S. *et al.* 2008) and (Perlmuter L.C. *et al.* 2012)). The prevalence of OH varies due to discrepancies of the definition. Generally OH ranges between 5% to 30% in community dwelling adults, and higher incidence rates are correlated with increased age (Masaki K.H. *et al.* 1998; Gupta V. & Lipsitz L.A. 2007; Tilvis R.S. *et al.* 1996). In nursing home residence and acute care patients, OH affects 50-68% of older adults (Ooi W.L. *et al.* 1997; Weiss A. *et al.* 2002). The prevalence of OH increases with age because of various age-related changes in blood pressure regulation (increased vascular stiffness, and decreased baroreflex sensitivity, α-1-adrenergic vasoconstrictor response to sympathetic stimuli, parasympathetic activity, renal and salt water conservation and left ventricular diastolic filling) (Gupta V. & Lipsitz L.A. 2007). OH is also associated with lower cognitive performance (Frewen J. *et al.* 2013), increased rate of developing atrial

fibrillation (Agarwal S.K. *et al.* 2013), increased rate of mortality (Masaki K.H. *et al.* 1998) and is a risk factor for future falls (Finucane C. *et al.* 2017)

Mechanisms Behind The Posture Transition

Transitioning from a supine to seated posture, positions the heart and brain in a vertical plane rather than a horizontal plane. This increases the gravitational force placed on the cardiovascular system and causes blood volume redistribution (Rowell L.B. 1993). To maintain arterial pressure, baroreflex-mediated increases in total peripheral resistance and heart rate compensate for the reduction in venous return (Rowell L.B. 1993). Additionally, stimulation of the otolith organs (vestibular apparatus) affects cerebral blood flow regulation (independent of blood pressure and $P_{ET}CO_2$), thus aiding in cerebral perfusion (Serrador J.M. *et al.* 2009).

Upon assuming the upright posture with standing, approximately 500 to 700 mL of blood is redistributed (Hainsworth R. 1985; Sclater A. & Alaqiakrishnan K. 2004). With standing, the lower limbs are loaded, causing muscle activation and subsequently vasodilation of the working muscle (Wieling W. *et al.* 2007; Sorond F.A. *et al.* 2009). This vasodilation is marked by up to 40% reductions in total peripheral resistance (TPRi) (Sprangers R.L. *et al.* 1991). The decrease in TPRi causes a pronounced drop in blood pressure where the depth of the blood pressure trough is strongly related to reductions in TPRi with active standing (Tanaka H. *et al.* 1996; Wieling W. *et al.* 2001). The large drop in blood pressure with active standing is more prominent than blood pressure troughs observed with passive head-up-tilt tests (Wieling W. *et al.* 2007) or a double leg thigh-cuff release (Sorond F.A. *et al.* 2009). This suggests that in addition to the gravitational effects on blood flow re-distribution, the working muscle is greatly contributing to the drop in blood pressure. This theory is supported by Wieling et al (2007) who reviewed various in vivo human studies, as well as mammal and rodent

studies, and found that resistance vessels in the muscles dilate in proportion to the intensity of activation, and that this vasodilation peaks at 4 seconds and returns to normal by 10 to 20 seconds (Wieling W. *et al.* 2007; Tschakovsky M.E. & Sheriff D.D. 2004).

In addition to lower limb muscle activation, increases in intra-abdominal pressure are thought to contribute to the large blood pressure drop in standing. With the legs and abdomen initially contracting during the standing transition, intra-abdominal pressure rises, placing a transient increase in venous return and a large increased pressure on the right atrium (10-15 mmHg) (Wieling W. *et al.* 1996; Wieling W. *et al.* 2007). This leads to activation of the cardiopulmonary mechanoreceptors which causes withdrawal of sympathetic vasoconstrictor tone, and lower vascular resistance for 6 to 8 seconds (Sprangers R.L. *et al.* 1991; Wieling W. *et al.* 1996; Wieling W. *et al.* 2007). Postural decreases in CO_2 (hypocapnia) are thought to contribute to the reduced cerebral blood flow when assuming the standing position (Serrador J.M. *et al.* 2006). A 1mmHg decrease in $P_{ET}CO_2$ accounts for a 3.5% decrease in cerebral blood flow velocity (Immink R.V. *et al.* 2013). Therefore if a posture change evokes a 3.5% decrease in $P_{ET}CO_2$, a 12% decrease in cerebral blood flow velocity is expected. In the literature, postural reductions in cerebral blood flow velocity of 15% and OxHb of 7% are noted after 5-minutes of standing (Immink R.V. *et al.* 2013).

The time frame in which reductions in mean arterial pressure are produced by muscle activation and right atrial pressure, line up with many reported signs of pre-syncope observed from 5-10 seconds of standing to within the first 20-30 seconds of standing (Wieling W. *et al.* 2001; Wieling W. *et al.* 2007). To counteract these initial hemodynamic responses, heart rate drastically increases within the first three seconds of standing (Wieling W. *et al.* 2007). Parasympathetic blockade demonstrates that this rise in heart rate is due to cardiac vagal withdrawal (Wieling W. *et al.* 2007; Borst C. *et al.* 1982; Wieling W. *et al.* 1991; Wieling W. *et al.* 1985; Wieling W. *et al.* 1983). Either

central command or feedback from the mechanoreceptors in the contracting muscles (muscle-heart reflex) (Hollander A.P. & Bouman L.N. 1975) are responsible for the very rapid cardiac vagal withdrawal and significant rise in heart rate (Wieling W. *et al.* 2007). Following this initial rise in heart rate, the baroreflex responds to the drop in blood pressure and mediates increases in sympathetic outflow which continues to increase heart rate and total peripheral resistance. The combination of increased heart rate and increased stroke volume results in a distinct transient rise in cardiac output (Wieling W. *et al.* 2007; Tanaka H. *et al.* 1996; Sprangers R.L. *et al.* 1991); However, with the large fall of peripheral vascular resistance there is still a drop in blood pressure (review by (Wieling W. *et al.* 2007)). Blood pressure reaches its lowest point approximately 7 to 9 seconds post transition (Kim Y.S. *et al.* 2011; Wieling W. *et al.* 2007) and then begins to recover. Blood pressure is typically recovered within 30 seconds from the onset of transition (Wieling W. *et al.* 2007). It is also important to note, that during standing the leg muscles contract which acts as a second pump, propelling blood up towards the heart and enhancing venous return.

Orthostatic hypotension can result from a disease or condition which prompts deficits in hemodynamic responses (Arnold A.C. & Shibao C. 2013). Physiological changes seen with age, such as reduced baroreflex sensitivity, parasympathetic tone, cardiac and venous compliance, hydration, blood volume, and impaired α_1-adrenergic vasoconstriction, can contribute to OH in older adults (Arnold A.C. & Shibao C. 2013).

Orthostatic Hypotension in Older Adults

Across all ages (13 to 83 year olds), the critical threshold of cerebral blood flow velocity for human consciousness lies at approximately 50% below baseline (supine) (Njemanze P.C. 1992). This lower limit of blood supply may be associated with the minimal energy level required to support

neuronal activity (Njemanze P.C. 1992). Signs of mental confusion during passive heat-up-tilt tests coincide with both a drop in cerebral blood flow velocity and OxHb (Madsen P. *et al.* 1998; Colier W.N. *et al.* 1997). Colier et al. (1997) performed an 80° head-up tilt test for 15 minutes with and without the removal of 500mL of blood (Colier W.N. *et al.* 1997). Participants were separated into i) showing signs of pre-syncope and ii) no signs of pre-syncope. The participant group demonstrating signs of pre-syncope had significantly greater reductions in oxygenation (-1.4±0.5 μM^{-1}) compared to the group with no signs of pre-syncope (-0.2±0.2 μM^{-1}). The authors suggest the inadequate supply of oxygen for the required functional demand preceded the onset of pre-syncope (Colier W.N. *et al.* 1997). It has been suggested by Krakow et al. (2000) that symptoms of pre-syncope during an 80° head-up tilt test (n=35, 53±19 years old, n=15 with orthostatic syncope) mainly occur when oxygenation and perfusion reach a critical value of less than 60% tSO_2 (Krakow K. *et al.* 2000). In participants with a history of orthostatic syncope and who experienced symptoms of pre-syncope or syncope during the tilt test, tSO_2 was reduced by 10%, OxHb was reduced by 18%, DeoxHb increased by 11% and cerebral blood flow velocity decreased by 16% (Krakow K. *et al.* 2000). When compared to control subjects, participants with a history of orthostatic syncope had significantly larger reduction in MAP (-10±11 mmHg), cerebral blood flow velocity (-13±9 cm/s), and tSO_2 (-5±3 %) during the tilt (Krakow K. *et al.* 2000). These findings implicate a threshold for cerebral function to be approximately -5% to -10% below resting supine tSO_2 values. This level of hypoperfusion represents a moderate to large reduction in oxygen saturation where sings of pre-syncope become apparent.

Although postural hypotension typically results in only transient drops of cerebral blood flow, for individuals with OH measureable cognitive deficits are evident (Yap P.L. *et al.* 2008; Frewen J. *et al.* 2013). In a group of older adults (65.5 years, n=2321) Yap et al. (2008) found that among hypotensive participants, greater cognitive impairment (MMSE score less than 24) was seen in individuals with OH

(Yap P.L. *et al.* 2008). Likewise, Frewen et al. (2013) found older adults (61±6 years) with supine hypertension and OH scored significantly less on cognitive tests (accumulated MMSE and MOCA scores) compared to older adults without OH (Frewen J. *et al.* 2013). Participants with sustained OH or unrecovered hypotension (hypotension 30 seconds post-transition) were associated with even lower cognitive performance scores (Frewen J. *et al.* 2013). Overall associations between OH and cognitive performance alone were not observed for either study, but when confounded by either hypotension or hypertension impairment is present (Yap P.L. *et al.* 2008; Frewen J. *et al.* 2013).

Following a posture transition, blood pressure recovery has been identified to either 1) quickly recover with an overshoot, 2) medium drop/slow recovery, or 3) have a large drop/non-recovery pattern (Romero-ortuno R. *et al.* 2011). The inability to recover is marked by inadequate cardiac output and vasoconstrictor failure (Freeman *et al.* 2011). Romero-ortuno et al. (2011) split a sample 442 hypertensive older adults (~72±7 years) into the three recovery categories described above (Romero-ortuno R. *et al.* 2011). Twenty-one percent of the sample fell into the third category (large drop in BP marked by no recovery), demonstrating the large proportion of hypertensive older adults experiencing unrecovered OH. Orthostatic intolerance symptoms were more prevalent in the non-recovery category (45%) versus the medium recovery (28%) or quick recovery (18%) groups (Romero-ortuno R. *et al.* 2011). Likewise, Frewen et al. (2013) found 15% of middle aged (61±6 years) adults did not recover by 30 seconds, and 5% had still not recovered by 90 seconds post stand (Frewen J. *et al.* 2013). At 90 seconds post stand Frewen et al. (2013) observed greater incidence rates of OH in hypertensive participants (7% incidence rate, 157±15 mmHg SBP, 81±10 mmHg DBP) compared to normotensive (3% incidence, 122±13 mmHg SBP, 68±9 mmHg DBP) counterparts (Frewen J. *et al.* 2013). These studies suggest non-recovery in 5% to 21% of middle aged and older adult groups following a posture transition (Frewen J. *et al.* 2013; Romero-ortuno R. *et al.* 2011).

The literature demonstrates contradicting evidence for an age related difference in postural responses of OxHb (Mehagnoul-Schipper D.J. *et al.* 2000b; Kim Y.S. *et al.* 2011; Edlow B.L. *et al.* 2010). Mehagnoul-Schipper et al. (2000) (Mehagnoul-Schipper D.J. *et al.* 2000b) showed that older adults (74±4 years) had a significant postural decreases (supine to 2-minute stand) in OxHb and TotHb (-4.6±2.2 and 3.1±2.2 µmol/L respectively) compared to young adults (27±7 years, -1.2±5.4 and 0.2±4.9 µmol/L respectively), suggesting cerebral oxygen regulation is altered with age (Mehagnoul-Schipper D.J. *et al.* 2000b). However more recently, Edlow et al. (2010) (Edlow B.L. *et al.* 2010) and Kim et al. (2011) (Kim Y.S. *et al.* 2011) have observed smaller postural decreases of OxHb in older adults compared to younger adults. Edlow et al. (2010) had 60 participants (20-78 years old) perform a supine-stand transition, where across all ages OxHb and TotHb declined and DeoxHb increased. A significant age effect for OxHb indicates a smaller postural decrease in OxHb with increasing age (30 years OxHb -4.6 to -3.8 $\mu molL^{-1}$, 60 years OxHb -2.9 to -2 $\mu molL^{-1}$) (Edlow B.L. *et al.* 2010). Edlow et al. (2010) concluded that global cerebral autoregulation is intact with age and the incongruity of OxHb with age could be attributed to varied baseline cerebral blood flow volumes with age, or altered cerebral blood flow distribution seen with age (Edlow B.L. *et al.* 2010; Sorond F.A. *et al.* 2005). Kim et al. (2011) compared the cerebrovascular and cardiovascular responses from baseline to the nadir of mean arterial pressure, and from baseline to 5 minutes of standing in older (59 years, IQR 52-65 years) and younger adults (29 years, IQR 27-33 years) (Kim Y.S. *et al.* 2011; Edlow B.L. *et al.* 2010). The baseline to nadir responses demonstrate significant age differences for mean arterial pressure at the level of the brain, cerebral blood flow velocity and OxHb. The young adults had a significantly larger drop in these measures compared to the older adults (Kim Y.S. *et al.* 2011). The baseline to 5 minutes of standing responses showed significant age differences for mean arterial pressure at the level of the brain, cerebral blood flow velocity, OxHb, and Deox Hb (Kim Y.S. *et al.* 2011). Again the young adults

had significantly larger changes in magnitude for the cerebrovascular measures (Kim Y.S. *et al.* 2011). Kim et al. (2011) indicated postural reductions of cerebral perfusion were less pronounced with age and anterior cerebrovascular control was not a cause for postural dizziness and falls in older adults (Kim Y.S. *et al.* 2011). However, Kim et al. (2011) did not consider varied individual responses, demonstrated by Romero-ortuno et al. (2011) (Romero-ortuno R. *et al.* 2011). A group average may have washed out non-recovery responders because of overshoot responders, and altered cerebral blood flow distribution with age may have impacted these results. The incongruent findings between Mehagnoul-Shipper et al. (2000) and Edlow et al. (2010) or Kim et al. (2011) could lie in different sample sizes and ages or source-detector differences used. Regardless, age related differences in cerebral blood flow and oxygenation in response to an orthostatic stress require further investigation. In particular, individual responses or group stratification, as seen by Romero-ortuno et al. 2011, needs to be investigated to identify if some older adults are in fact at risk of cerebral hypoperfusion.

Orthostatic Hypotension and Blood Pressure

The literature presents evidence for a relationship between high blood pressure and the incidence rates of OH in older adults. In 1995 Raiha et al. found that 28% of older adults (~74±6 years) had systolic OH (≥ 20 mmHg drop in systolic blood pressure) 3-minutes into standing (Raiha I. *et al.* 1995). Although the majority of participants were hypertensive (>60%) Raiha and colleagues reportedly found only higher levels of blood pressure (systolic, diastolic and mean) to significantly predispose participants to systolic OH (Raiha I. *et al.* 1995). The data from Romero-ortuno et al. (2011) indicates that among hypertensives, the portion of participants in the non-recovery group of blood pressure has a higher baseline value for systolic and diastolic blood pressure, a lower nadir, and as mentioned before, a higher incidence of OH (Romero-ortuno R. *et al.* 2011). These data suggest

that higher blood pressures are more detrimental to older adults when performing a posture change. Frewen et al. (2013) elude to the same conclusion, where OH was significantly more prevalent in hypertensives versus normotensives at 20, 30, 60, and 90 seconds post transition (Frewen J. *et al.* 2013). Similarly, in a population based study (n=722, MOBILIZE Boston Study) of older adults, the prevalence of systolic OH at 1 minute and 3 minutes post transition were significantly higher in uncontrolled hypertensives (19% and 11% prevalence, 154±15 mmHg systolic blood pressure) versus normotensive (2% and 1% prevalence, 122±11 mmHg systolic blood pressure) and controlled hypertensive (5% and 1% prevalence, 122±11 mmHg systolic blood pressure) participants (Gangavati A. *et al.* 2011). This suggests that normotensive blood pressure or normotensive blood pressure achieved by pharmaceutical intervention is associated with a lowered occurrence of systolic OH. Moreover, in the group of participants with controlled hypertension, there was no difference in fall rates between participants with or without OH (20% and 22% fell more than once, respectively) (Gangavati A. *et al.* 2011). However, for participants with un-controlled hypertension, participants with systolic OH fell significantly more than participants without OH (39% and 17% fell more than once, respectively) (Gangavati A. *et al.* 2011). These findings suggest that if blood pressure is uncontrolled (hypertensive) and OH is evident, the risk of falling is significantly more than if OH was not present. Also, controlled hypertension appears to be protective of falls in those with known OH.

Pharmacological Effects

Medications have been implicated with OH in as many as 66% of orthostatic hypotensive cases (Craig G.M. 1994). Antihypertensive medications cause blood volume depletion, vasodilation, reduced myocardial contractility, and diminished sympathetic outflow, amongst other physiological effects. The contributions of these blood pressure lowering medications to OH and falls are still un-

clear. OH is associated with hypertension, and thus, the association of OH and antihypertensive medications may lie with the underlying cause of elevated blood pressure (Hajjar I. 2005). The association between polypharmacy and OH is much clearer. Due to multiple medical conditions in the elderly, poly medication and/or medications which lead to OH are often prescribed to older adults, placing them at greater risk of developing OH.

Blood Pressure Lowering Medications

Susceptibility to OH with medications is related to the interference by medications with reflex responses, such as vasoconstriction, heart rate or cardiac output (seen with alpha- and beta-blockers, and calcium channel blockers), as well was volume depletion seen with diuretics (Hopson J.R. *et al.* 1993; Kamaruzzaman S. *et al.* 2010). However, it is unclear if OH is a direct consequence of antihypertensive medications or if it is associated with the underlying hypertension (Hajjar I. 2005).

Thiazide diuretics inhibit reabsorption of sodium (Na^+) and chloride (Cl^-) ions at the distal convoluted tubules in the kidneys. This increases urinary sodium excretion and extracellular fluid excretion. Loop diuretics act at the loop of Henle by blocking sodium, chloride and potassium co-transporters, which decreases sodium reabsorption leading to fluid excretion and decreased volume (Kaplan N.M. & Lieberman E. 2002). Use of thiazide diuretics for greater than a month is accompanied by decreased peripheral vascular resistance (Conway J. & Lauwers P. 1960).

The renin-angiotensen-aldosterone system (RAAS) can be inhibited at various points by ACE-inhibitors or angiotensin-receptor blockers (ARB) (Hajjar I. 2005). When extracellular fluid volume is reduced, granular cells within the kidney produce renin, which activates the circulating angiotensinogen (produced by the liver), to angiotensen I. ACE then converts angiotensen I to angiotensen II. Angiotensen II stimulates arteriole vasoconstriction and activates the adrenal cortex in

the kidney to simulate aldosterone release and sodium reabsorption. Angiotensen II also stimulates the cardiovascular control center to increase sympathetic activation to the cardiac tissue and vasculature (Silverthorn DU 2007). These pathways increase blood volume and cardiac output which leads to increases in blood pressure. ARBs block the angiotensen II AT_1 receptors (directly blocking Angiotensen II), which causes vasodilation, reduces secretion of vasopressin, and reduces the production of aldosterone (lowers blood volume). ACE-inhibitors block the conversion of angiotensen I to angiotensen II and also increase NO availability and increase parasympathetic outflow, causing vasodilation and lower blood pressure (Hajjar I. 2005; Silverthorn DU 2007). In a review of medications on postural OH in the elderly, Hajjar (2005) states that ARBs and ACE-inhibitors are accompanied by low rates of orthostatic intolerance, which may be in part from enhanced baroreflex sensitivity seen with taking ACE-inhibitors (Hajjar I. 2005). Hajjar implies ACE-inhibitors and ARBs are better antihypertensive medications to take when attempting to avoid OH (Hajjar I. 2005).

Beta-blockers (β-blockers) block epinephrine and norepinephrine on beta-adrenergic receptors, which mediates a reduction in sympathetic activation (smooth muscle, cardiac, pulmonary, kidney tissue). There are various types of β-adrenoceptors (β_1, β_2, β_3,) which have varying pharmacological effects when blocked. β_1-blockers (most commonly used for blood pressure lowering) decrease renin section which decreases angiotensin II and reduces cardiac contractility and cardiac output. β_1-blockers also reduce baroreflex sensitivity by reducing sympathetic outflow (Hajjar I. 2005; Kaplan N.M. & Lieberman E. 2002). Hajjar (2005) suggests β-blocker use is less likely to exacerbate OH, conversely, Kamaruzzaman (2010) suggests the use of β-blockers are independently associated with OH in elderly women (60-80 years old) (Kamaruzzaman S. *et al.* 2010; Hajjar I. 2005).

Alpha-adrenoceptor antagonists (α-blocker) and calcium channel blockers may increase the incidence of OH (Hajjar I. 2005). Alpha-blockers act on the α-adrenergic receptors in smooth vascular

muscle. By blocking catecholamines (epinephrine and norepinephrine) from binding to the receptor, sympathetic stimulation is blocked, thus reducing arterial resistance. Calcium channel blockers block L-channels which inhibit the influx of calcium ions into cardiac and smooth muscle cells. This reduces the strength of the myocardial contraction, decreases conduction of impulses in the cardiac muscle and reduces vascular resistance causing vasodilation (Hajjar I. 2005; Kaplan N.M. & Lieberman E. 2002).

As mentioned in the previous section, the study by Gangavati et al. (2011) shows the association between lower blood pressure (with or without antihypertensive medications) and lower incidence rates of OH (Gangavati A. *et al.* 2011). This suggests that the underlying elevated blood pressure can account for the OH and treatment of hypertension can lower incidence rates of OH (Gangavati A. *et al.* 2011). Conversely, various studies have identified an association between antihypertensive medications and prevalence of OH (pepersack T. *et al.* 2013; Craig G.M. 1994; Poon I.O. & Braun U. 2005; Kamaruzzaman S. *et al.* 2010; Hajjar I. 2005). A large population based study (n=3775) of older women (60-80 years) clearly demonstrates both hypertension and antihypertensive medications as a cause of OH (Kamaruzzaman S. *et al.* 2010). Of the older women, OH was identified in 28% of the participants, and the incidence rate increased with age (Kamaruzzaman S. *et al.* 2010). Both uncontrolled hypertension and taking 3 or more medications (versus none) was significantly associated with OH (Kamaruzzaman S. *et al.* 2010). Regardless of diagnoses of hypertension or treatment status, elevated blood pressure was a strongly and significantly associated with OH. Additionally, the individuals with OH were proportionately on more beta-blockers, diuretics, ACE inhibitors, and alpha-blockers compared to participants without OH (all $p<0.05$) (Kamaruzzaman S. *et al.* 2010). The incongruent finding for differentiating the cause of OH (hypertension versus medications) remains unclear. In a review of publications found in Ovid (PubMed) from 1980 to 2011,

Pepersck et al. (2013) were unable to definitively provide evidence for a connection between specific medications and OH (pepersack T. *et al.* 2013). Clearly there is ample support for both suggested causes (hypertension and antihypertensive medication) of OH.

Polypharmacy

The additive effect of medications can inhibit compensatory mechanisms of blood pressure regulation which may increase the development of OH. If an individual is on both an β-blocker and a diuretic, both the sympathetic response and blood volume are reduced, which would increase the risk of OH (Poon I.O. & Braun U. 2005). The incidence of OH increases by taking more causative medications (defined by Poon et al. as alpha-blockers, diuretics, anti-depressant and anti-psychotic medications) (Poon I.O. & Braun U. 2005). In a group of older adults (82±5 years), participants not on any causative medications had a 35% prevalence rate of OH (Poon I.O. & Braun U. 2005). However, when looking at individuals on 1, 2 or 3+ causative medications the incidence rates of OH rose to 58%, 60% and 65% respectively (Poon I.O. & Braun U. 2005). These findings suggest that the prevalence of OH increases with the number of causative medications used, which may impact the development of OH (Poon I.O. & Braun U. 2005). These findings are supported by a publication by Craig (1994) where the average orthostatic hypotensive participant (mean age 80 years) took 2 medications (antihypertensive, antidepressant, and anti-Parkinson medications) but the range was in fact between 0-9 different medications per person (Craig G.M. 1994). Craig (1994) found 56% of older adults were taking diuretics, 26% taking benzodiazepine (psychoactive drug - relaxant), 24% anti-depressants, 22% anti-parkinsonian therapy, 12% beta-blockers, 8% calcium antagonist, 4% angiotensin converting enzyme (ACE) inhibitors, and 2% were taking alpha blockers (Craig G.M. 1994). Since multiple medications compromise differing means of regulating blood pressure, it was suggested that any older

adult taking two or more medication may be at risk of OH (Craig G.M. 1994). More recently, Kamaruzzaman et al. (2010) tested 3775 participants between 60 and 80 years old and found the prevalence of OH was strongly associated with the number of antihypertensive medications (Kamaruzzaman S. *et al.* 2010). Kamaruzzaman et al. found participants who were not on any antihypertensive medications compared to participants on 3 or more antihypertensive medications were more likely to have OH (odds ratio: 2.24 95%CI 1.47-3.4, p<0.001) (Kamaruzzaman S. *et al.* 2010). The findings by Poon and Braun, Craig, and Kamaruzzaman et al. suggest a relationship between OH and multiple antihypertensive medications (Kamaruzzaman S. *et al.* 2010; Craig G.M. 1994; Poon I.O. & Braun U. 2005).

Blood Pressure Lowering Medications & Cerebral Blood Flow

Concerns of cerebral hypoperfusion or compromised cerebral autoregulation with the use of blood pressure lowering medications have been challenged over the years (Lipsitz L.A. *et al.* 2005; Zhang R. *et al.* 2007; Periard D. *et al.* 2012; Frei A. & Muller-Brand J. 1986; Muller M. *et al.* 2012). As far back as 1986 when Frei et al. tested 20 hypertensive adults upon study commencement and after 8 weeks of enalapril (ACE inhibitor), it has been shown that cerebral blood flow (133Xenon) is not adversely (significantly) effected by blood pressure lowing medications (Frei A. & Muller-Brand J. 1986). More recently in 2012, Muller et al. evaluated cerebral blood flow with MRI in 575 participants who all had atherosclerotic disease (57±10 years) (Muller M. *et al.* 2012). Participants were evaluated upon the beginning of the study and 3.9 years later (Muller M. *et al.* 2012). Cerebral blood flow declined from 52.3±9.8 to 50.7±10.3 ml/min/100ml over the course of the study, and regression analysis (adjusted for age, sex, follow up time and vascular risk) determined untreated and poorly controlled hypertension and high systolic blood pressure were significantly associated with reduced

cerebral blood flow. Furthermore, successfully treated hypertensive participants, compared to participants without hypertension, did not show a significant difference in the decline of cerebral blood flow, suggesting treated hypertension is as effective in maintaining cerebral blood flow as aging without hypertension. Amongst hypertensive participants (n=469), participants using angiotensin receptor blockers did not show a decline in cerebral blood flow where other medications did (Muller M. *et al.* 2012). These findings suggest controlled hypertension by use of antihypertensive medications do not cause cerebral hypoperfusion at rest. Not only is cerebral blood flow unaffected by long-term use of antihypertensive medications, it has been shown that intensive blood pressure lowering (<130/80 mmHg) in hypertensive older adults (75±4 years) may in fact increases cerebral blood flow (spin labeling MRI) when compared to a typical blood pressure lowering regime (<140/85 mmHg) (Tryambake D. *et al.* 2013). Tryambake et al. 2013 found that participants on antihypertensive medications (ACE inhibitors, ARB, β-Blockers, calcium channel blockers and diuretics, or a combination), aiming to achieve a blood pressures of <130/80 mmHg had significantly greater cerebral blood flow in whole grey matter compared to participants aiming to achieve a blood pressure of <140/85 mHg (Tryambake D. *et al.* 2013). The authors suggest intensive blood pressure lowering shifts the autoregulatory curve upward and leftward whereby reversing the rightward shift observed with the development of hypertension (Tryambake D. *et al.* 2013). Intact cerebral autoregulation has also been shown by other researchers to be unaffected by long-term use of antihypertensive medications (Lipsitz L.A. *et al.* 2005; Zhang R. *et al.* 2007; Periard D. *et al.* 2012).

In 2005 Lipsitz et al. tested 51 older adults (70-72±4 years) at study entry and 6 months later (Lipsitz L.A. *et al.* 2005). Participants were separated into one of three groups, normotensive (blood pressure <140/90 not suing any blood pressure medications), controlled hypertensive (blood pressure <140/90 using long term antihypertensive medications) and uncontrolled hypertensive (>160 systolic

blood pressure with or without antihypertensive medications). Uncontrolled hypertensive participants were treated with lisinopril, an ACE inhibitor, with or without hydrochlorothiazide, a diuretic (or nifedipine, a calcium channel blocker, or an angiotensin receptor blocker if not tolerated). Treatment reduced CVRi, did not impair autoregulation and significantly increased cerebral blood flow velocity and carotid artery distensibility (Lipsitz L.A. *et al.* 2005). This study suggested antihypertensive therapy may preserve vascular function, cerebral autoregulation and improve cerebral perfusion (Lipsitz L.A. *et al.* 2005). Similarly, Zhang et al. (2007) tested normotensive (SBP 120±7mmHg, DBP 74±6mmHg, 46±11 years) mild hypertensive (SBP 143±7mmHg, DBP 88±4mmHg, 49±11 years) and moderately hypertensive (SBP 163±11mmHg, DBP 101±9mmHg, 47±12 years) adults, and found that long term use of blood pressure lowing medications maintain cerebral autoregulation and perfusion (Zhang R. *et al.* 2007). All participants in the Zhang et al. 2004 paper were tested during supine rest and during a 10 minute 70° head-up tilt test. Testing took place before and after 3-4 months of losartan/hydrochlorothiazide (an angiotensin receptor2 antagonist/diuretic) use by the hypertensive participants. Prior to the medication intervention, moderate hypertensive participants had significantly higher CVRi and TPRi values compared to the control group. Following the 3-4 months of blood pressure lowering, cerebral blood flow velocity and Q were unchanged but CVRi and TPRi decreased in the moderate hypertensive group. These study results suggested that following losartan/hydrochorothiazide use, cerebral blood flow velocity is unchanged in participants with mild and moderate hypertension and when compared to controls, brain perfusion is not compromised (Zhang R. *et al.* 2007). During the head-up tilt test, responses between the control and hypertensive groups were similar. However, transfer function gain between changes in blood pressure and cerebral blood flow velocity were significantly reduced in participants with moderate hypertension. The gain values in the moderate hypertensives were restored to levels observed in the control group after 3-4

months of antihypertensive medication, suggesting an improved dynamic autoregulation with blood pressure lowering by medication.

Balance Control (Stability)

Impaired balance is significantly associated with fall risk in older adults (60 years and older) (Muir S.W. *et al.* 2010). Stability measurements or balance activities are therefore often used as a screening tool to determine if any balance impairments are evident, and to identify individuals at risk of a future fall (Berg K.O. *et al.* 1992).

Balance is maintained by the central nervous system which integrates somatosensory, vestibular and visual feedback (Johansson R. & Marqnusson M. 1991). With age these sensory systems become compromised by the deterioration of cutaneous somatosensory receptors, muscle spindles, golgi tendon organs, chondrocytes in cartilage surfaces, visual acuity, contrast sensitivity, dark adaption, depth perception, vestibular hair cells, nerve conduction speed, myelination, central processing and response initiation, amongst others (review by (Pasma J.H. *et al.* 2014)). In addition to a diminished sensory systems with age, reduced force production by muscle atrophy and muscle remodeling (tendons thicken and stretch causing reduced force production) contribute to balance impairments (Pasma J.H. *et al.* 2014).

Balance is the relation of the center of mass (COM) to the area of the base of support (Maki B.E. & McIlroy W.E. 1997; Pollock A.S. *et al.* 2000; Hall S. 1991), and balance control is the ability to regulate these relationships (Maki B.E. & McIlroy W.E. 1997). COM displacement out of the base of support results in an unbalanced object (Pollock A.S. *et al.* 2000; Bell F. 1998). The multiple sensory systems used for balance control provide redundancies, where a temporary loss of one system can be compensated for by another (Winter D.A. 1995; Horak F.B. *et al.* 1990; Pasma J.H. *et al.* 2014). Horak

et al. (1990) demonstrated such redundancies by testing three different participant groups, participants with somatosensory loss, vestibular loss, and normal participants (Horak F.B. *et al.* 1990). By using six different combinations of perturbations and compromising either the somatosensory system (proprioception), vision, or both, the exposure of redundant systems was evident. Maintenance of balance in the normal control group was always present despite compromising two balance systems. However, when a condition compromised both vision and proprioception (tilting the support platform forward), the group with vestibular loss had a large amount of sway (Horak F.B. *et al.* 1990). When either vision or proprioception alone was compromised, balance was maintained by the intact somatosensory and vision systems respectively (Horak F.B. *et al.* 1990; Winter D.A. 1995). With age, physiological and pathological alterations can affect multiple sensory systems and therefore compromise balance and the stability of an individual.

Postural stability is often measured by the displacement of the center of pressure (COP). COP marks the single location on the supporting surface where the vertical reaction vector would act (Winter D.A. 1990). COM marks the point where the mass or weight of a body acts. Distinction between COP and COM is clear when looking at the initiation of walking where the COP moves towards the posterior aspect of the ankle, and moves laterally towards the direction of the swing extremity (Winter D.A. 1995). COM moves anteriorly and laterally towards the stance extremity used to load the body weight (Winter D.A. 1995). With the initiation of walking and other dynamic movement tasks, the COM is required to shift from a stable position (alignment with COP) to a less stable position where the COP and COM are no longer aligned. The greater the separation distance of COP and COM, the greater amount of postural control is required. Protective distances may represent a need to preserve stability (Martin M. *et al.* 2002). The anterior-posterior (AP) and medial-lateral (ML) displacements of COP can be measured (Prieto T.E. *et al.* 1996), where ML directional sway is

dominated by hip abductor and adductor muscles, and AP movements are predominantly governed by ankle muscles used for plantar- and dorsiflexion (Winter D.A. 1995). If the ankle muscles are unable to maintain balance during excessive instability, seen with internal (turning, reaching, bending) and external pertuberations (platform translations), the hip flexor and extensor muscles react in order to move the COM posteriorly or anteriorly to regain stability (Winter D.A. 1995). Balance control is a critical aspect of static balance (standing) and dynamic balance (walking), which are both compromised with age.

Gait & Balance with Age

Normal aging is accompanied by diminished lower extremity strength, slower reaction times, various pathological conditions (such as Parkinson's Disease), visual impairment, polypharmacy, and vestibular dysfunction (neural and sensory hair cell deterioration), which all compromise the ability to maintain balance, thus increasing fall risk (review by (Ambrose A.F. *et al.* 2013)). Measures of static stability, particularly ML sway amplitude, are predictive of future fall risk in older adults with or without a recent history of falling (Maki B.E. *et al.* 1994). Stability of dynamic walking on a treadmill is poorer in fall-prone older adults compared to young adults and healthy aging adults (Granata K.P. & Lockhart T.E. 2008). Dynamic movements, such as intra-individual step length variability, double support time, gait speed, cadence, and step-time variability, are predictive of multiple falls (Callisaya M.L. *et al.* 2011). Evidently, various age related postural balance differences and gait differences are associated with falls.

Age differences (approximately, 20-30 years old and more than 60 years old) in balance control are seen by uncoordinated and stiff movements, where step length and height are reduced, along with reduced capabilities to shift weight when experiencing a balance perturbations (Ko Su *et al.*

2009; Ambrose A.F. *et al.* 2013; Jensen J.L. *et al.* 2001; Maki B.E. & mcIlroy W.E. 2006). Older adults (72±4 years) are more likely to use a compensatory recovery step in response to lower perturbation magnitudes when compared to young adults (26±5 years) (Jensen J.L. *et al.* 2001). In a 2006 review paper on limb movements for balance recovery, Maki and McIlroy identify that older adults are less able to control ML stability, are more dependent on arm reactions to aid in rebalancing, but are less able to execute rapid reach-to-grasp tasks (Maki B.E. & mcIlroy W.E. 2006). The authors provide evidence supporting the notion of reduced musculoskeletal capacity, sensory function and/or neural processing with age (Maki B.E. & mcIlroy W.E. 2006). These findings indicate age related deficits in sensory systems and ultimately balance control (review by (Maki B.E. & mcIlroy W.E. 1996)).

Postural balance control (regulating COM to the area of the base of support) is achieved by either compensating/reacting to an unexpected pertuberations, or predicting/anticipating a balance disturbance and minimizing the affects via balance strategies (Maki B.E. & McIlroy W.E. 1997). Many of the gait and postural changes seen with age (ex. slower self-selected walking speeds, greater step-to-step variability or reduced stride length) may be related to fitness (Roma M.F. *et al.* 2013) and/or balance strategies used to prevent, or minimize anticipated balance disturbances (Maki B.E. & McIlroy W.E. 1997). Learned motor control strategies are influenced by various movement patterns and represent a 'chosen' movement pattern (Cappozzo A. 1983). The chosen pattern is based on functional and structural constraints of the task, as well as choosing the most effective task to maintain balance (Cappozzo A. 1983). The sit-stand transition is an activity of daily living which exhibits age related movement strategies.

Sit-stand Transition and Age

Sit-stand posture changes are challenging for many older adults and difficulty performing these transitions are reportedly associated with an increased fall risk (Yoshida K. *et al.* 1983). A sit-stand transition requires a great deal of lower limb strength and a wide range of motion in the lower limb joints (Wretenberg P. & Arborelius U.P. 1994) to move the center of mass forwards and upwards (Riley PlOl *et al.* 1997). It is sometimes thought to be physically more challenging than walking or stair climbing because of the joint torques and range of motion needed (Lomaglio M.E. & Eng J.J. 2005). In community dwelling older adults (79±4 years), sit-stand transition times are highly dependent on lower limb strength; however, sensorimotor, balance, and psychological factors (visual contrast sensitivity, lower limb proprioception, tactile sensitivity, simple foot reaction time, postural sway, body weight, and reported pain, anxiety, and vitality) can account for almost half of the variance in transition times (Lord S.R. *et al.* 2002). Selective movement strategies for the sit-stand transition varies between older adults (65-81 years) and young adults (22-34 years), and between movement strategies in older adults (Papa E. & Cappozzo A. 2000). Papa and Cappozzo (2000) separated older adults into two groups based on starting dorsiflexion or plantar-flexion position of the ankle (Papa E. & Cappozzo A. 2000). When comparing older adults with ankle dorsiflexion to young adults (similar foot orientation) at the seat-off position (first stage of the transition), older adults had greater trunk flexion and increased velocity than young adults (Papa E. & Cappozzo A. 2000). This seat-off position allows older adults to generate more momentum than young adults and also brings their COM closer to their base of support (Papa E. & Cappozzo A. 2000). After seat-off, older adults had higher whole body rotational momentum which reduced muscular effort, and only after the COM was brought over the base of support, the older adults began to elevate. The young adults would combine the rotational movement with elevation for a more efficient movement strategy. These results indicated a lower

functional capacity of muscular strength and reduced coordination in older adults versus young adults with the same starting foot position (Papa E. & Cappozzo A. 2000). Although transition times are similar, motor strategies differ between older adults starting with dorsiflextion of the ankle and plantar-flexion of the ankle (Papa E. & Cappozzo A. 2000). Prior to seat-off, participants starting with plantar-flexion had a larger rotational momentum of the head, arms and torso, which causes a large counterbalance to the backward gravitational force (Papa E. & Cappozzo A. 2000). In this same group, body elevation was delayed to a greater extent than the older adults starting with dorsiflextion, which was assumed to be because of a greater risk for posterior balance instability (Papa E. & Cappozzo A. 2000). This study by Papa et al. (2000) identifies some of the strategy-related determinants of the sit-stand transition (speed, foot positioning, trunk position/movement, and arm movement) which all impact performance on the sit-stand task (Janssen W.G.M. *et al.* 202).

There are three task-related challenges with the sit-stand transition; moving the COM forwards, elevating the COM, and stabilizing the whole body over a much more narrow base of support (Riley PlOl *et al.* 1997). Papa et al. (2000) identify age related differences in moving the COM forwards, and elevating the COM (Papa E. & Cappozzo A. 2000), where Akram and McIlroy (2011) identify differences in stabilization following a sit-stand transition (Akram S.B. & McIlroy 2011). In a comparison of young (23±4 years) and older (74 ±8 years) adults with no history of falls, a method of quantifying the dynamic kinematics in a sit-stand transition was calculated (Akram S.B. & McIlroy 2011). Akram and McIlroy (2011) recorded 15-20 seconds of data following the onset of transition. The dynamic phase of the transition was marked from the beginning of the transition until participants reached a natural quiet stance sway (Akram S.B. & McIlroy 2011). Natural sway was collected from the last two seconds of standing. The time point at which sway was no longer within the 95% CI of the natural sway collection, marked the end of the dynamic stability measurement. The time from the

beginning of the transition to the end-time point of dynamic stability marks the duration of sway stabilization (milliseconds). In both the AP and ML directions, older adults had significantly longer stabilization times (AP: 8777±2632 ms, ML:8127±2420 ms) compared to young adults (AP: 6942±1779 ms ML: 6927±1950 ms), suggesting older adults have a reduced ability to achieve stability (Akram S.B. & McIlroy 2011). Older adults also had significantly larger amplitudes of COP sway excursion (longer COP path) in both the AP and ML directions, which reflects the differences in stability control (Akram S.B. & McIlroy 2011).

Ambulatory gait monitoring

Ambulatory gait monitoring is defined as the use of sensors fixed to the body which provide an opportunity to both observe and record quantitative gait characteristics while not being restrained to a specific location such as a lab (Selles R.W. *et al.* 2005). Ambulatory gait monitoring can be collected by foot pressure insoles, footswitches, inertial measurement units, electromyography signals, gyroscopes for angular velocity and accelerometers for linear acceleration (Taborri J. *et al.* 2016). For the purpose of this thesis accelerometers will be the focus of discussion. Via use of accelerometers, sub-phases of the swing phase can be calculated (initial-swing or toe-off, mid-swing and terminal-swing or heel-strike) (Taborri J. *et al.* 2016). Additional gait characteristics are often calculated based off of the toe-off and heel-strike time points. Toe-off marks the beginning of the swing phase and heel-strike marks the termination of the swing phase as well as the start of the stance phase. The time from toe-off to toe-off or heel-strike to heel-strike constitutes a single gait cycle (Selles R.W. *et al.* 2005).

An increase in gait variability is the reduced ability to effectively control gait between strides (Hausdorff J.M. 2005) and increased gait instability is seen with age (Terrier P. & Reynard F. 2015).

Terrier et al. 2015 differentiated the increase in gait variability associated with age to be due to an accelerated rate of instability seen during 40-50 years of age versus a slow and progressive decline of stability across the lifespan (Terrier P. & Reynard F. 2015). In young adults gait variability has been correlated to CBFV while walking on a treadmill and performing a cognitive task (Gatouillat A. *et al.* 2015). Increased step-to-step time variability in older adults is a significant predictor of falls and is significantly correlated to strength, balance, gait speed, functional status and metal health (Hausdorff J.M. 2005) and thus a useful, non-invasive tool to predict falls in older adults.

Gait Speed and Age

The central nervous system reacts to and anticipates balance disturbances by activating various muscle groups in order to readjust the COM and regain stability. With a quite static stand the COM is always within the base of support (Winter D.A. 1995). During walking the COM is always outside the base of support (other than brief double support phases), and the balance is thus archived by the swing limb trajectory (Winter D.A. 1995). During walking the ankle muscles can only fine tune accelerations of the body's COM because the dynamic balance task is governed by the placement of the swing foot (Winter D.A. 1995). Therefore, walking requires greater angular movement, motor control and coordination of the hip, knee and ankle joints (Winter D.A. 1995). Walking is a complex and dynamic movement which taxes postural control in some older adults. Consequently, various indices of gait are indicative of poor balance control and fall risk.

Gait speed is associated with falls in older adults (Quach L. *et al.* 2011). A nonlinear relationship between gait speed (determined by the 4-meter walk test) and falls exists, where slow walkers are at risk of falling indoors and fast walkers are at risk of falling outdoors (Quach L. *et al.* 2011). Furthermore, a decline in gait speed (0.15 meters/second/year) is known to be a predictor of

future falls (Quach L. *et al.* 2011). Slower gait speeds are also associated with cognitive decline in non-demented older adults (Ble A. *et al.* 2005). In a study by Ble et al. (2005) executive function in older adults (75 years) was strongly and independently associated with walking speed on a 7-meter obstacle course which was set at a fast pace (Ble A. *et al.* 2005). These relationships were not found with a 4-meter usual-pace walking test, presumably because the obstacle course required more attention (Ble A. *et al.* 2005). The authors suggest executive function is required and is challenged in more complex lower extremity motor tasks versus highly practiced skills (usual-pace 4-meter walk test) (Ble A. *et al.* 2005). The slower gait speeds observed by Quach et al., in relation to fall risk, and Ble et al., in relation to cognition, identifies a loss of function and deterioration of motor control centers and processing regions of the frontal lobe (Ble A. *et al.* 2005; Quach L. *et al.* 2011).

Cardio- and cerebrovascular hemodynamic responses in association to postural stability, gait speed and falls

Acute and prolonged reductions in BP on standing might be associated with cerebral hypoperfusion (Edlow B.L. *et al.* 2010; Mehagnoul-Schipper D.J. *et al.* 2000b; Gutkin M. & Stewart J.M. 2016). A reduction in CBF large enough to cause postural instability is alluded to in the literature (Shaw B.H. & Claydon V.E. 2014; van Wijnen V.K. *et al.* 2017; Lipsitz L.A. 1985; Hossain M. *et al.* 2001; Shaw B.H. *et al.* 2015). However, the impact of reduced CBF on postural stability has never been thoroughly investigated.

In a meta-analysis on OH and elderly adults by Pepersack et al. (2013), OH was significantly associated with gait disorders (OR: 1.23, CI 1.02-1.46) and frequent falls (OR: 1.54, CI 1.04-2.22) (pepersack T. *et al.* 2013). OH was also significantly associated with myocardial infarctions (OR:1.24, CI 1.02-1.3), transient ischemic attacks (OR: 1.68, CI 1.12-2.51), systolic hypertension (OR: 1.35, CI

1.09-1.68), cardiac rhythmic abnormalities (OR: 1.21, CI 1.03-1.42), and carotid artery stenosis (OR: 1.67, CI 1.23-2.26) (pepersack T. *et al.* 2013). These findings describe a relationship between poor cardiovascular health, poor blood pressure regulation, and poor balance control. Craig (1994) found similar results in a group of elderly adults (n=50, 63-97 years with a mean age of 80 years) with OH, where 64% of participants had a fall, 44% had poor mobility, 38% unsteadiness, 22% confusion, 14% postural symptoms, 12% fractures, 10% dementia, 8% blackouts, 6% reluctant to stand, 6% pallor or tiredness (Craig G.M. 1994). These findings suggest OH is accompanied by signs of hypoperfusion in the cerebral vasculature (confusion, blackouts, pallor) and poor balance control (falls, poor mobility, unsteadiness, postural symptoms). Pepersack et al. and Craig et al. have identified relationships between cardio- and cerebrovascular health instability and falls in older adults.

Various authors have investigated blood pressure responses during an orthostatic stress (active posture change or passive tilt test) and its association to falls or balance control. In the absence of measuring cerebral blood flow or oxygenation, blood pressure can lend insight to the hemodynamic responses which may be occurring at the level of the brain. Heitterachi et al. (2002) investigated blood pressure responses to a 60° head-up tilt test and fall rates over a 12-month period (Heitterachi E. *et al.* 2002). The blood pressure response of a passive head-up tilt test differs from an active stand, yet both maneuvers challenge the cardiovascular system and provide information about the system's function. Heitterachi et al. found 51% of the older adults (n=70, 77±6 years) fell one or more times during a one year follow up (Heitterachi E. *et al.* 2002). When comparing fallers to non-fallers, fallers demonstrated significantly larger reductions in SBP when tilted, and poorer SBP recovery (3-minutes post tilt). Where 22% of the fallers had a decrease of SBP equal to or greater than 20 mmHg at 3-minutes post tilt and only 6% of the non-fallers demonstrated this hypotension. The authors concluded that poor blood pressure recovery seen with tilting was associated with a 70%

increased risk of falling (RR=1.71, 95%CI=1.14-2.59). Five percent of the fallers reported 'fainting' or blacking-out' as the cause of at least one fall. These same participants (fainting/blacking-out) demonstrated significantly larger SBP drops with tilting compared to fallers not reporting signs of pre-syncope as the cause of a fall. These findings indicate that reductions in SBP and unstable SBP recovery to a tilt test are predictors of falls in older adults (Heitterachi E. *et al.* 2002).

Relative to a passive tilt test, an active stand exaggerates the transient reduction in blood pressure and better mimics activities of daily living. Finucane et al. 2017 collected beat-beat continuous recordings of BP during an active stand protocol in older adults (50+ years) (Finucane C. *et al.* 2017). It was found that delayed OH recovery and sustained OH were both independent risk factors for a future fall, unexplained fall and injurious fall in adults 50+ years old (Finucane C. *et al.* 2017). Kario et al. (2011) investigated the relationship between blood pressure responses during a supine-to-stand transition and falls in older adults (n=266, 76±5 years) (Kario K. *et al.* 2001). By means of a manual sphygmomanometer, blood pressure was measured in the supine position, immediately after standing and 2-minutes after standing. A battery of postural control tests assessing responses to surface perturbations and altered visual conditions were conducted, as well as a 12-month follow-up of fall history were also collected. When separating fallers (31% of participants) from non-fallers, SBP was significantly lower in fallers at all time points (Kario K. *et al.* 2001). When participants were separated into 5 different SBP groups, falls occurred 2.8 times more often in the lower blood pressure groups (<140 mmHg) (Kario K. *et al.* 2001). Falls were less common in hypertensives (treated or not) versus normotensives. This finding is in opposition to much of the literature which supports an association of hypertension and higher prevalence of OH, where OH is associated with fall risk (Frewen J. *et al.* 2013; Gangavati A. *et al.* 2011; Duschek S. *et al.* 2009; Romero-ortuno R. *et al.* 2011; Ooi W.L. *et al.* 2000; Wu J.S. *et al.* 2008). Kario and colleagues did not find fall risk to be associate with the

postural balance tests (p=0.1) however, standing SBP was a negative predictor of falls (Kario K. *et al.* 2001). A 10 mmHg increase in standing SBP reduced falls by 22%, implying that a lower standing SBP is seen to be a predictor of falls in older adults (Kario K. *et al.* 2001). Kario and colleagues' study results support the observations made by Romero-ortuno et al. (2011). Romero-ortuno et al. found that a lower standing SBP was indicative of poorer blood pressure recovery and increased prevalence of OH symptoms (Romero-ortuno R. *et al.* 2011). Kario and colleagues' findings are also complemented by Mehagnoul-Schipper et al. (2000) who found a significant association between smaller postural decreases in OxHb (by an active stand) and higher baseline SBP (r=0.4) and DBP values (r=0.51) (Mehagnoul-Schipper D.J. *et al.* 2000a). Smaller OxHb decreases and smaller DeoxHb increases were also significantly associated to higher postural DBP increases (r=0.52, r=-0.46, respectively) (Mehagnoul-Schipper D.J. *et al.* 2000a). During an active stand protocol in older adults (75±7 years), Mehagnoul-Schipper et al. 2001 found that two participants experienced dizziness and light-headedness without an OH decrease in BP but they did have pronounced reductions in both OxHb (Mehagnoul-Schipper D.J. *et al.* 2001). The authors suggested that cerebrovascular hemodynamics may fail to compensate fully for postural changes in BP, placing some older adults at risk of cerebral hypoperfusion following an active stand (Mehagnoul-Schipper D.J. *et al.* 2001).

Sorond et al. (2010) examined the relationships between cerebrovascular function and gait speed in community-dwelling older adults (n=765, age: 78±5 years) (Sorond F.A. *et al.* 2010). Gait speed is a known predictor of falls in older adults (Quach L. *et al.* 2011; Sorond F.A. *et al.* 2011), and slow gait speed has been associated with poor cerebrovascular regulation (Sorond F.A. *et al.* 2011). In the study by Sorond et al. 2010, CR_{CO2} was used to measure cerebrovascular function and gait speed was evaluated using a 4-meter walk test. Slower gait speed was significantly associated with a reduced CR_{CO2} response. The relationship between CR_{CO2} and falls alone was not significant; However, when

the CR_{CO2} responses were split into quintiles, the lowest quintile group had significantly more falls compared to the highest quintile group (Sorond F.A. *et al.* 2010). The authors concluded, impaired cerebral blood flow regulation was associated with slower gait speed and falls in their sample of older adults (Sorond F.A. *et al.* 2010).

More recently, soluble vascular cell adhesion molecule-1 (sVCAM-1), a biomarker of endothelial dysfunction has shown to be associated with impaired cerebrovascular function in older adults (Tchalla A.E. *et al.* 2015). Elevated sVCAM-1 is significantly associated with reduced resting CBFV, cerebral vasomotor reserve, slower gait speed and increased odds of an injurious fall in older adults (78±5 years old) (Tchalla A.E. *et al.* 2015). Lower resting CBFV, marked by a combined left and right anterior and middle cerebral arteries in older adults (81±6 years of age) has also shown to be associated with slower gait speed and chair rise time (Ezzati A. *et al.* 2017). Yet to date CBF during over-ground walking and its' relationship to gait speed has not been assessed in older adults.

The aforementioned studies imply that inadequate blood pressure regulation and insufficient blood pressure recovery from a posture change are related to greater reduction in cerebral oxygenation, higher prevalence of OH and increased risk of falls in older adults. Furthermore, lower resting cerebrovascular hemodynamics were also associated with reduced gait speed, a known predictor of future falls. Yet to date there have not been any studies investigating cerebral perfusion during an active transition (to standing or walking) and its relationship to balance control, gait speed and falls in older adults.

Summary

Orthostatic hypotension is an impended risk factor for future falls (Finucane C. *et al.* 2017). Syncope, and signs of it, suggests moments of cerebral hypoperfusion, yet cerebral blood flow and oxygenation have not been investigated alongside measures of balance control, gait dynamics or falls.

The mechanisms underlying transient cerebral hypoperfusion require further investigation to identify if cerebral hypoperfusion is associated with postural instability, altered gait characteristics, gait speed and falls in older adults.

Thesis Objectives

General objective

The purpose of this thesis was to investigate relationships between cerebral hypoperfusion and postural instability and compromised gait strategies, with implications for future falls in older adults. This study will improve baseline knowledge regarding reductions in blood pressure and the risk of cerebral hypoperfusion in older adults with the hopes to distinguish mechanisms that might underlie a greater risk for some older adults of having a future fall and with the goal of improving the health of older adults.

Specific questions and hypotheses Chapter 3:

A. Do older adults have varied cerebrovascular responses to a transition to standing?

   It is hypothesized that some older adults will have cerebral hypoperfusion while standing.

B. Do individuals with posture related reductions of tSO_2 have impaired postural stability?

   It is hypothesized that older adults with cerebral hypoperfusion will also have greater measures of postural instability.

C. Do different posture transitions (supine-sit-stand and sit-stand compared to supine-stand) reduce the impact of reduced tSO_2 resulting in enhanced postural stability?

   It is hypothesized that a brief sitting pause time (supine-sit-stand) will increase tSO2 nadir values and improve postural stability. It is also hypothesized that a sit-stand will result in a higher tSO2 value and be associated with better postural stability compared to a supine-stand transition.

D. Is reduced tSO_2 associated with falls (within 6-months of testing)?

   It is hypothesized that older adults with cerebral hypoperfusion will have an increased likelihood of having a future fall.

Specific questions and hypotheses Chapter 4:

A. Do older adults have varied cerebrovascular responses to a transition to walking?

   It is hypothesized that some older adults will have cerebral hypoperfusion during walking.

B. Do older adults with posture related reductions of tSO_2 during walking have increased step-step variability or slower gait speeds?

   It is hypothesized that older adults with cerebral hypoperfusion will have increased step-step variability, compromised gait strategies and slower gait speeds.

C. Is vascular stiffness associated with cerebral hypoperfusion while walking?

   It is hypothesized that older that with stiffer arteries will have cerebral hypoperfusion while walking.

CHAPTER 2. GENERAL METHODS AND MATERIALS

This chapter describes the participant populations and experimental measurements used throughout the study protocols (Table 2). Methodologies specific to each study will be described in each corresponding chapter.

Table 2-1. Overview of Study Population, Equipment and Procedures

Study Title	Population	Equipment	Additional Procedures
1. Cerebrovascular hemodynamics and postural stability in older adults	65 years & older (fallers & non-fallers)	- ECG - Finometer - NIRS - Mobil-O-graph - NWBB	
2. Cerebral hypoperfusion during over-ground walking is related to increased gait variability and vascular stiffness in older adults	65 years & older (fallers & non-fallers)	- ECG - Portapres - TCD-X - NIRS - accelerometers	cfPWV IMT cCC cDC cPP

ECG electrocardiogram, *NIRS* near-infrared spectroscopy, *NWBB* Nintendo Wii balance boards, *TCD* transcranial Doppler ultrasound, $P_{ET}CO_2$ end-tidal CO_2, CR_{CO2} cerebrovascular reactivity to Carbon dioxide, *cfPWV* carotid-femoral pulse wave velocity, *IMT* intima medial thickness, *cCC* carotid artery compliance coefficient, *cDC* carotid artery dispensability coefficient, *cPP* carotid pulse pressure.

Participant Population

The target population for each study is described in detail within each pertaining chapter. However, in general, older adults recruited were ≥65 years old. With the exception of 3 community dwelling older adults all other older adults were from conjugate living at one of the Schlegel Villages in Ontario Canada. All participants were asked to avoid moderate to strenuous levels of exercise 24 hours prior to testing (Pescatello L.S. & Kulikowich J.M. 2001), to refrain from consuming alcohol or caffeine (Kurtz A.Ml *et al.* 2013) within four hours of testing and to arrive to testing 2-h postprandial. Upon arrival to the testing location, participants completed a brief health questionnaire (Appendix A). The health questionnaire was a self-report questionnaire which was used to identify the exclusion criteria (neuromuscular and neurological conditions, diabetes, stroke or any recent (within 3 months) myocardial infarctions). The health questionnaire also included additional information from participants including past and current health, physical activity habits, history of smoking, balance confidence and fear of falling, recent nutritional intake and current medications.

Experimental Measurements

Multiple Schlegel Villages locations were used for the studies involving older adult participants. The intent of having multiple testing locations was to maximize recruitment by limiting the amount of travel to the testing site.

Hemodynamic Trending

Assessment of Cardiovascular Hemodynamics

Heart rate was continuously monitored using a 3-lead electrocardiogram (ECG, Finapres Medical Systems, Amsterdam, The Netherlands). Arterial blood pressure (ABP) was recoded continuously using noninvasive finger-cuff photoplethysmography (Portapres, Finometer, Medical Systems, Amsterdam NL), where the cuff was placed on the right-hand middle finger. The Portapres does not differ substantially from invasive intra-arterial pressure during rest or posture transitions and represents a reliable means for collecting ABP during orthostatic stress (Imholz BPM *et al.* 1990). The Portapres has an off-line analysis (Beatscope) program, and the Finometer has a real time analysis system to reconstruct the finger arterial pressure waveform to a brachial arterial pressure waveform. These photoplethysmography devices also used a glycerine-filled pressure transducer to account for differences in hydrostatic pressure between the finger and brachial arterial sites. The Finometer further reduced pressure differences between finger arterial pressure and brachial pressure by using a return-to-flow function which is known to reduce pressure differences to less than 4 mmHg (±8 mmHg) between the two methods (Guelen I *et al.* 2008). Both photoplethysmography devices used a technique called Modelflow to calculate stroke volume (SV). Modelflow integrated a three-element model of arterial impedance with the arterial pressure wave to reliably track beat-to-beat differences in stroke volume (Harms M *et al.* 1999). Estimates of SV were used to calculate an output measure of cardiac output (Q) in real time by the Finometer and offline by the Portapres. To minimize the effects of body size on differences in blood volume and hemodynamic responses, Q was normalized (Q_i) to body surface area (BSA)(Equation 2 -1) (DuBois D & DuBois EF 1916; Wang Y *et al.* 1992). Stroke volume (SV) and total peripheral resistance (TPR) were calculated (Equation 2-2, Equation 2-3) and adjusted to BSA (SV_i, TPR_i) when using the Portapres. Arterial blood pressure was collected with a manual sphygmomanometer and stethoscope at the beginning of testing. The manual ABP was used to adjust the beat-by-beat blood

pressure if a difference of five or more millimeters of mercury existed between the manual ABP and the Finometer/Portapres device. Manual blood pressures were collected in duplicate or triplicate if there existed large variability within the measure. Mean arterial pressure (MAP) and pulse pressure (PP) were calculated (Equation 2-4, Equation 2-5). To account for the differences in hydrostatic pressure from a supine to an upright position, MAP at the level of the brain (BP_{MCA}) was adjusted according to the distance from the heart to the level of the middle cerebral artery (Equation 2-6). It is important to note that this calculation relies on the assumption that intracranial and venous pressures are relatively low and constant, and that they are proportional to the arterial pressure for a closed circulatory system (Zhang R. *et al.* 2007).

Body surface area = $(W^{0.425} \times H^{0.725}) \times 0.007184$

W: weight in kilograms H: height is in centimeters

Equation 2-1. Body Surface Area (kg*cm)

Stroke volume = cardiac output/heart rate*1000

Equation 2-2. Estimate of Stroke Volume (ml/beat)

Total peripheral resistance = mean arterial pressure/cardiac output

Equation 2-3. Estimate of Total Peripheral Resistance (mmHg/L/min)

MAP = systolic blood pressure + 1/3 diastolic blood pressure

Equation 2-4. Estimate of Mean Arterial Pressure (mmHg)

Pulse pressure = systolic blood pressure – diastolic blood pressure

Equation 2-5. Pulse Pressure (mmHg)

BP_{MCA} = mean arterial pressure - (heart to MCA distance in cm * 0.78)

The constant 0.78 represents the density of blood

Equation 2-6. MAP at the MCA Level (mmHg/cm)

The Powerlab acquisition system and the Chart 7 software (PowerLab; AD Instruments, Colorado Springs CO USA, 2003) were used to sample beat-by-beat RRI, ABP, and TCD (described below) data at 1000 Hz, providing a basic resolution of 1 millisecond. The data was subsequently transferred into Excel (Microsoft Corp., Redmond WA USA, 2010) for further analysis. The R-R sequences was visually inspected, and the data considered as artifacts was manually removed.

Assessment of Cerebrovascular Hemodynamics

A 2-MHz range gated (pulse wave) Transcranial Doppler ultrasound (TCD) system was used (Multigon Industries, Elmsford, NY, USA, TCD-X; Atys medical, Soucieu en Jarrest, France) to insonate the MCA and collect a peak flow velocity tracing. The MCA travels laterally and slightly anteriorly, thus the probe was placed over the transtemporal window, slightly facing the anterior direction (giving it a zero-angle insonation), and at a depth of 35 to 55 mm (Panerai R.B. 2009; Purkayastha S. & Sorond F. 2012; Aaslid R. *et al.* 1982). The angle of insonation is a determinant of cerebral blood flow velocity (Equation 1-2), where an angle greater than 60° significantly increases the resultant calculated velocity and should therefore was not used. In addition to depth and probe placement, tone and pitch (strength of the velocity tracing) were used to confirm MCA insonation (Zwiebel W.J. & Pellerito J.S. 2005). The TCD

probe was always placed on the right side of the head, unless a TCD signal was only found on the left side of the head.

In addition to the limitations of Doppler ultrasound mentioned above (turbulent flow, pulsatility, angle of insonation) the assumption of having a circular vessel can impact blood flow calculations (Eq. 1-3). Vessel area is quantified by using the vessel diameter, which is assumed to be circular. With age structural changes to the vessels may cause changes in geometry, whereby significantly larger internal carotid artery and middle cerebral artery diameters are seen with age (Rai A.T. *et al.* 2013).

NIRS provides non-invasive, continuous sample (10 Hz) of cerebral tissue oxygenation. NIRS was used to collect OxHb, DeoxHb, TotHb, and tSO_2 (PortaLite: Artinis Medical Systems BV, Netherlands). The PortaLite NIRS device has three optodes (LED light sources) which alternate between 760 and 850 nm wavelengths. The NIRS device has a single detector which constructs three source-detector distances (2, 3, and 4 cm). All source-detector distances were collected, however only the source-detector distance of 4 cm was used for analysis. Source-detector distances less than 3 cm are not recommended as they are greatly contaminated by scalp and skull tissue (Kohri S. *et al.* 2002; Pellicer A. & Bravo M.C. 2011; Pellicer A. & Bravo M.C. 2011; Hare H.V. *et al.* 2013). In a study by Kohri et al. (2002), the contribution ratio of the cerebral tissue to the optical signals was 33%, 55% and 69% at source detector distances of 2, 3 and 4 cm respectively (Kohri S. *et al.* 2002). A source-detector distance of 4 cm resulted in a tissue sampling of 2 cm below the skins surface which reduced the contribution of extracerebral tissue. This sampling depth was restricted to the outer cortex and hence there was an inability to monitor deep brain regions (basal ganglia – often performed during cognitive stimulation) (review by (Quaresima V. *et al.* 2012)).

The NIRS device was positioned alongside the TCD probe and placed on the forehead. The exact positioning of the NIRS device was in accordance with the international 10-20 EEG electrode placement (right: Fp2, F4, F8. left: Fp1, F7, F3) (Perrey S. 2008). This optode and detector placement

sampled Brodmann Area 10 (Anterior prefrontal cortex: executive function), Brodmann Area 8 (Frontal eye field: visual attention), and Broadman areas 45 and 47 (Inferior frontal gyrus: inhibition and language), which are supplied by the MCA and ACA.

Small changes in the optode-to-skin contact can lead to large changes in the NIRS signal (Pellicer A. & Bravo M.C. 2011). Movement artifacts (caused by head movement) lead to alterations in light coupling and add noise to the signal (Scholkmann F. *et al.* 2010). The movement artifacts, often seen in neonates and animals, affect the quality of the NIRS signal and can be resolved using various processing techniques (for a review see (Cui X. *et al.* 2010)). To ensure continuous optode-to-skin contact, the NIRS device was secured with a tenser bandage wrapped around the head.

The differential pathlength factor accounts for scattering of the near infrared light. Due to changes in tissue properties with age (ex. brain atrophy), the differential pathlength factor increases with age (Claassen J.A.H.R. *et al.* 2006). To date there are no set differential pathlength factors established for adults older than 50 years (Duncan A. *et al.* 1996). However, Classen and Colier (2006), report using a set differential pathlength factor of 6.6 (set to that of a 50 year old) for adults 68-87 (Claassen J.A.H.R. *et al.* 2006). The same differential pathlength factor of 6.6 was used in the current thesis for all adults.

$$\triangle Y = y_i - y_{avg}$$

Equation 2-7 Relative Change in NIRS Signals

It is also important to acknowledge the effects of thermoregulation on changes and flow redistribution in the skin of the forehead (Miyazawa T. *et al.* 2013; Kirilina E. *et al.* 2012). Miyazawa et al. (2013) demonstrate significant increases in oxygenated hemoglobin (OxHb) during cycling at a work rate equal to 60% of age predicted max heart rate (Miyazawa T. *et al.* 2013). Following five minutes of

exercise, cooling was applied to the forehead, cerebral blood flow velocity (TCD) remained elevated yet OxHb and skin blood flow significantly diminished (Miyazawa T. *et al.* 2013). This implies that the OxHb can be impacted by skin blood flow (Miyazawa T. *et al.* 2013). It has also been shown that task-evoked changes in OxHb contain extra-cranial artifacts of venous volume (Kirilina E. *et al.* 2012). The decrease in venous volume during the task was confirmed by the MRI signal and attributed to alterations in sympathetic outflow observed with cognitive and emotional processes (Kirilina E. *et al.* 2012). These findings suggest caution should be taken when interpreting results which employ dynamic exercises (equal to or greater than 60% of age predicted max heart rate) or activities which may cause additional stress (Miyazawa T. *et al.* 2013; Kirilina E. *et al.* 2012).

NIRS software (Oxysoft: Artinis Medical Systems BV, Netherlands) was used to convert the NIRS signals into Excel and then uploaded to Chart 7 to extract beat-to-beat data. Once all the cardiovascular and cerebrovascular beat-to-beat data were cleaned and time aligned, the data was resampled at 1 Hz (MatLab, mathWorks, Natick MA, USA) to allow between participant comparisons and construction of group averaged graphs.

Vascular Properties

With age, central elastic arteries become stiffer and the prevalence of systolic hypertension becomes greater, consequently central pulse pressure widens (Swaminathan R.V. & Alexander K.P. 2006). The pulse wave of the carotid artery is a valid estimate of aortic pulse pressure (Kelly R.P. *et al.* 1989; Chen C.H. *et al.* 1996), and it represents a gauge of pulse pressure entering the cerebral circulation. Central pulse pressure was collected by a high-fidelity tonometer (SPT-301, Millar Instruments, Houston TX USA) over 20-30 cardiac cycles. The tonometer was placed 1cm below the internal and external carotid artery bifurcation. The carotid distension waveforms were calibrated against the Portapres/Finometer's reconstructed brachial pressure waves (MAP and DBP), to account for

holding pressure of the tonometer and to obtain an accurate carotid pressure waveform (Hirata K. *et al.* 2006b).

The speed of a pressure wave traveling along an arterial segment was determined by the density of blood, the arterial diameter and the stiffness of the elastic material (Nichols W.W. & O'Rourke M.F. 2005). As the structure of an elastic vessel becomes stiffer blood travels through it at a greater velocity. The calculated distance a pulse pressure wave travels between two sites along the arterial tree, for a given amount of time, is referred to as the pulse wave velocity (PWV) (Equation 2-8) (Nichols W.W. & O'Rourke M.F. 2005; Hirata K. *et al.* 2006a). PWV is informative of arterial stiffening and can represent central (carotid-femoral) or peripheral (brachial-ankle) vasculature. Central PWV progressively increases with age, suggesting elastic degeneration and stiffening of central vessels (Hirata K. *et al.* 2006a).

$$PWV = (L_D - L_P) / (T_D - T_P)$$

L is the length/distance, T is the arrival time of the pulse wave, subscript P is the proximal site and subscript D is the distal site

Equation 2-8 Pulse Wave Velocity

Carotid-femoral PWV was collected simultaneously at the carotid (below common carotid bifurcation) and femoral artery sites. Pulse pressure waves were recorded for 20-30 cardiac cycles by Doppler ultrasound (Doppler Box, Compumedics DWL, Singen DE). To clearly identify the foot of each pressure wave, a low-pass 5-30 Hz filter was applied (Robertson A.D. *et al.* 2010a) and the maximum 2nd derivative of each waveform was calculated (Chiu Y.C. *et al.* 1991). The distance in cm was measured from the suprasternal notch to each corresponding measurement site (carotid and femoral). The surface distance between sites was calculated as suprasternal notch-to-femoral minus suprasternal notch-to-

carotid (Wong A.K. *et al.* 2014). The distance between sites was then divided by the difference in arrival time from the R-peak in the cardiac cycle to the foot of the arterial pressure wave.

Measures of Stability

Nintendo Wii Balance Boards

The Nintendo Wii Balance Board (NWBB) (Nintendo, Koyoto, Japan) was developed as a gaming controller but has recently been used in place of force plates. The NWBB is a portable (3.5 kg, L 25cm, W 26.5cm, and H 5.3cm), inexpensive device (less than 1% of a force plate cost), which uses Bluetooth technology to wirelessly transmit data to a customized nearby software program (Laboratory Virtual Instrument Engineering Workbench (LabView, National Instruments, Austin TX USA). The NWBB is comprised of a 16-bit pressure sensor in each corner which detects vertical ground reaction forces on the surface of the board. The COP path can be calculated by the weighted average of the vertical forces. The data collected by the NWBB is sampled at 100 Hz which is sufficient to record movements seen with quiet standing (0.01 – 10Hz). Less than 2 Hz of COP fluctuations are reportedly based on visual and vestibular information, and greater than 2 Hz of COP postural sway is based on proprioceptive information (Tanabe H. *et al.* 2012).

The NWBB demonstrates good to excellent COP path length test-retest reliability (intraclass correlation coefficient = 0.66 – 0.94) during a quiet stand with eyes open/closed and during single/double limb supports (Clark R.A. *et al.* 2010). When compared to a force plate, the NWBB demonstrates excellent COP path length accuracy (intraclass correlation coefficient = 0.77 – 0.89) during eyes open/closed and with a single/double support, making it a valid (>0.75) (Lee J. *et al.* 1989) means of calculating COP (Clark R.A. *et al.* 2010). The NWBB also demonstrates sensitivity to subtle movement variations associated with visual tasks (magnitude and dynamics of body sway) in older adult (73±7 years) (Koslucher F. *et al.* 2012).

Wear and tear of a NWBB (tested up to 4 years of use) does not significantly affect the performance of the board (Bartlett H.L. *et al.* 2014). However, using the same board(s) for all protocols within a study reduces uncertainty of the force measurements and produce a relative measure with the same device (Bartlett H.L. *et al.* 2014). Thus, the same NWBB was used across all participants and studies. COP displacement was characterized as the root mean square (RMS) (Lafond D. *et al.* 2004), which is the magnitude of the COP excursion. The RMS was calculated (Matlab) from the COP in both the AP and ML directions.

Limitations of the NWBB includes the inability to collect sheer forces and moments. Shear forces are known to increase as a task becomes more dynamic. Although this is less important during a quiet stand, the data collected during the dynamic phase of the posture transitions likely presented with non-vertical loads, and these data lacked shear force information. Furthermore, the calculation of COP traditionally incorporates shear forces and moments, and therefore the COP calculation may be less accurate. However, the first 2-s of standing data (marked by upright posture) were removed from analysis and thus should not include highly dynamic movement from the transitions and thus sheer force data.

A second limitation of the NWBB is that it cannot be used interchangeably with a force plate (Pagnacco G. *et al.* 2013; Lee J. *et al.* 1989; Huurnink A. *et al.* 2013; Clark R.A. *et al.* 2010; Pagnacco G. *et al.* 2014). Simultaneous measurement of vertical forces by the NWBB placed on top of a force plate has demonstrated linearity (r=0.99) and similar errors between device outcomes (Huurnink A. *et al.* 2013). These findings suggest the NWBB can be a useful measure of COP and that it is unlikely the estimates of COP sway will produce false balance test conclusions (as seen during a single-leg balance task) (Huurnink A. *et al.* 2013). However, the NWBB has demonstrated biases towards higher mean COP path length values (Clark R.A. *et al.* 2010), and overestimates of the COP path velocity and mean absolute COP sway values when compared to a force plate (Huurnink A. *et al.* 2013). These biases do not disqualify the

NWBB from use in research, although caution should be considered when interpreting results (Clark R.A. *et al.* 2010).

Accelerometer Data

To capture gait variables, a tri-axial accelerometer (16g accelerometer data logger x16-mini, Gulf Coast Data Concepts, LLC, Waveland, MS, USA) was placed on the lateral plane of the left ankle and sampled at 50 Hz. The accelerometer data loggers were small (0.6 oz, L 2cm, W 1cm, H 0.5cm), portable (2GB flash memory), and were transfer compatible with Windows via a universal serial bus (USB) interface. With use of accelerometers it is important to note some concerns of the device, primarily, i) the requirement of gravity to account for acceleration, ii) post processing load, iii) drift error iv) placement of sensors on body segments (Taborri J. *et al.* 2016).

A customized Matlab program (Matlab R2015a; The Mathworks Inc, Natick, MA, USA) was used for feature extraction (toe-off, mid-heel swing and heel-strike, figure 5-1), cropping of turns, computing gait variable and time aligning data to beat-to-beat measures (e.g. BP and CBF). To identify the timing of each gait feature the data were filtered at 100 Hz and the timing and amplitude of toe off, mid heel swing and heel strike were extracted from the raw signal and used for further analysis (Selles R.W. *et al.* 2005).

Statistical Analysis

All statistical analysis was completed using IBM SPSS version 20 (IBM SPSS Statistics 20; IBM Corp, Armonk, NY, USA), and all tests were considered significant at $p \leq 0.05$ and trends were reported at $p \leq 0.1$.

Participant Grouping- Participants demonstrated varying tSO_2 response to a transition to upright posture (supine-stand and supine-walk). As in previous studies Romero-Ortuno et al. 2011 (Romero-ortuno R. *et al.* 2011), the participants were split into groups (regulators and impaired-regulators) based on their tSO_2 values from delta baseline to nadir and initial standing (Chapter 4 – supine-stand experiment) and tSO_2 values from baseline and nadir (Chapter 5 – supine-walk experiment). A TwoStep cluster analysis (k-cluster) was used to automatically create the number of clusters (participant groups) and only a good cluster quality (silhouette measure of cohesion and separation of 0.5 to 1.0) were considered acceptable.

Sample Size - A sample size could not be calculated in the traditional manner as the current investigations were comparing responses within group. In reference to the comprehensive population study titled The Irish Longitudinal Study on Ageing (TILDA), it was anticipated that three distinct morphological responses in BP and tSO_2 would be evident following a supine-stand transition (Romero-ortuno R. *et al.* 2011). As mentioned above, a k-means cluster analysis was performed and we hypothesized that two groups with unequal numbers in each cluster would be identified. Given the percent distribution of participants in the TILDA study (small drop/overshoot = 33%, medium drop/just recovery = 50% and large drop/no recovery = 17%) we had aimed to recruit 100 participants so that the number of participants in the large drop/no recovery cluster would = 17 or greater. We recruited 77 participants and thus 2 clusters were identified resulting in 19% of participants being part of the susceptible group.

Effect of group, condition and time - Two-way mixed ANOVAs (general linear model in SPSS) were used to assess the main effect of condition, group and time. The supine-stand experiment (Chapter 4) assessed three levels for condition, two levels for group and four levels for time. The supine-

walk experiment (Chapter 5) assessed two levels for condition and two levels for group. For all ANOVAs if Mauchly's test of Sphericity was significant the Greenhouse-Geisser correction was used. If a significant interaction was found, Tukey's honest significance test (HSD) was used to further evaluate significant levels.

For group comparisons of gait variability data, a Mann-Whitney U Test and a Levene's Test for equality of variance was performed. Corrections for multiple tests were not applied, thus not all variables with a $p \leq 0.05$ are truly significant. A correction was not applied as this is an exploratory study requiring additional power to accurately assess multiple comparisons on non-continuous data. A Friedman's Test was used to analyze differences between conditions.

Group characteristics comparisons –All nominal data were tested using a Chi-square test with the Fisher's Exact Test correction factor (Phi was used to estimate the effect size when significance was found).

CHAPTER 3. CEREBROVASCULAR HEMODYNAMICS AND POSTURAL STABILITY IN OLDER ADULTS

Introduction

Impaired blood pressure (BP) recovery on standing following supine rest occurs in approximately 21% of older adults (Romero-ortuno R. *et al.* 2011) and is an independent risk factor for future falls, unexplained falls and injurious falls in older adults (Finucane C. *et al.* 2017). Impaired balance is also significantly associated with fall risk in older adults and measures of stability are therefore often used to identify older adults at risk of a future fall (Muir S.W. *et al.* 2010); (Berg K.O. *et al.* 1992).

Older adults who experience significant and/or sustained postural reductions in BP may also demonstrate reduced cerebral blood flow (CBF) (Novak P. 2016) which could lead to a subsequent fall (Finucane C. & Kenny R.A. 2017). Although cerebral autoregulation is considered intact in older adults (Lipsitz L.A. *et al.* 2000), the posture related drop in CBF is compounded by age-related declines in CBF (de la Torre 2012; Leenders K.L. *et al.* 1990; Chen Y. *et al.* 2011), and this might also place some older adults at risk of cerebral hypoperfusion. The impact of the initial drops in, and recovery of, CBF and or cerebral oxygenation (tSO_2) on balance control in older adults is unknown.

Introduction of a sitting-pause time during a supine-stand transition has been shown to improve postural stability in older adults (Johnson EG. & Meltzer J.D. 2012) yet it is unknown if this is due to the increased allotted time for BP, CBF and tSO_2 to recover before standing. Therefore, the purpose of the present investigation was to test the hypotheses: i) that individuals with posture related reductions of tSO_2 will have impaired postural stability, and ii) that posture transitions including adaptation to upright posture (supine-sit-stand and sit-stand compared to supine-stand) will reduce the impact of posture transition on tSO_2 resulting in enhanced postural stability. In a follow-up, prospective phase of the study,

the posture related reductions in tSO_2 were investigated with respect to subsequent falls over the next 6-months in these older adults.

Methods

Participant Description

Seventy-seven older adults aged 69-100 years old (57 females; age 86.6±6.6 years; height 160±9 cm; weight 68±14 kg) gave written and informed consent to volunteer in the present study which was reviewed and approved by the Office of Research Ethics at the University of Waterloo and the Schlegel-University of Waterloo Research Institute for Aging. Seventy-four of the participants were in conjugate living at one of the Schlegel Villages in Ontario Canada while three participants were community dwelling. Participants arrived 2 h postprandial to testing where they completed a brief health questionnaire (past health, current health, physical activity levels, medications). The health questionnaire indicated that all participants were free of neuromuscular and neurological conditions as well as free of diabetes, stroke or any recent (within 3 months) myocardial infarctions. Participants were also required to complete a minimum of 1-min of unassisted static standing.

General Protocol

All participants randomly completed three active transitions: i) supine-stand, ii) supine-sit-stand (with a 10-s sitting pause time), iii) sit-stand. The three transitions were preceded by a practice transition (supine-stand) to ensure familiarity and tolerance to the testing. All transitions began with 10 min of supine rest, followed by an assisted transition into the standing position. Assistance to a sitting position was provided by the research team whereby one researcher placed a hand behind the participants' left shoulder and another behind the left elbow. As the participant moved to the standing position, an assistant placed her/his feet correctly, with the feet together. The feet were on average

(across conditions) 10.8±2.1 cm apart. If assistance for the sitting-standing transition was required, each researcher placed one hand under the upper arm but released the upper arm once the participant was in the seat-off position. Participants were asked to stand for 180-s but could terminate the test at any time by siting down or grabbing a hold one of the research assistants spotting them. At 1-min of standing no participant had terminated the testing for any condition. By 2-min, 8 participants had terminated testing for the supine-stand and sit-stand conditions, and 7 participants had terminated the test for the supine-sit-stand condition.

Total body water was (TBW) was estimated using a body impedance analysis (MF-BIA QuadScan 4000: Bodystat LTD, Isle of Man, UK) with electrodes placed on the right wrist, middle finger, ankle and toe with the participant in a supine position and arms and legs abducted from the body (Sun S.S. *et al.* 2003).

Hemodynamics

Continuous monitoring of heart rate (HR; electrocardiogram, Finapres Medical Systems, Amsterdam, The Netherlands) and continuous arterial finger BP by plethysmography (Finometer Pro; Finapres Medical Systems, Arnheim, The Netherlands) were recorded at 1kHz (PowerLab, ADInstruments, Colorado Springs, CO, USA) and processed (LabChart 7, ADInstruments, Colorado Springs CO). Estimates of stroke volume from analysis of the finger pulse wave, and calculated cardiac output and total peripheral resistance were normalized to body surface area (DuBois D & DuBois EF 1916)(SVi, Qi and TPRi respectively).

A near infrared spectroscopy device (NIRS; PortaLite, Artinis Medical Systems BV, Netherlands) was used to collect relative changes in oxygenated, deoxygenated, and total hemoglobin content (OxHb, DeoxHb, and TotHb respectively) as well as cerebral oxygenation (tSO_2) was calculated from OxHb and TotHb. The NIRS device was placed over the prefrontal lobe in accordance with the international 10-20

EEG land marking system (right: Fp2, F4, F8. left: Fp1, F7, F3) (Perrey S. 2008). A source detector distance of 4 cm was used for the OxHb, DeoxHb and TotHb signals to reduce signal contamination from surrounding tissues (Kohri S. *et al.* 2002). The NIRS signal was later processed into beat-by-beat data points where the mean hemoglobin values were extracted from each beat.

Resting arterial blood pressure and calculated central SBP and DBP (cSBP and cDBP) as well as arterial stiffness (augmentation index, AI; augmentation index at 75 bpm, AI@75; pulse wave velocity, PWV) were assessed in the supine resting position using the Mobil-O-Graph cuff placed over the brachialis artery (Mobil-O-Graph, I.E.M. GmbH, Strolberg, Germany). The Mobil-O-Graph detects the oscillometric waveform and uses customized software (ARCSolver) to apply transfer function analysis and reconstruct the central waveform. Subsequently, the shape and timing of the central pulse wave are used to calculate AI, AI75 and PWV. The Mobil-O-Graph has been validated against a well-established non-invasive estimation of central BP known as SphymoCor for both central hemodynamics and measures of arterial stiffness (Weiss W. *et al.* 2012; Luzardo L. *et al.* 2012).

Self-reported questionnaire

The self-reported health status questionnaire, modified from Robertson 2013 (Appendix A, (Robertson A.D. 2013)), was verbally administered to each participant upon arrival to the testing session. Participants reported on vision, past health behaviours such as smoking status and physical activity, health conditions such as heart failure, kidneys or liver disease (listed in table 3-1), current health concerns such as irregular heart beats and pain with walking, current medications (prescribed and over-the-counter) and perceived balance (fear of falling and balance confidence).

Time scale and averaging

Resting baseline values were averaged over 30-s of supine or seated rest (from -45-s to -15-s prior to a transition). Time at zero seconds indicates upright posture. Nadir signifies the average of the three lowest tSO_2 beats following upright posture. Delta nadir represents the differences between the resting baseline average and the nadir. Initial standing is characterized by a 20-s average starting 2-s after upright posture. At one-min, two-min and three-min of standing a 20-s average was calculated (40 to 60-s, 100 to 120-s and 150 to 170-s respectively, Fig. 3-1).

To identify the presence of initial orthostatic hypotension (IOH) the difference in BP from the 30-s baseline average to the lowest single interpolated 1-s of standing data was calculated. A drop in SBP ≥40 mmHg or a DBP drop ≥20 mmHg within the first 15-s of standing classified an individual to have IOH (Wieling W. *et al.* 2007; Finucane C. *et al.* 2014). To characterize participants with orthostatic hypotension (OH) and sustained OH (SOH) BP was calculated into 5-s averages between 30-s to 175-s after standing (30 values). OH was then determined from a postural drop from baseline to the lowest single 5-s average in BP where a drop ≥20 mmHg for SBP or ≥10 mmHg for DBP classified an individual to have OH. SOH was defined as a reduction in SBP ≥20 mmHg or DBP ≥10 mmHg during 12 of the 24 5-s averages following 1-m of upright posture (Finucane C. *et al.* 2014).

Postural Stability

A single Nintendo Wii Balance Board (Nintendo, Koyoto, Japan) collected (100Hz) center of pressure (COP) displacement. Bluetooth technology was used to wirelessly transmit the data from the Nintendo Wii Balance Board to a customized nearby software program (LabView, National Instruments, Austin TX USA). Postural stability measures were later analyzed alongside cardio- and cerebrovascular variables by means of a customized Matlab program (Matlab R2012a; The Mathworks Inc, Natick, MA, USA). Stability data were analyzed in the anterior-posterior (AP), medial-lateral (ML) and combined AP +

ML directions. Measures of postural stability were calculated as the root mean square (RMS; Eq. 1) and total path length (TPL; Eq. 2) over a 20- s during initial standing and at 1-min, 2-min and 3-mins of standing (Fig. 3-1).

Fall History Reports

Fall history reports encompassed a 104 item report completed by a Schlegel Village team member where the participants resided. Fall reports included information regarding location and time of day of falls as well as questions surrounding pre-existing medical conditions, medical explanation for fall or being pushed or bumped by someone. The 3 participants who did not reside in a Schlegel Village reported never having any previous falls however no follow-up was conducted to investigate retrospective falls. Therefore, 74 participants were included for fall analysis. The total number of fall reports recorded within 6 months after testing included 23 reports (excluding 1 slip relating to a known cause) pertaining to 12 individuals. One additional faller (2 falls) was removed from further analysis due to developing an intracranial bleed during the follow-up period.

Statistical analysis

All statistical analysis was completed using IBM SPSS version 20 (IBM SPSS Statistics 20; IBM Corp, Armonk, NY, USA), and all tests were considered significant at $p \leq 0.05$ and trends were considered at $p \leq 0.1$.

Participant Grouping- Participants demonstrated varying abilities to maintain cerebral oxygenation during the transitions and while standing. Therefore, participants were split into two groups (regulators and impaired-regulators). The regulators had a higher baseline and higher standing tSO_2 as well as a relatively small tSO_2 postural drop compared to the impaired-regulators. A TwoStep cluster analysis (k-

cluster) was used to automatically create the number of clusters (participant groups) and only a good cluster quality (silhouette measure of cohesion and separation of 0.5 to 1.0) was considered acceptable. The three-point delta nadir and 1-min average of tSO_2 during the supine-stand transition were used as the continuous k-clustering variables, similar to the grouping based on blood pressure regulation described by Romero-Ortuno et al. (Romero-ortuno R. *et al.* 2011), to separate participants into the two groups. The first group was able to regulate tSO_2 by demonstrating minimal decreases in tSO_2 with standing (regulators n=62) and the second group included individuals with a marked decrease in tSO_2 to nadir and/or impaired regulation of tSO_2 in the first minute of standing (impaired-regulators, n=15).

Effects of group, condition and time - Three two-way mixed ANOVAs (general linear model in SPSS) were used to assess the main effect of i) transition type and group for all hemodynamic and stability measures, ii) group and time for tSO_2 and all postural stability measures, iii) transition type and time for tSO_2 and all postural stability measures. Three levels of repeated measures were used for within-subject evaluation for the type of transition (transition: supine-stand, supine-sit-stand, sit-stand), two levels of between-subject factors were used to evaluate group effects (group: regulators vs. impaired-regulators) and four levels of within-subject factors were used asses the effects of time (time: delta nadir for tSO_2 and initial 20-s average for postural stability, as well as 1-min, 2-min and 3-min averages for tSO_2 and postural stability measures). For all ANOVAs if Mauchly's test of Sphericity was significant the Greenhouse-Geisser correction was used. If a significant interaction was found, Tukey's honest significance test (HSD) was used to further evaluate significant levels.

Group comparisons – An ANOVA in SPSS version 20.0 was run for all group comparisons. All nominal data were tested using a Chi-square test with the Fisher's Exact Test correction factor (Phi was used to estimate the effect size when significance was found).

Results

Group characteristics (Table 3-1)

There were no significant differences between the regulator and impaired-regulator groups for age, BSA, or TBW, however BMI was higher and there were more women (p=0.037 and p=0.018 respectively) in the regulators group compared to the impaired-regulators group. Although not significant, the impaired-regulators had a trend (p=0.091) for increased prospective falls within 6-months after testing. The regulators group had a higher supine HR, central SBP, central PP, AI and AI75 (all $p<0.05$). According to the self-reported questionnaire there were no group differences in physical activity however there were trends for higher incidence rates of heart failure, congenital heart disease, kidney/liver disease, irregular heart beats and lower reports of joint pain in the impaired-regulators compared to the regulators (p=0.048, p=0.095, p=0.022, p=0.042 and p=0.065 respectively). There were significantly more impaired-regulators prescribed aldosterone antagonists (p=0.022) and proton pump (p=0.006) inhibitors and a trend for more impaired-regulators prescribed ≥3 BP lowering medications (p=0.097). There were no significant differences in the occurrence of IOH, OH or SOH between groups.

– Group and condition effects –

Resting baseline hemodynamics (Table 3-2)

Heart rate and tSO_2 were higher at baseline in the regulators (p=0.085 and p=0.001) compared to impaired-regulators. There was an effect of condition on HR, SBP, DBP, MAP, PP, Qi, SVi, and TPRi (all $p\leq0.05$) where the differences lie between all conditions with the exception of HR, SBP and PP (differences exist between supine-stand and supine-sit-stand vs. sit stand).

Delta resting to nadir hemodynamics (Table 3-2)

An interaction (p=0.001) was observed for tSO_2 where the impaired-regulators had progressively lower tSO_2 delta values during the supine-stand compared to the supine-sit-stand and the supine-sit-stand versus the sit-stand (Fig 3-3 and 3-4). Tukey's HSD post-hoc analysis did not reveal any differences between conditions for the regulators group. There were significant group differences observed for tSO_2 during the supine-stand and supine-sit-stand posture changes but not during the sit-stand transition (Fig. 3-3 and Fig 3-4). A larger discrepancy between OxHb and DeoxHb (marked by DiffHb) was observed between groups (p=0.032, greater differences noted in the impaired-regulators) and between all transitions (p<0.001, Table 3-2). When investigating changes in TotHb, OxHb and DeoxHb, post-hoc analysis describes a constant nadir value for regulators but effects of condition for the impaired-regulators (differences noted between sit-stand transition and the other two transitions beginning with a supine baseline).

Heart rate had an interaction effect (p=0.012) whereby the impaired-regulators had a smaller HR response upon standing with the supine-stand transition versus the supine-sit-stand and sit-stand (Fig. 5-2). Both SVi and Qi increased upon standing, SVi had a trend (p=0.093) to increase more during the sit-stand versus the supine-sit-stand and Qi tended to increase (p=0.055) to a greater extent during the supine-stand versus the supine-sit-stand transition. Systolic BP, MAP, PP, MAPmca and TPRi decreased (all p≤0.05) more during the supine-stand compared to the supine-sit-stand and sit-stand transitions. DBP also decreased (p=0.006) more during the supine-stand versus the supine-sit-stand transition.

Initial standing (2 to 22-s) postural stability (Table 3-3)

Both RMS AP and ML demonstrated a main effect of condition (p=0.094 and p=0.039) with increased RMS values during the supine-stand versus the sit-stand transitions. Interactions for TPL, TPL

AP and TPL ML (p=0.009, 0.035 and 0.007 respectively) suggested the impaired-regulators have poorer postural stability than the regulators following all three transitions. Furthermore, the regulators did not have any differences in TPL, TPL AP or TPL ML between transition types but the impaired-regulators had poorer postural stability following the supine-stand versus sit-stand. The impaired-regulators also had longer TPL AP following the supine-sit-stand compared to the sit-stand and longer TPL ML following the supine-stand versus supine-sit-stand (Fig. 3-4).

1-minute (40 to 60-s) (Table 3-2, 3-3 and Figures 3-2 and 3-3)

The sit-stand transition resulted in a lower HR (p=0.058) and a higher SBP, DBP, MAP, PP and MAPmca (all p≤0.05) compared to the supine-stand and supine-sit-stand transitions (Table 3-2). It was also found that the impaired-regulators had lower PP (p=0.027), PPTotHb (0.084) and tSO_2 (p<0.001) versus the regulators at 1-min. Significant interactions for TotHb, OxHb, and DeoxHb revealed that there were no observed differences between transition types for the regulators group. However, the impaired-regulators had differences between supine-sit-stand and sit-stand transitions for TotHb as well as the sit-stand transition compared to the other two transitions for DeoxHb. There were no post-hoc differences for OxHb. Measures of postural stability reveal impaired-regulators have greater instability compared to regulators for TPL, TPL AP and TPL ML (p=0.006, 0.013 and 0.006 respectively, Table 3-3).

2-minute (100 to 120-s) (Table 3-2, 3-3 and Figures 3-2 and 3-3)

Diastolic BP, Qi, SVi, and TPRi had main effects of condition (p=0.052, 0.007, 0.03, and 0.041 respectively) where a higher DBP and TPRi and a lower Qi were observed following the sit-stand versus supine-stand as well as a lower SVi and Qi during the sit-stand versus the supine-sit-stand transition (Table 3-2).

At 2-min of standing tSO_2 was significantly (p=0.002) lower in the impaired-regulators group throughout all transition types. There was also a trend for a lower PPTotHb (p=0.086) in the impaired-regulators group across transitions. Significant interactions for TotHb, OxHb and DeoxHb suggest differences between conditions for the impaired-regulators but no differences between transition types for the regulators (Tbl 3-2). Furthermore, post-hoc analysis identified group differences in OxHb and TotHb following the supine-stand and supine-sit-stand transitions (Tbl 3-2).

Measures of postural stability suggest impaired-regulators have poorer TPL, TPL AP and TPL ML (p=0.002, 0.015 and 0.002 respectively) across all three transition types. Main effects of condition for TPL, TPL AP and TPL ML (p=0.024, 0.081 and 0.044 respectively) suggest the supine-stand versus sit-stand resulted in greater measures of instability (TPL, TPL AP and TPL ML) as well as the supine-sit-stand versus sit-stand (TPL and TPL AP). An interaction effect was observed for RMS AP (p=0.065) however Tukey HSD post-hoc analysis did not reveal any significant group or condition differences.

3-minute (150 to 170-s) (Table 3-2, 3-3 and Figures 3-2 and 3-3)

At the 3-min point after standing, an interaction (p=0.033) for HR revealed impaired-regulators had a lower HR following all three transition types compared to regulators. As well, the impaired-regulators had a lower HR during the supine-sit-stand versus supine-stand transition (Table 3-2). Main effects of condition for BP measures identified a lower DBP, MAP, PP, and MAPmca during the supine-stand compared to the sit-stand. Cardiac output and SVi were lower and TPRi were higher following the sit-stand transition compared to the other two transition types (main effect condition p=0.046, 0.045 and 0.026 respectively).

The impaired-regulators had lower (p=0.011) tSO_2 during all three transitions. Interactions for TotHb, OxHb and DeoxHb (p=0.014, 0.037 and 0.023 respectively) identified group differences in TotHb and OxHb for the supine-stand and supine-sit-stand transitions; no differences between transition types

were observed for the regulators group however the impaired-regulators had decreases in TotHb and DeoxHb between the supine-sit-stand and sit-stand transitions as well as the supine-stand versus sit-stand transition for DeoxHb.

At three minutes of standing the impaired-regulators had poorer postural stability throughout all three transition types, this was marked by increased TPL, TPL AP and TPL ML ($p=0.023$, 0.025 and 0.077 respectively).

– Condition by time effects –

An interaction ($p=0.028$) was found for tSO_2. Post hoc analysis identified an effect of time where delta nadir had a lower tSO2 value compared to 2-minutes, as well during the supine-stand the delta nadir was significantly lower than any of the other time points and during the supine-sit-stand the delta nadir was significantly lower than it was at 3-min.

Effects of time ($p<0.001$) were observed for RMS ML, RMS AP, TPL, TPL AP and TPL ML. Tukey HSD analysis suggested initial standing had great measures of instability compared to 1-min, 2-min and 3-min of standing as well as 1-min of standing has greater postural instability compared to 2-min of standing.

– Group by time effects –

A significant interaction for tSO_2 was found for all three transition types (Fig. 3-5). Tukey HSD analysis identified significant differences between regulators and impaired-regulators at all four time points (delta three-point nadir, 1-min, 2-min and 3-min) throughout all three transitions. No differences were observed between various time intervals for the regulators group. To the contrary, the impaired-regulators had differences in tSO_2 at all time points during the supine-stand and supine-sit-stand, and

they also demonstrated a lower delta nadir compared to all other time points during the sit-stand transition.

Significant group differences ($p<0.05$) at all time points (initial, 1-min, 2-min and 3-min standing) identify reduced tSO_2 and increased TPL in the impaired-regulators compared to the regulators when compressing data from the three conditions into time by group averages and standard deviations (Fig. 3-6); these results confirmed the hypothesis that impaired regulators with lower levels of tSO2 had significantly poorer postural stability not only in the first 20-s after standing, but also in continued standing at 1-min, 2-min and 3-min.The root mean square for AP and ML had significant ($p<0.001$) main effects of time during all three transitions. A significant interaction was found for TPL during all three transitions where differences between regulators and impaired-regulators occurred during initial standing (Fig 3-5). Additionally, during the supine-sit-stand at 1-min and 2-min significant differences in TPL were evident between groups and during the sit stand at 1-min significant differences were present between groups. For the impaired-regulators group, TPL during initial standing was larger than any other 20-s average for all three transitions. For regulators, TPL during initial standing was larger than any other time point during the supine-stand, and sit-stand and it was larger than the two-min average during the supine-sit-stand. Total path length in the ML plane had an interaction ($p=0.002$) for the supine-stand transitions where group differences were observed during initial standing and for both the regulators and impaired-regulators had greater TPL ML values during initial standing versus 1-min, 2-min and 3-min time intervals. During the supine-sit-stand and sit-stand transitions a main effect for time (initial standing versus all other time points) and group (greater TPL ML for impaired-regulators) were found. Total path length in the AP plane had an effect of time ($p<0.001$, different between all time points) for the supine-stand and interactions for the supine-sit-stand ($p=0.022$) and sit-stand ($o=0.002$) transitions. Tukey HSD analysis identified the interactions to have greater TPL AP in the impaired-regulators during

initial standing and at 1-min compared to regulators as well as in the impaired-regulators they had greater instability at initial standing compared to 1-min, 2-min and 3-min time points.

Discussion

In this study, we identified two groups of older adults based on the magnitude of the initial drop in tSO_2 and the absolute values of tSO_2 after standing for 1-min. This analysis classified the groups as regulators and impaired-regulators. The results confirmed the first hypothesis that impaired-regulator participants, with lower levels of tSO_2, had significantly poorer postural stability not only in the first 20-s after standing, but also in continued standing at 1-min, 2-min and 3-min. Further, and consistent with the second hypothesis, brief 10-s, or longer, sitting preceding the stand in the impaired-regulator group resulted in significantly less impact on tSO_2 and improved measures of postural stability. In a follow-up over the next 6-months, there was a trend ($p=0.091$) in the data suggesting that older adults who had poorer regulation of the cerebral oxygenation (tSO_2) had an increased risk of falling compared to older adults with higher levels of tSO_2.

Postural reductions in tSO_2 and stability

This is the first study to show that approximately 20% of older adults had a reduction in tSO_2 on standing that was associated with greater, quantitatively assessed, postural instability. The drop to nadir in tSO_2 from baseline was significantly greater in the impaired-regulators compared to the regulators group for the supine-stand and supine-sit-stand conditions, but not for the sit-stand condition (Figure 3-4). Similarly, during initial standing, TPL, TPL AP and TPL ML were significantly greater in the impaired-regulators group compared to the regulators group for all three conditions (Figure 3-4). A significant group effect for reduced tSO_2 and increased TPL in the impaired-regulators group was found at initial, 1-min, 2-min and 3-min of standing (Table2, Fig. 3-6). With the exception of TPL ML at 3-min (which was a

trend), a significant group effect for increased TPL, TPL AP and TPL ML remained at 1-min, 2-min and 3-min.

A lower HR and BP was found in the impaired-regulators group (Figure 3-2) which contributed to the lower Qi ($p>0.05$, figure 3-2). Total peripheral resistance index was higher in the impaired-regulators and is likely maintaining blood pressure despite it still being low. Arterial blood pressures demonstrate large group differences and large standard deviations (at nadir - regulators vs impaired-regulators, SBP: 122.80 ± 28.71 and 104.28 ± 24.47, DBP: 54.54 ± 20.46 and 61.09 ± 16.05). This suggests a large range and variability between participants for the blood pressure response. Although, lower CBF can occur in spite of a maintained arterial pressure (Novak P. 2016), the lower blood pressure response in the impaired-regulators potentially contributes to lower CBF and tSO_2. It is also noteworthy to point out that in spite of the impaired-regulators having a lower HR response upon standing MAP was still lower, suggesting there could be some impairment of the baroreflex or a possible resetting of the baroreflex to a new blood pressure point. Alterations of the baroreflex can be the result of diminished sensing and processing of the neural signals to central command centers or increased stiffening of the arterial vasculature resulting in reduced distension required to trigger the mechanoreceptors (Kornet L. *et al.* 2005).

There are varied causes for individuals to have low tSO_2 and be classified as an impaired-regulator. As mentioned above, alterations in the function of the baroreflex could contribute to reduced arterial blood pressure and thus CBF. Conditions such as heart failure (HF) and different blood pressure lowering medications can also have equal implications on reduced CBF and tSO_2. Studies have shown that individuals with HF have lower levels of CBF velocity (Loncar G. *et al.* 2011) and significantly greater reductions in CBF velocity while upright compared to age and sex matched controls (Fraser K.S. *et al.* 2015). The current study found tSO_2 to be significantly reduced at rest (supine and seated) as well as during upright posture, furthermore the results of the delta nadir values imply the impaired-regulators

had a significantly larger reduction in tSO_2 compared to the regulators group from baseline to upright posture. Therefore, not only did the impaired-regulators exhibiting lower tSO_2 during supine rest but they also demonstrated larger postural reductions and lower tSO_2 while standing.

Significantly more participants in the impaired-regulators group were on aldosterone antagonists (p=0.022) which are known to significantly reduce blood pressure (Wolf R.I. *et al.* 1966; Johnston L.C. & Grieble H.G. 1967). A trend (p=0.097) for more impaired-regulators to be on 3 or more blood pressure lowering medication was also found suggesting some older adults may compromise their orthostatic response for the control of hypertension. These results suggest the lower arterial blood pressures could be attributed to blood pressure lowering medications which could have a similar effect on reduced tSO_2 as an impaired baroreflex or a condition such as HF. The increased pervasiveness of BP lowering medications in the impaired-regulators group likely reflects both the prevalence of hypertension and the effect on BP reduction in participants with low tSO_2. Although, aggressive BP lowering in uncontrolled hypertension (from >160 mmHg SBP to < 140 mmHg SBP) has been shown to improve CBF velocity (Lipsitz L.A. *et al.* 2005), the BP values of the impaired-regulators had a much lower SBP (125±15 mmHg), potentially contributing to cerebral hypoperfusion.

Interventions to minimize change in tSO_2 and stability

Cerebral oxygenation at delta nadir and TPL AP and TPL ML during initial standing were not different between conditions for the regulators group (Figure 3-4). These results suggest that the regulators were able to regulate cerebral oxygenation despite greater orthostatic stress imposed upon them by the supine-stand condition. Similarly, the regulators group did not demonstrate differences in initial postural stability among conditions despite being required to move their center of mass through different transition patterns (ex. supine-stand vs. sit-stand).

In contrast, the effect of condition positively impacted both delta tSO_2 and initial postural stability for the impaired-regulators. The delta tSO_2 progressively improved between the supine-stand vs. supine-sit-stand and the supine-sit-stand vs the sit stand. Likewise, TPL ML significantly improved for the impaired-regulators during the supine-sit-stand and sit-stand compared to the supine-stand. These results suggest that even a short 10-s sitting pause time can minimize the postural reduction of tSO_2 with positive implications on postural stability. Postural stability, marked by changes in TPL AP, also improved for the impaired-regulators when comparing the supine-stand and supine-sit-stand vs. the sit-stand condition. The significantly reduced tSO_2 in the impaired-regulators may be causing reduced oxygen delivery to the cerebral centers responsible for processing postural stability or it may be causing light-headedness and dizziness leading to greater measures of postural instability. These results support Johnson and Meltzer 2012 findings of a positive effect on postural stability following a sitting-pause time (Johnson EG. & Meltzer J.D. 2012). These results also suggest the impaired-regulators are at increased risk of a future fall compared to the regulators group because of their significantly increased measures of postural instability (Muir S.W. *et al.* 2010; Berg K.O. *et al.* 1992), however a sitting-pause time may minimize such outcomes.

Falls risk and tSO_2

To date the majority of research has focused on the relationship between postural BP responses and falls in older adults (Finucane C. *et al.* 2017; Finucane C. & Kenny R.A. 2017; Juraschek S.P. *et al.* 2017). Juraschek et al. 2017 reported BP responses within 1-min of standing to be most strongly related to dizziness and falls in older adults while Finucane et al. 2017 identified OH at 40-sec and 2-min to be better predictors of falls than BP within the first 15-sec of standing (Finucane C. *et al.* 2017; Juraschek S.P. *et al.* 2017). These associations of BP to falls suggest a link between cerebral hypoperfusion causing fall events, however not all postural reductions in BP result in cerebral hypoperfusion (Novak P. 2016)

therefore this can sometimes be misleading. Sorond et al. 2010 identified a link between impaired cerebrovascular regulation and increased fall rates in older adults and this has since been supported by Ezzati et al. 2017 and Tchella et al. 2015 who have found gait speed, a predictor of falls (Callisaya M.L. *et al.* 2011), to be associated with reduced and impaired cerebral blood flow (Ezzati A. *et al.* 2017; Tchalla A.E. *et al.* 2015). However, this is the first study to show that cerebral hypoperfusion was associated with an increased likelihood (p=0.091) of having a future fall.

Limitations

Despite a sample size of n=77 older adults, the current study was relatively under powered due to the large variability in the cardiovascular and cerebrovascular hemodynamic responses. The protocol involved only a single performance of each condition all taken on a single day/time of day, where the orthostatic responses are known to be variable; this suggests a different response could be rendered on a different day/time (Vara-Gonzalez L. *et al.* 2006). The current study collected cerebrovascular hemodynamics with a NIRS device where different devices are likely to utilize varied algorithms to construct the outcome variables associated with relative changes in hemogolobin. Therefore, comparing absolute values between studies should be a consideration. The estimated SV calculated by the Modelflow algorithm of the plethysmography devices integrates a three-element model of arterial impedance with the arterial pressure wave to track beat-to-beat differences in stroke volume during rest (Harms M *et al.* 1999). However, recent data suggests the Modelflow method does not accurately estimate SV during dynamic fluctuations in SV, such as during orthostatic stress (Gibbons T. 2017). Thus, calculated Q which is derived from SV may in be higher than perceived.

Conclusion

Older adults with posture related reductions of tSO_2 had impaired postural stability. A 10-s sitting pause time minimized the impact of the posture related reduction in tSO_2 and enhanced postural stability. In a prospective follow-up over the subsequent 6-months, there was a trend suggesting older adults with impaired-regulation of tSO_2 also had an increased risk of falling compared to older adults with higher levels of tSO_2. It is unknown what the implications of a low tSO_2 upon standing and while upright are on cognition and ultimately the quality of life among older adults.

Tables and Figures

Table 3-1: Subject Characteristics

Characteristic	Regulators (n=62)	Impaired-regulators (n=15)	p-value	Phi (ES)
Age, years	86.3±6.9	87.6±5.0	N.S.	-
Sex (women), % (n)	80.6 (50)	46.7 (7)	0.018	0.307
BMI (kg/m^2)	27.2±5	24.2±3.4	0.037	-
Height (cm)	159.8±8.8	163.3±10.6	N.S.	-
Weight (kg)	69.3±13.9	65.1±14.1	N.S.	-
BSA (m^2)	1.72±0.18	1.70±0.22	N.S.	-
TBW (L): control n=51, hypoperfusion n=10	28.7±5.2	29.8±6.6	N.S.	-
Brachial SBP, mmHg	136±22	125±17	0.071	-
Brachial DBP, mmHg	68±9	65±11	N.S.	-
Brachial PP, mmHg	68±19	60±11	N.S.	-
Retrospective fallers within 6 months before data collection (past falls), % within group (n)	10 (6)	13 (2)	N.S.	-
Prospective fallers within 6 months after data collection (future falls), % within group (n)	10 (6)	28 (4)	0.091	0.211
Mobil-O-Graph Data				
Central hemodynamics				
Heart rate, bpm	69±10	63±10	0.048	
Central SBP, mmHg	123±19	111±14	0.020	
Central DBP, mmHg	78±10	76±12	N.S.	
Central PP, mmHg	46±13	35±7	0.004	
Augmentation Index @75 [90%CI], %	35.4±12.3	24.6±17.2	0.008	
Augmentation Pressure, mmHg	19.2±10.5	12.4±8.2	0.025	
Reflection Magnitude	67±6	64±9	N.S.	
PWV	13.6±1.6	13.5±1.0	N.S.	
Physical Activity (Self-report questionnaire)				
Sedentary, % (n)	30 (15)	23 (3)	N.S.	-
Active, % (n)	48 (24)	46 (6)	N.S.	-
Highly Active, % (n)	22 (11)	31 (4)	N.S.	-
Past Health (Self-report questionnaire)				
Heart attack, % (n)	11 (7)	27 (4)	N.S.	-
Heart failure, % (n)	3 (2)	20 (3)	0.048	0.270
Open heart surgery, % (n)	3 (2)	7 (1)	N.S.	-
Congenital heart disease, % (n)	2 (1)	13 (2)	0.095	0.240
Atrial Fibrillation, % (n)	13 (8)	20 (3)	N.S.	-
Hypertension, % (n)	42 (26)	40 (6)	N.S.	-
High cholesterol, % (n)	29 (18)	27 (4)	N.S.	-
Sleep Apnea, % (n)	3 (2)	7 (1)	N.S.	-
Emphysema/pneumonia, % (n)	15 (9)	20 (3)	N.S.	-
Asthma/bronchitis, % (n)	13 (8)	7 (1)	N.S.	-
Kidney/liver disease, % (n)	2 (1)	20 (3)	0.022	0.328

Smoking (never), % (n)	54 (33)	64 (9)	N.S.	-
Smoking (ex-smoker), % (n)	46 (28)	36 (5)	N.S.	-
Current Health (Self-report questionnaire)				
Irregular heart beat, % (n)	6 (4)	27 (4)	0.042	0.262
Persistent cough, % (n)	15 (9)	13 (2)	N.S.	-
Wheezing/shortness of breath, % (n)	13 (8)	27 (4)	N.S.	-
Memory complaints, % (n)	15 (9)	0 (0)	N.S.	-
Fatigue (general) , % (n)	29 (18)	13 (2)	N.S.	-
Headaches, % (n)	13 (8)	7 (1)	N.S.	-
Dizziness/light-headedness, % (n)	18 (11)	33 (5)	N.S.	-
Any pain (joint pain always recorded), % (n)	45 (28)	20 (3)	0.065	-0.203
Fear of falling (score 0 to 10)	3.3±2.4	3.0±2.6	N.S.	-
Balance confidence (score 0 to 10)	5.2±2.4	5.1±2.7	N.S.	-
Medications				
Aldosterone antagonist % (n)	1.6 (1)	20.0 (3)	0.022	0.328
Alpha adrenoreceptor antagonist % (n)	9.7 (6)	0.0 (0)	N.S.	-
Angiotensin receptor blocker % (n)	19.4 (12)	13.3 (2)	N.S.	-
ACE inhibitor % (n)	17.7 (11)	33.3 (5)	N.S.	-
Beta blocker % (n)	21.0 (13)	33.3 (5)	N.S.	-
Calcium channel blocker % (n)	32.3 (20)	13.3 (2)	N.S.	-
Proton pump inhibitor % (n)	33.9 (21)	73.3 (11)	0.006	0.317
Polypharmacy (≥ 3 BP lowering meds) % (n)	14.5 (9)	33.3 (5)	0.097	0.193

BMI body mass index, *BSA* body surface area, *TBW* total body water, *BP* blood pressure*, SBP* systolic BP, *DBP* diastolic BP, *MAP* mean arterial pressure, *PWV* pulse wave velocity, *E.S.* effect size*, N.S.* not significant (p≥0.1)

Table 3-2: Cardiovascular and cerebrovascular hemodynamics between groups and conditions

Characteristic	Supine-stand		Supine-sit-stand		Sit-stand		Significance
	Regulators	Impaired-reg.	Regulators	Impaired-reg.	Regulators	Impaired-reg.	
Baseline: supine or seated (-45 to -15 sec average of beat-beat data)							group*con
HR, bpm	68.78 ± 10.28	64.04 ± 10.11	68.56 ± 9.48	63.44 ± 9.67	71.29 ± 10.94†††‡	66.26 ± 8.00	**con*gr
SBP, mmHg	144.65 ± 37.91	135.80 ± 24.89	145.75 ± 37.89†	140.87 ± 23.27	152.98 ± 40.99†††‡	152.18 ± 26.55	**con
DBP, mmHg	72.05 ± 17.25	70.71 ± 17.32	72.77 ± 17.23†	74.22 ± 16.24	78.30 ± 19.46†††‡	81.00 ± 17.80	**con
MAP, mmHg	96.25 ± 23.26	92.40 ± 19.23	97.10 ± 23.23†	96.43 ± 17.96	103.19 ± 25.85†††‡	104.73 ± 19.88	**con
PP,mmHg	72.60 ± 24.75	65.09 ± 12.84	72.98 ± 24.83	66.65 ± 12.34	74.68 ± 25.48†††‡	71.18 ± 15.13	**con
Qi, L/min/m^2	2.45 ± 0.95	2.29 ± 0.89	2.45 ± 0.94†	2.07 ± 0.62	2.18 ± 0.84†††‡	1.93 ± 0.62	**con
SVi, mL/m^2	36.12 ± 14.66	36.80 ± 14.84	36.11 ± 14.54†	34.25 ± 14.41	31.01 ± 12.59†††‡	30.58 ± 12.23	**con
TPRi, mHg/L/min/m^2	15.42 ± 8.45	17.52 ± 9.40	15.67 ± 8.81†	19.47 ± 9.75	18.87 ± 11.53†††‡	23.34 ± 12.98	**con
Skin temp (Celcius)	34.54 ± 5.83	35.24 ± 0.87	34.56 ± 6.07	35.18 ± 1.02	34.52 ± 5.92	34.67 ± 1.68	**int:-
tSO_2, percent	62.94 ± 5.14	57.76 ± 8.46	62.81 ± 4.94	57.33 ± 9.01	62.76 ± 4.52	56.86 ± 9.07	**gr
DiffHb, µMol	4.04 ± 2.92	2.68 ± 1.63	4.01 ± 2.97	2.58 ± 1.47	2.58 ± 2.44†††‡	2.15 ± 1.86	**con
TotHb, µMol	0.02 ± 0.15	0.00 ± 0.00	0.00 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	-
PPTotHb, µMol	0.69 ± 0.31	0.55 ± 0.27	0.68 ± 0.28	0.54 ± 0.29	0.73 ± 0.38	0.59 ± 0.28	N.S.
OxHb,µMol	0.01 ± 0.06	0.00 ± 0.00	0.00 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	-
PP OxHb, µMol	0.59 ± 0.25	0.47 ± 0.24	0.58 ± 0.23	0.45 ± 0.27	0.63 ± 0.31	0.52 ± 0.25	N.S.
DeoxHb, µMol	0.01 ± 0.09	0.00 ± 0.00	0.00 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	-
PP DeoxHb, µMol	0.12 ± 0.06	0.12 ± 0.06	0.11 ± 0.06	0.13 ± 0.08	0.12 ± 0.08	0.09 ± 0.04	**int:-
Three point nadir (lowest three tSO_2 values averaged)							
HR, bpm	77.52 ± 11.87	74.99 ± 12.73	76.41 ± 11.46	68.38 ± 10.94	77.37 ± 12.53	69.93 ± 10.61	**int:d,e,g,h
SBP, mmHg	122.80 ± 28.71	104.28 ± 24.47	135.03 ± 35.78†	126.37 ± 25.71	141.28 ± 30.23††	133.67 ± 22.06	**con
DBP, mmHg	61.09 ± 16.05	54.54 ± 20.46	67.91 ± 16.21†	63.78 ± 19.20	69.51 ± 15.82††	66.14 ± 19.44	**con
MAP, mmHg	81.66 ± 18.70	71.12 ± 21.12	90.28 ± 21.16†	84.64 ± 20.03	93.43 ± 19.17††	88.65 ± 19.31	**con
PP,mmHg	61.70 ± 20.89	49.74 ± 12.10	67.35 ± 25.98	62.60 ± 17.10	71.77 ± 21.61	67.53 ± 13.62	**int:d,e,g

MAPmca, mmHg	57.97 ± 19.41	46.73 ± 21.71	66.71 ± 21.69†	59.97 ± 20.58	69.75 ± 19.61††	63.98 ± 19.92	**con
Qi, L/min/m^2	3.24 ± 1.52	2.77 ± 1.14	2.94 ± 1.20†	2.64 ± 1.34	2.79 ± 1.02††	2.64 ± 1.04	**con
SVi, mL/m^2	42.44 ± 20.01	38.54 ± 18.13	39.36 ± 18.06	39.40 ± 20.36	37.25 ± 14.99	39.00 ± 17.31	*con
TPRi, mHg/L/min/m^2	11.98 ± 10.97	12.37 ± 8.91	13.43 ± 9.32†	16.08 ± 10.89	14.60 ± 10.62	15.96 ± 11.25	**con
Skin temp (Celcius)	35.60 ± 1.07	35.17 ± 0.91	35.60 ± 1.07	35.09 ± 1.06	35.57 ± 1.04	34.64 ± 1.68	**int:e,f,h,i
tSO_2, percent	61.02 ± 5.22	50.65 ± 5.94	61.29 ± 4.97	52.11 ± 6.38	61.25 ± 4.71	53.64 ± 8.25	**con,**gr,*int:e
DiffHb, µMol	2.59 ± 2.86	0.36 ± 1.88	2.59 ± 2.92	0.85 ± 1.46	2.02 ± 2.58	1.25 ± 1.82	**int:e
TotHb, µMol	-1.11 ± 2.57	-0.69 ± 1.31	-0.97 ± 2.73	0.02 ± 1.58	-0.67 ± 0.98	-1.40 ± 0.93	**int:j
PPTotHb, µMol	0.68 ± 0.39	0.49 ± 0.29	0.65 ± 0.31	0.47 ± 0.28	0.66 ± 0.34	0.58 ± 0.36	*gr
OxHb,µMol	-1.28 ± 1.87	-1.50 ± 1.12	-1.20 ± 1.94	-0.85 ± 0.91	-0.61 ± 0.79	-1.15 ± 0.83	*con
PP OxHb, µMol	0.57 ± 0.31	0.42 ± 0.25	0.55 ± 0.25	0.43 ± 0.23	0.56 ± 0.28	0.50 ± 0.25	N.S.
DeoxHb, µMol	0.18 ± 0.85	0.81 ± 0.91	0.23 ± 0.94	0.88 ± 0.90	-0.06 ± 0.42	-0.25 ± 0.34	**int:e,f,g,h
PP DeoxHb, µMol	0.14 ± 0.10	0.15 ± 0.12	0.12 ± 0.07†	0.10 ± 0.07	0.11 ± 0.07	0.15 ± 0.16	*con
Three point Delta nadir (nadir average minus supine average)							
HR, bpm	7.51 ± 11.90	10.95 ± 9.91	7.85 ± 5.99	4.94 ± 6.60	6.01 ± 5.48	3.66 ± 6.58	**int:d,e
SBP, mmHg	-27.92 ± 17.50	-33.80 ± 13.62	-15.58 ± 27.05†	-14.50 ± 15.98	-19.16 ± 25.18††	-18.51 ± 9.67	**con
DBP, mmHg	-14.97 ± 13.30	-18.20 ± 10.63	-7.29 ± 13.15†	-10.44 ± 11.13	-12.56 ± 15.91	-14.86 ± 8.66	**con
MAP, mmHg	-19.28 ± 13.97	-23.40 ± 11.14	-10.05 ± 16.84†	-11.79 ± 11.80	-14.76 ± 18.63	-16.08 ± 8.00	**con
PP,mmHg	-12.95 ± 10.58	-15.60 ± 7.67	-8.06 ± 17.91†	-4.06 ± 11.35	-6.60 ± 12.22††	-3.65 ± 8.81	**con
MAPmca, mmHg	-19.28 ± 13.97	-23.40 ± 11.14	-9.95 ± 16.64†	-11.79 ± 11.80	-14.37 ± 16.23††	-16.08 ± 8.00	**con
Qi, L/min/m^2	0.72 ± 1.02	0.72 ± 0.87	0.41 ± 0.79†	0.58 ± 0.95	0.49 ± 0.63	0.70 ± 0.68	*con
SVi, mL/m^2	5.41 ± 12.47	5.27 ± 10.39	2.05 ± 12.44	5.14 ± 12.03	4.59 ± 8.67‡	8.42 ± 10.67	*con
TPRi, mHg/L/min/m^2	-4.66 ± 6.90	-6.68 ± 6.24	-2.76 ± 5.27†	-3.39 ± 3.99	-5.14 ± 8.76‡	-7.38 ± 4.55	**con
Skin temp (Celcius)	0.04 ± 0.43	-0.07 ± 0.08	-0.04 ± 0.09	-0.09 ± 0.11	-0.00 ± 0.03	-0.03 ± 0.05	N.S.
tSO_2, percent	-1.92 ± 1.37	-7.12 ± 4.70	-1.52 ± 1.67	-5.21 ± 6.36	-1.51 ± 1.40	-3.22 ± 4.83	**int:d,e,f,g,h
DiffHb, µMol	-1.37 ± 1.15	-2.32 ± 1.56	-1.36 ± 1.25†	-1.73 ± 0.89	-0.54 ± 0.79††‡	-0.90 ± 0.87	**con,*gr
TotHb, µMol	-0.93 ± 2.02	-0.69 ± 1.31	-0.78 ± 2.25	0.02 ± 1.58	-0.63 ± 0.94	-1.40 ± 0.93	**int:f
PPTotHb, µMol	-0.02 ± 0.24	-0.06 ± 0.24	-0.04 ± 0.20	-0.08 ± 0.20	-0.07 ± 0.25	-0.01 ± 0.30	N.S.

OxHb,µMol	-1.15 ± 1.48	-1.50 ± 1.12	-1.07 ± 1.63†	-0.85 ± 0.91	-0.59 ± 0.76††	-1.15 ± 0.83	*con
PP OxHb, µMol	-0.02 ± 0.19	-0.05 ± 0.13	-0.03 ± 0.16	-0.02 ± 0.15	-0.06 ± 0.20	-0.02 ± 0.15	N.S.
DeoxHb, µMol	0.22 ± 0.71	0.81 ± 0.91	0.29 ± 0.80	0.88 ± 0.90	-0.04 ± 0.42	-0.25 ± 0.34	**int:e,f,g,h
PP DeoxHb, µMol	0.02 ± 0.07	0.04 ± 0.13	0.00 ± 0.07	-0.02 ± 0.06	-0.00 ± 0.07	0.07 ± 0.15	**int:f,i
1-minute (40-60 sec)							
HR, bpm	75.55 ± 15.22	71.38 ± 10.62	76.02 ± 14.98	70.75 ± 9.61	74.86 ± 15.18	70.04 ± 9.08	*con
SBP, mmHg	150.04 ± 32.66	132.34 ± 27.44	150.91 ± 33.23	136.98 ± 28.95	155.49 ± 30.30†††‡	146.70 ± 24.63	**con
DBP, mmHg	76.90 ± 15.56	69.20 ± 17.22	76.28 ± 15.72	72.32 ± 19.12	79.33 ± 14.21†††‡	75.92 ± 16.54	**con
MAP, mmHg	101.28 ± 20.24	90.25 ± 19.45	101.16 ± 20.35	93.88 ± 21.27	104.71 ± 18.44†††‡	99.52 ± 17.77	**con
PP,mmHg	73.14 ± 21.99	63.14 ± 17.76	74.62 ± 23.11	64.66 ± 17.84	76.16 ± 21.29†††‡	70.78 ± 17.60	**con,**gr
MAPmca, mmHg	77.61 ± 20.75	65.57 ± 20.11	77.49 ± 20.79	69.20 ± 21.96	81.04 ± 18.84†††‡	74.84 ± 18.53	**con
Qi, L/min/m^2	2.53 ± 0.97	2.45 ± 0.91	2.65 ± 0.99	2.36 ± 0.96	2.43 ± 0.83	2.33 ± 0.83	N.S
SVi, mL/m^2	33.91 ± 14.86	35.38 ± 14.74	35.52 ± 16.50	34.45 ± 15.23	32.85 ± 12.79	34.42 ± 14.39	N.S
TPRi, mHg/L/min/m^2	17.87 ± 13.01	16.73 ± 11.03	16.21 ± 10.57	19.26 ± 13.84	17.89 ± 10.79	19.51 ± 12.75	N.S.
Skin temp (Celcius)	35.59 ± 1.04	35.13 ± 0.85	35.59 ± 1.07	35.07 ± 1.03	35.57 ± 1.04	34.65 ± 1.66	**int:e,f,i
tSO_2, percent	62.27 ± 4.47	54.75 ± 9.14	61.76 ± 4.51	54.00 ± 8.68	61.98 ± 4.54	54.91 ± 8.76	**gr
DiffHb, µMol	2.27 ± 2.55	1.01 ± 1.51	2.24 ± 2.63	1.24 ± 1.15	2.19 ± 2.55	1.87 ± 1.50	**int:e,g,h
TotHb, µMol	-1.04 ± 3.28	0.54 ± 1.55	-0.91 ± 3.29	0.74 ± 1.92	-0.54 ± 0.84	-1.06 ± 0.84	**int:f
PPTotHb, µMol	0.60 ± 0.31	0.46 ± 0.22	0.58 ± 0.27	0.46 ± 0.19	0.65 ± 0.35‡	0.49 ± 0.25	*con,*gr
OxHb,µMol	-1.40 ± 2.33	-0.57 ± 1.00	-1.34 ± 2.35	-0.31 ± 1.27	-0.47 ± 0.79	-0.67 ± 0.72	**int:j
PP OxHb, µMol	0.51 ± 0.25	0.41 ± 0.20	0.50 ± 0.22	0.41 ± 0.17	0.55 ± 0.28	0.45 ± 0.21	*con
DeoxHb, µMol	0.37 ± 1.20	1.10 ± 0.92	0.43 ± 1.21	1.04 ± 1.01	-0.07 ± 0.44	-0.39 ± 0.28	**int:e,f
PP DeoxHb, µMol	0.10 ± 0.06	0.11 ± 0.10	0.09 ± 0.05	0.09 ± 0.07	0.10 ± 0.07	0.11 ± 0.08	**con
2-minute (100-120 sec)							
HR, bpm	73.83 ± 14.99	70.89 ± 11.34	73.79 ± 15.08	69.80 ± 9.64	72.97 ± 15.07	70.20 ± 8.99	N.S.
SBP, mmHg	155.05 ± 30.24	138.54 ± 23.71	153.22 ± 27.86	146.47 ± 28.82	156.40 ± 29.24	145.39 ± 23.10	N.S.
DBP, mmHg	78.26 ± 13.41	73.02 ± 17.38	77.71 ± 12.37	76.03 ± 18.05	79.42 ± 13.85	76.73 ± 17.44	*con
MAP, mmHg	103.86 ± 17.87	94.86 ± 18.35	102.88 ± 16.26	99.51 ± 20.60	105.08 ± 17.85	99.62 ± 18.26	N.S

PP,mmHg	76.79 ± 21.77	65.52 ± 15.31	75.52 ± 20.82	70.44 ± 17.69	76.98 ± 20.60	68.66 ± 14.58	N.S.
MAPmca, mmHg	80.12 ± 18.20	69.84 ± 18.70	79.14 ± 16.46	74.84 ± 21.29	81.37 ± 18.30	74.71 ± 18.81	N.S.
Qi, L/min/m^2	2.60 ± 0.92	2.38 ± 0.94	2.68 ± 0.89	2.29 ± 0.87	2.49 ± 0.85††	2.21 ± 0.81	**con
SVi, mL/m^2	35.13 ± 13.36	34.55 ± 15.96	36.16 ± 13.13	33.73 ± 14.75	34.14 ± 12.64‡	32.72 ± 14.71	**con
TPRi, mHg/L/min/m^2	16.63 ± 10.06	17.61 ± 12.56	15.53 ± 9.33	20.52 ± 13.82	17.15 ± 10.33	20.58 ± 13.74	**con
Skin temp (Celcius)	35.75 ± 0.97	35.28 ± 0.78	35.78 ± 0.96	35.07 ± 1.01	35.70 ± 1.00††	34.64 ± 1.72	**con,*int:e,f
tSO_2, percent	61.59 ± 4.31	55.41 ± 8.40	61.14 ± 4.60	55.37 ± 8.84	61.78 ± 4.60	56.47 ± 8.47	*con,**gr
DiffHb, µMol	2.19 ± 2.54	1.32 ± 1.49	2.14 ± 2.66	1.59 ± 1.41	2.24 ± 2.63	2.09 ± 1.54	**int:e,g
TotHb, µMol	-0.92 ± 3.33	1.13 ± 1.71	-0.75 ± 3.35	1.46 ± 2.35	-0.37 ± 0.88	-0.72 ± 0.88	**int:f,g,h
PPTotHb, µMol	0.65 ± 0.32	0.50 ± 0.29	0.63 ± 0.28	0.49 ± 0.22	0.68 ± 0.36	0.53 ± 0.27	*gr
OxHb,µMol	-1.41 ± 2.37	0.01 ± 1.15	-1.31 ± 2.42	0.17 ± 1.57	-0.36 ± 0.78	-0.33 ± 0.67	**int:g,h
PP OxHb, µMol	0.55 ± 0.26	0.44 ± 0.26	0.54 ± 0.23	0.43 ± 0.20	0.58 ± 0.29	0.46 ± 0.22	N.S.
DeoxHb, µMol	0.49 ± 1.34	1.12 ± 0.86	0.56 ± 1.31	1.29 ± 1.04	-0.01 ± 0.58	-0.40 ± 0.43	**int:e,f
PP DeoxHb, µMol	0.10 ± 0.07	0.08 ± 0.06	0.10 ± 0.06	0.08 ± 0.04	0.11 ± 0.08	0.11 ± 0.08	*con
3-minute (150-170 sec)							
HR, bpm	72.99 ± 14.63	71.42 ± 11.06	75.51 ± 10.53	68.94 ± 9.81	75.29 ± 11.44	70.20 ± 8.92	**int:d,g,h,i
SBP, mmHg	155.92 ± 30.38	138.42 ± 22.55	152.87 ± 29.70	143.46 ± 25.77	156.60 ± 29.00	146.72 ± 23.21	N.S.
DBP, mmHg	78.22 ± 12.79	72.69 ± 17.71	77.19 ± 12.06	74.83 ± 18.23	79.69 ± 13.84	76.96 ± 18.20	**con
MAP, mmHg	104.12 ± 17.45	94.60 ± 17.87	102.42 ± 16.63	97.71 ± 19.80	105.32 ± 17.73	100.22 ± 18.87	**con
PP,mmHg	77.70 ± 22.45	65.73 ± 16.34	75.68 ± 22.71	68.64 ± 15.14	76.91 ± 20.57	69.76 ± 14.09	N.S.
MAPmca, mmHg	80.40 ± 17.89	69.77 ± 18.10	78.67 ± 16.94	72.80 ± 20.28	81.60 ± 18.19	75.31 ± 19.45	*con
Qi, L/min/m^2	2.68 ± 0.92	2.50 ± 0.95	2.69 ± 0.96	2.30 ± 0.91	2.54 ± 0.90	2.23 ± 0.82	**con
SVi, mL/m^2	36.32 ± 13.36	36.26 ± 16.33	36.24 ± 13.29	34.45 ± 15.90	34.48 ± 12.91	33.01 ± 14.75	**con
TPRi, mHg/L/min/m^2	15.48 ± 8.13	16.04 ± 12.19	15.27 ± 8.47	19.95 ± 13.97	16.41 ± 8.40	20.58 ± 13.97	**con
Skin temp (Celcius)	35.81 ± 0.93	35.33 ± 0.80	35.85 ± 0.93	35.10 ± 1.04	35.77 ± 0.97	34.65 ± 1.72	**int:e,f
tSO_2, percent	61.56 ± 4.26	56.78 ± 6.78	61.41 ± 4.49	55.73 ± 8.95	61.85 ± 4.84	55.96 ± 7.74	**gr
DiffHb, µMol	2.34 ± 2.61	1.56 ± 1.49	2.46 ± 2.69	1.87 ± 1.50	2.45 ± 2.71††	2.23 ± 1.70	**con
TotHb, µMol	-0.65 ± 3.53	1.51 ± 1.58	-0.44 ± 3.50	1.56 ± 2.22	-0.33 ± 1.03	-0.59 ± 0.88	**int:f,g,h

PPTotHb, µMol	0.66 ± 0.31	0.52 ± 0.29	0.66 ± 0.30	0.51 ± 0.20	0.68 ± 0.36	0.51 ± 0.23	N.S.
OxHb,µMol	-1.24 ± 2.48	0.27 ± 1.13	-1.02 ± 2.51	0.36 ± 1.58	-0.26 ± 0.92	-0.19 ± 0.64	**int:g,h
PP OxHb, µMol	0.56 ± 0.25	0.46 ± 0.26	0.56 ± 0.24	0.44 ± 0.19	0.59 ± 0.29	0.45 ± 0.21	N.S.
DeoxHb, µMol	0.60 ± 1.45	1.23 ± 0.81	0.58 ± 1.41	1.20 ± 0.92	-0.07 ± 0.66	-0.40 ± 0.44	**int:e,f
PP DeoxHb, µMol	0.11 ± 0.07	0.08 ± 0.06	0.10 ± 0.06	0.09 ± 0.05	0.11 ± 0.08	0.09 ± 0.05	N.S.

Abbreviations: SBP systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *PP* pulse pressure, *MAPmca* mean arterial pressure at the level of the middle cerebral artery, *Qi* cardiac output index, *SVi* stroke volume index, *TPRi* total peripheral resistance index, tSO_2 cerebral tissue saturation, *TotHb* total hemoglobin, *PPTotHb* pulse pressure total hemoglobin, *OxHb* oxygenated hemoglobin, *PPOxHb* pulse pressure oxygenated hemoglobin, *DexHb* deoxygenated hemoglobin, *PPDeoxHb* pulse pressure deoxygenated hemoglobin.

Statistical analysis: in reference to the following comparisons, * denotes p≤0.1, ** denotes p≤0.05. *gr* denotes group effect, *con* denotes effect of condition, *int* denotes interaction effect. Effect of condition: † denotes differences between supine-stand and supine-sit-stand, †† denotes difference between supine-sit-stand and sit-stand, ‡ denotes differences between supine-sit-stand and sit-stand.

Group by condition interaction (*int*) comparisons for within group: *int:a* regulator group: supine-stand vs. supine-sit-stand, *int:b* regulator group: supine-stand vs. sit-stand, *int:c* regulator group: supine-sit-stand vs. sit-stand, *int:d* impaired-regulator group: supine-stand vs. supine-sit-stand, *int:e* impaired-regulator group: supine-stand vs. sit-stand, *int:f* impaired-regulator group: supine-sit-stand vs. sit-stand,

Group by condition interaction (int) comparisons between groups *int:g* supine-stand: regulator group vs. impaired-regulator group, *int:h* supine-sit-stand: regulator group vs. impaired-regulator group, *int:i* sit-stand: regulator group vs. impaired-regulator group, *int:j* Tukey's HSD did not identify, *N.S.* not significant (p≥0.1).

Table 3-3: Postural stability by group and condition

Characteristic	Supine-stand		Supine-sit-stand		Sit-stand		Significance
	Regulators	Impaired-reg.	Regulators	Impaired-reg.	Regulators	Impaired-reg.	
Initial standing (2-22 sec)							
RMS AP, cm	0.617 ± 0.274	0.673 ± 0.179	0.597 ± 0.193	0.662 ± 0.278	0.548 ± 0.160	0.609 ± 0.152	**con
RMS ML, cm	0.494 ± 0.256	0.560 ± 0.211	0.475 ± 0.204	0.508 ± 0.176	0.437 ± 0.191††	0.444 ± 0.153	*con
TPL, cm	41.947 ± 16.878	67.098 ± 30.214	40.639 ± 18.224	59.992 ± 27.418	39.543 ± 16.741	53.299 ± 19.480	**int:e,g,h,i
TPL AP, cm	31.742 ± 13.294	48.863 ± 23.890	30.770 ± 13.524	46.528 ± 23.568	30.293 ± 13.799	41.478 ± 17.150	**int:e,f,g,h,i
TPL ML, cm	20.775 ± 9.570	35.672 ± 15.430	20.224 ± 10.980	28.565 ± 11.452	19.116 ± 9.181	25.200 ± 8.885	**int:d,e,g,h,i
1-minute (40-60 sec)							
RMS AP, cm	0.445 ± 0.167	0.475 ± 0.160	0.429 ± 0.165	0.422 ± 0.100	0.457 ± 0.239	0.466 ± 0.110	N.S.
RMS ML, cm	0.332 ± 0.170	0.354 ± 0.144	0.327 ± 0.176	0.290 ± 0.103	0.324 ± 0.183	0.364 ± 0.202	N.S.
TPL, cm	30.788 ± 12.804	45.064 ± 20.322	31.378 ± 14.566	39.953 ± 19.173	31.352 ± 16.177	41.148 ± 14.879	**gr
TPL AP, cm	24.451 ± 11.289	35.154 ± 16.593	24.832 ± 11.711	31.047 ± 16.712	25.242 ± 12.552	33.004 ± 12.375	**gr
TPL ML, cm	13.831 ± 6.157	21.042 ± 11.289	14.267 ± 7.982	19.001 ± 9.353	13.476 ± 8.589	18.134 ± 7.820	**gr
2-minute (100-120 sec)							
RMS AP, cm	0.392 ± 0.136	0.412 ± 0.105	0.377 ± 0.123	0.425 ± 0.145	0.394 ± 0.141	0.356 ± 0.108	*int:j
RMS ML, cm	0.274 ± 0.144	0.328 ± 0.156	0.260 ± 0.131	0.288 ± 0.114	0.255 ± 0.126	0.329 ± 0.211	N.S.
TPL, cm	28.180 ± 12.270	40.100 ± 20.563	27.265 ± 10.340	39.072 ± 16.080	26.398 ± 9.815††	33.270 ± 11.240	**con**gr
TPL AP, cm	22.473 ± 10.615	30.861 ± 18.533	21.692 ± 8.124	30.505 ± 14.963	21.546 ± 8.784	25.801 ± 10.086	*con**gr
TPL ML, cm	12.442 ± 6.513	19.018 ± 9.601	12.207 ± 6.680	18.011 ± 7.342	11.166 ± 5.061	15.628 ± 6.061	**con**gr
3-minute (150-170 sec)							
RMS AP, cm	0.400 ± 0.163	0.460 ± 0.155	0.433 ± 0.288	0.402 ± 0.114	0.415 ± 0.238	0.441 ± 0.147	N.S.
RMS ML, cm	0.270 ± 0.248	0.300 ± 0.120	0.290 ± 0.204	0.320 ± 0.130	0.305 ± 0.256	0.341 ± 0.178	N.S.
TPL, cm	27.432 ± 11.365	36.487 ± 19.642	28.800 ± 12.336	39.950 ± 17.910	28.268 ± 13.802	34.568 ± 12.757	**gr
TPL AP, cm	21.921 ± 9.198	29.210 ± 18.955	23.011 ± 10.145	31.533 ± 15.928	22.223 ± 9.681	26.946 ± 10.084	**gr
TPL ML, cm	12.118 ± 6.717	16.093 ± 5.600	12.739 ± 7.002	18.165 ± 7.543	12.937 ± 9.218	16.323 ± 7.166	*gr

ML medial-lateral plane, *AP* anterior-posterior plane, *RMS* root mean square, *TPL* total path length

Statistical analysis: in reference to the following comparisons, * denotes p≤0.1, ** denotes p≤0.05. *gr* denotes group effect, *con* denotes effect of condition, *int* denotes interaction effect. Effect of condition: † denotes differences between supine-stand and supine-sit-stand, †† denotes difference between supine-sit-stand and sit-stand, ‡ denotes differences between supine-sit-stand and sit-stand.

Group by condition interaction (*int*) comparisons for within group: *int:a* regulator group: supine-stand vs. supine-sit-stand, *int:b* regulator group: supine-stand vs. sit-stand, *int:c* regulator group: supine-sit-stand vs. sit-stand, *int:d* impaired-regulator group: supine-stand vs. supine-sit-stand, *int:e* impaired-regulator group: supine-stand vs. sit-stand, *int:f* impaired-regulator group: supine-sit-stand vs. sit-stand,
Group by condition interaction (int) comparisons between groups *int:g* supine-stand: regulator group vs. impaired-regulator group, *int:h* supine-sit-stand: regulator group vs. impaired-regulator group, *int:i* sit-stand: regulator group vs. impaired-regulator group, *int:j* Tukey's HSD did not identify, *N.S.* not significant (p≥0.1).

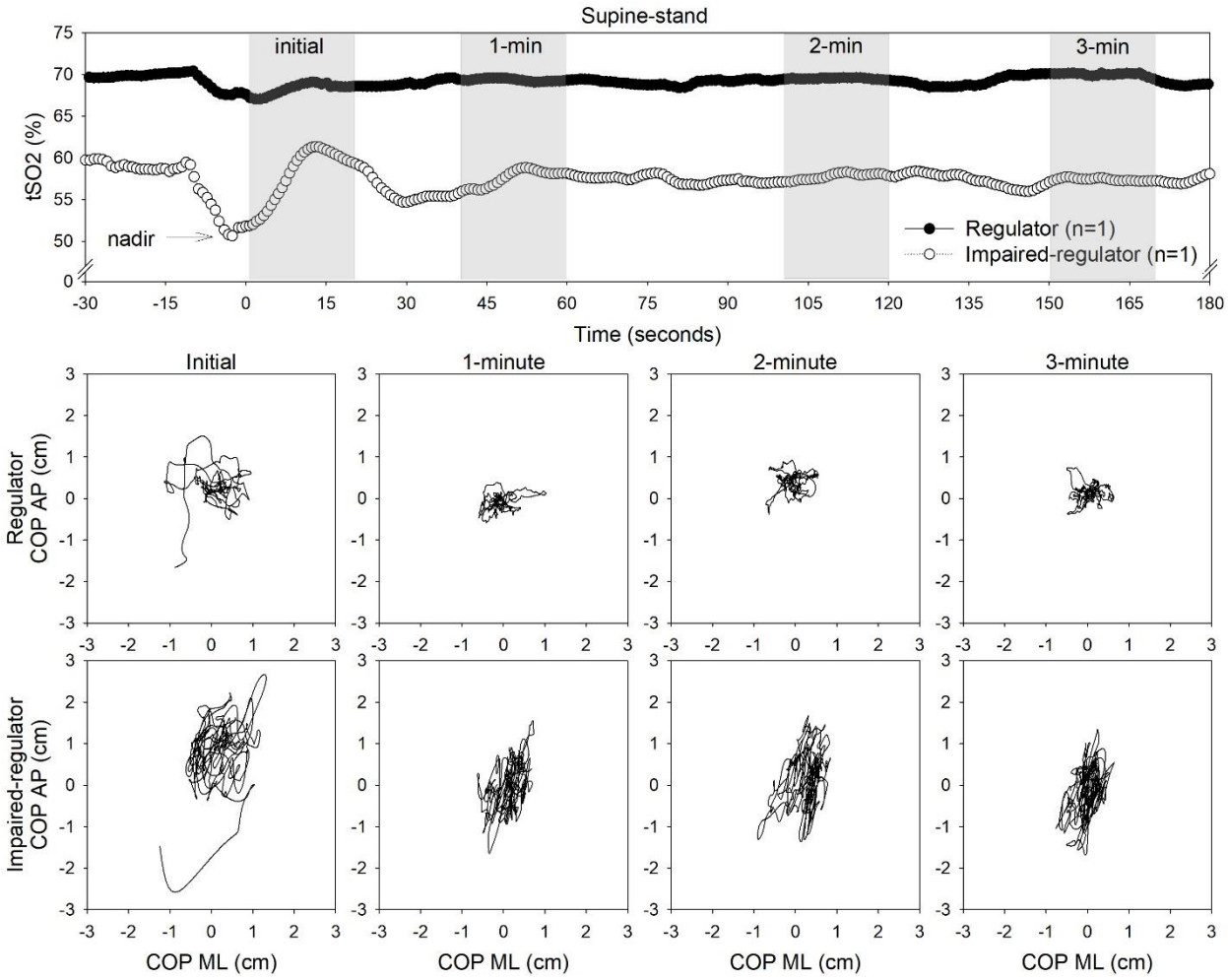


Figure 3-1: Cerebral tissue saturation (tSO_2) and center of pressure (COP) for a single participant in the regulators group (black filled circles) and a single participant from the impaired-regulators group (white circles), during a supine-stand transition. Upper panel represents tSO_2 response and the grey filled rectangles represent the initial, 1-min, 2-min and 3-min time points used to extract a 20 sec average for analysis of postural stability. The lower panels represent COP sway in the anterior posterior (AP) and medial-lateral (ML) planes for the two participants.

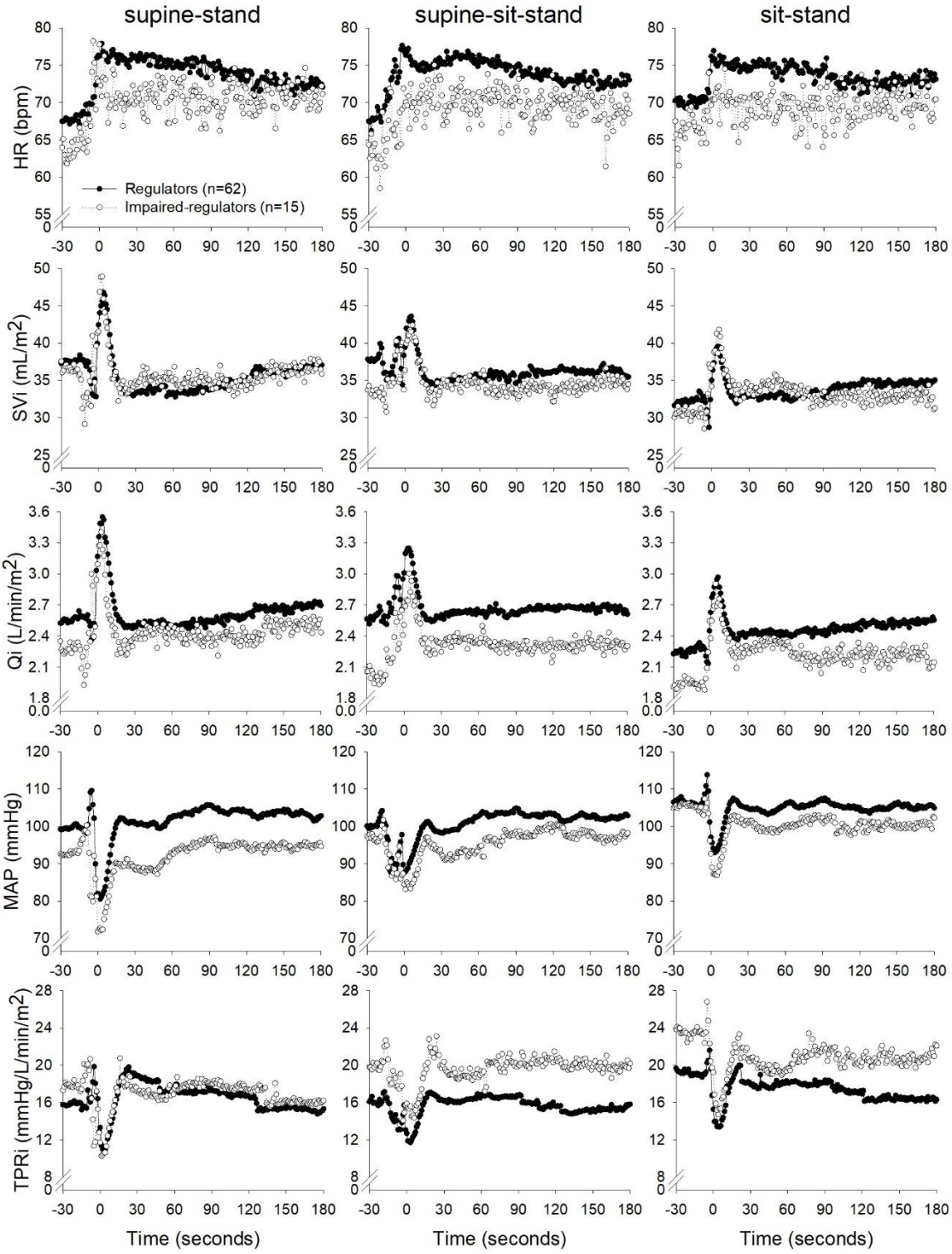


Figure 3-2: Cardiovascular responses to a supine-stand, supine-sit-stand and sit stand transition. Time at zero marks upright posture, negative time represents rest and active transition, positive time represents standing. Black filled circles mark mean values of second-by-second data of regulators group (n=62); white circles mark the postural response of the impaired-regulators group (n=15). *HR* heart rate, *MAP* mean arterial pressure, *Qi* cardiac output index, *SVi* stroke volume index, *TPRi* total peripheral resistance index.

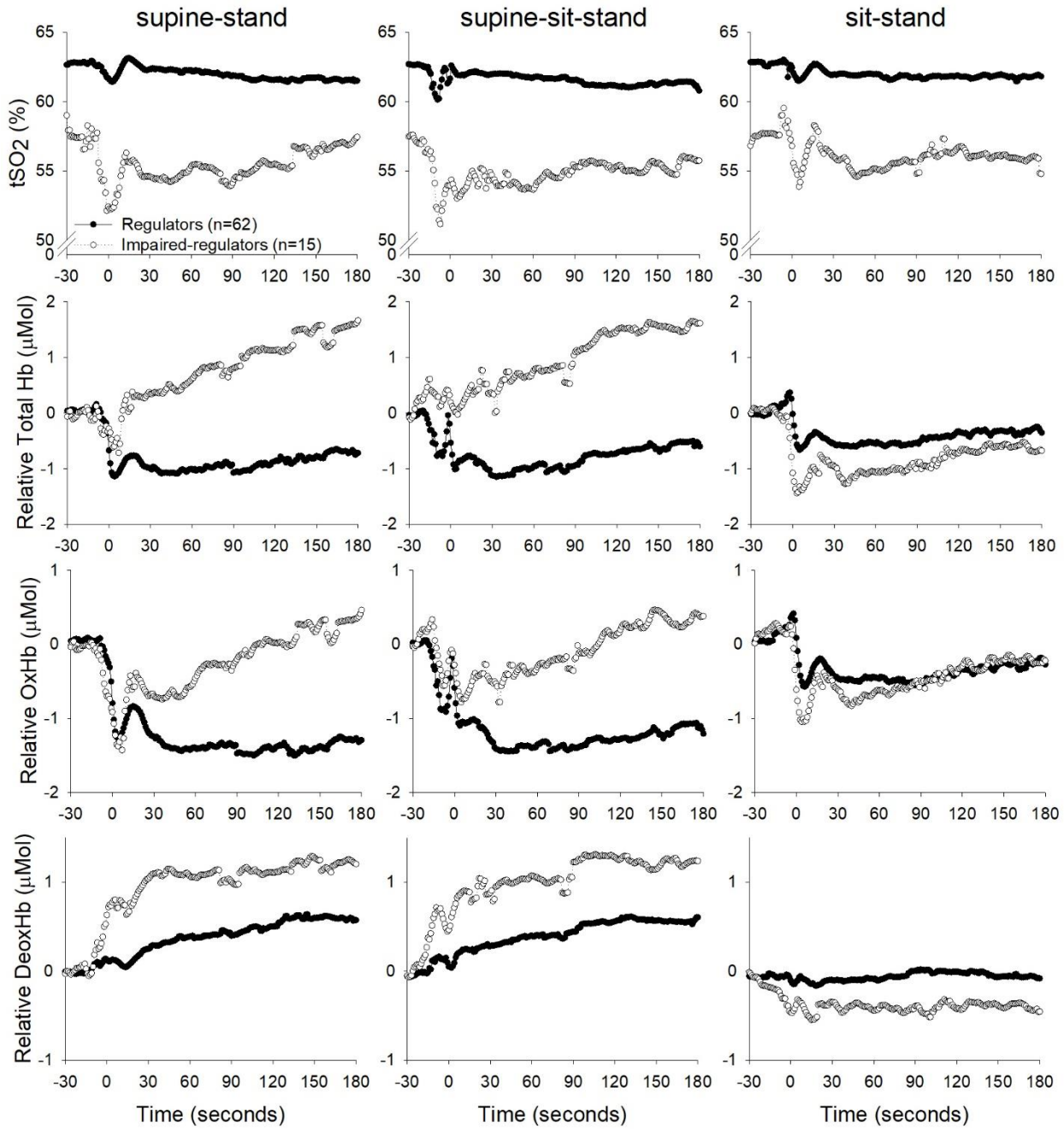


Figure 3-3: Cerebrovascular hemodynamic responses to a supine-stand, supine-sit-stand and sit stand transition. Time at zero marks upright posture, negative time represents rest and active transition, positive time represents standing. Black filled circles mark mean values of second-by-second data of regulators group (n=62); white circles mark the postural response of the impaired-regulators group (n=15).*tSO_2* cerebral tissue saturation, *TotHb* total hemoglobin, *OxHb* oxygenated hemoglobin, *DeoxHb* deoxygenated hemoglobin.

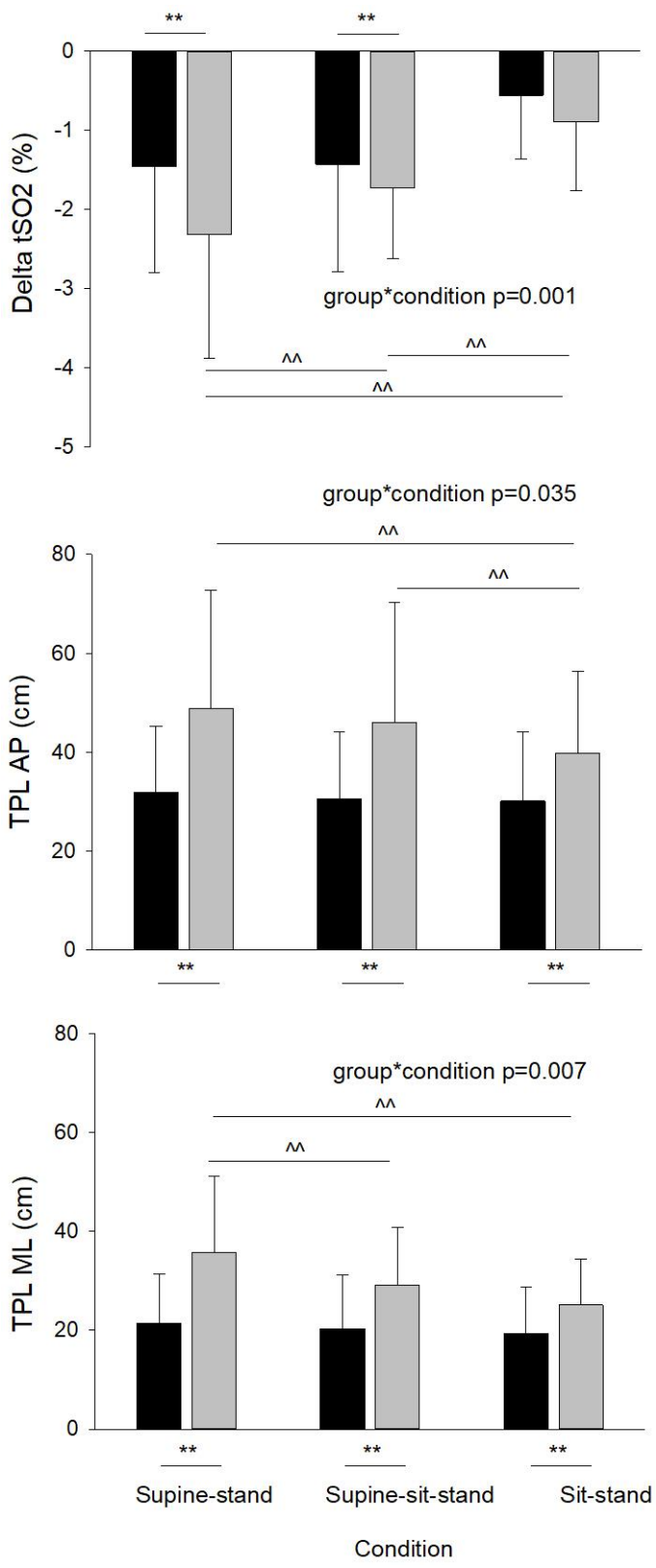


Figure 3-4: Delta cerebral tissue saturation (tSO_2) and initial standing total path length (TPL) during the supine-stand, supine-sit-stand and sit-stand conditions. TPL in the anterior-posterior (AP) and medial-lateral (ML) planes are displayed. Data represents mean and standard deviations for the regulators (black filled bars) and impaired-regulators (grey filled bars) groups.

Significant group by condition interactions were found for all three measures. Tukey's HSD test identified comparison differences where ** denotes significant group differences, ^^ denotes significant differences between conditions for the impaired-regulators group.

No significant difference across transitions were observed for the regulators group but the impaired-regulators demonstrated a progressive improvement of their delta tSO_2 from supine-stand, to supine-sit-stand to sit-stand transitions. Similarly, when looking at TPL AP and ML the regulators had no differences between conditions but the impaired-regulators had significantly different measures of postural stability between conditions.

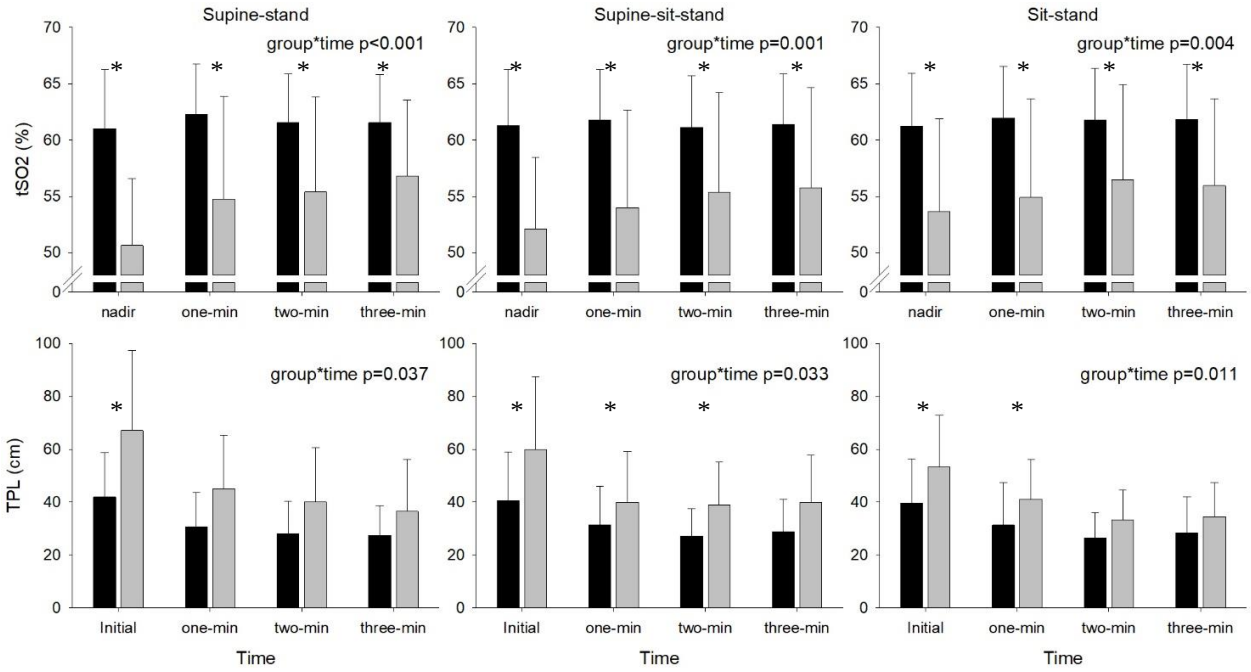


Figure 3-5: Cerebral tissue saturation (tSO_2) and total path length (TPL) during the supine-stand, supine-sit-stand, and sit-stand transitions. The tSO_2 nadir was calculated as the three-point average of lowest values while the initial TPL was taken over the first 20s. All subsequent values at 1-min, 2-min and 3-min for tSO_2 and TPL were averages of 20-s. Data are the mean and standard deviation for the regulators (black bars) and impaired-regulators (grey bars) groups. Significant group by time interactions were found for all tSO_2 and TPL transitions. * marks Tukey's HSD differences $p \leq 0.05$ between groups.

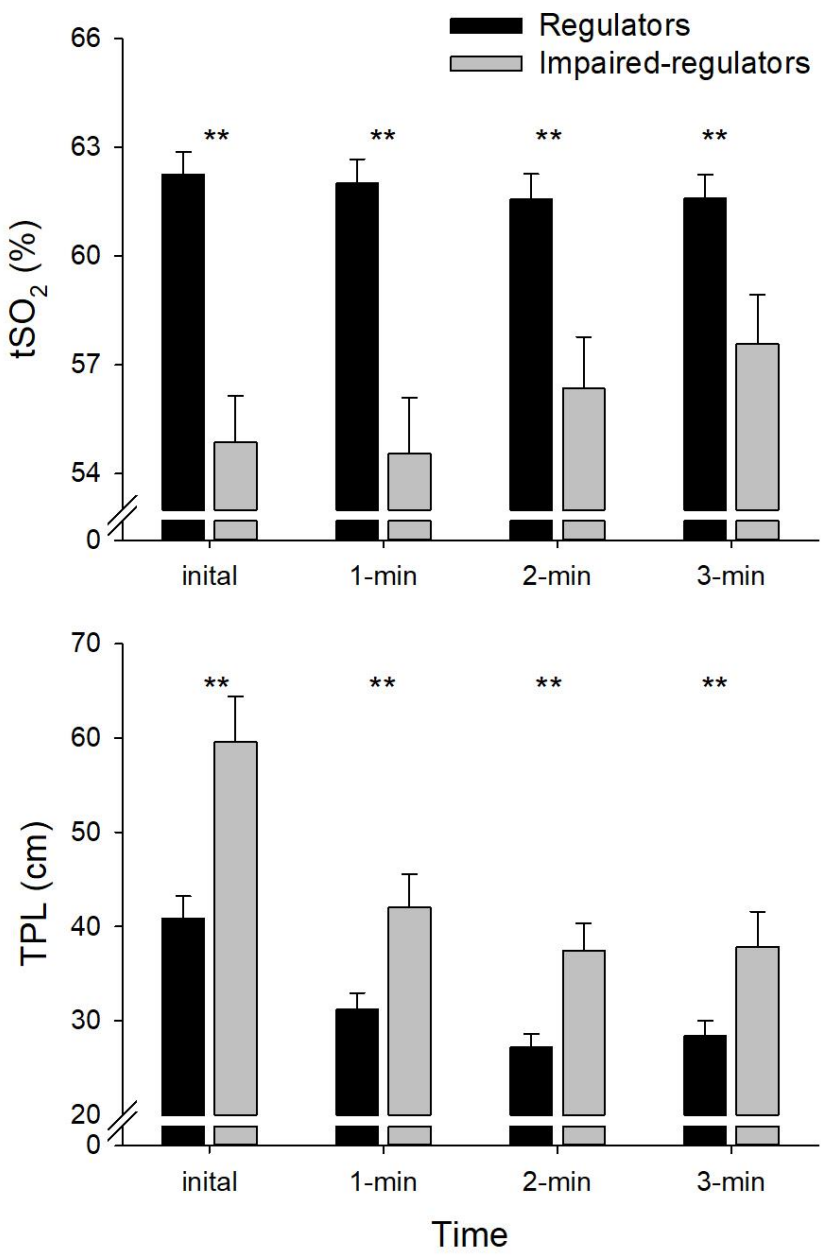


Figure 3-6: Collapsed data from the three conditions for cerebral tissue saturation (tSO_2) and total path length (TPL) between groups. The responses to the three conditions (supine-stand, supine-sit-stand and sit-stand) were averaged/collapsed to represent a single average and standard deviation for each group at each time point. The initial, 1-min, 2-min and 3-min for tSO_2 and TPL values were averages of 20-s. Data are the mean and standard deviation for the regulators (black bars) and impaired-regulators (grey bars) groups. Significant ($p \leq 0.05$) group differences (**) were found for all tSO_2 and TPL transitions.

CHAPTER 4. CEREBRAL HYPOPERFUSION DURING OVER-GROUND WALKING IS RELATED TO INCREASED GAIT VARIABILITY AND INCREASED VASCULAR STIFFNESS IN OLDER ADULTS

Introduction

Posture-related cerebral hypoperfusion is related to impaired arterial blood pressure (BP) regulation and is thought to contribute to a large proportion of falls in older adults (Finucane C. *et al.* 2017). The previous study (Chapter 3) demonstrated that lower arterial BP and reduced cerebral oxygenation (tSO_2) during a transition to standing were associated with postural instability and an increased likelihood of having a future fall. However, transitioning from rest to walking better reflects a typical activity of daily living. During exercise cerebral blood flow (CBF) increases (Fisher J.P. *et al.* 2013) and with age CBF becomes progressively reliant on cardiac output (Qi) to maintain flow (Bronzwaer A.G.T. *et al.* 2017). It is unknown how tSO_2 and CBF of older adults respond when going from a resting position to walking and if cerebral hypoperfusion still exists in light of an active muscle pump to assist venous return and elevate cardiac output while walking (O'Hare C. *et al.* 2017).

Walking is a complex and dynamic movement (Winter D.A. 1995) which taxes postural control in some older adults. Balance strategies are often used by older adults to minimize balance disturbances and prevent falls (Maki B.E. & McIlroy W.E. 1997). Adapted strategies are seen by altered gait such as greater step-step variability and slower self-selected walking speed (Ko Su *et al.* 2009; Ambrose A.F. *et al.* 2013; Jensen J.L. *et al.* 2001; Maki B.E. & mcIlroy W.E. 2006; Papa E. & Cappozzo A. 2000; Akram S.B. & McIlroy 2011). Dynamic movements, such as gait speed and step-time variability, are predictive of multiple falls in older adults (Callisaya M.L. *et al.* 2011). It is unknown how adaptive strategies to walking (step-step variability) relate to cerebral hypoperfusion during walking.

Stiffer arterial vessels marked by increased pulse wave velocity (PWV) have been correlated to lower CBF and higher cerebrovascular resistance, suggesting a relationship between stiffer vessels and altered cerebrovascular hemodynamics and an increased risk of cerebral hypoperfusion (Robertson A.D. *et al.* 2010a). Increased PWV has also been found in fallers when compared to non-fallers (Wong A.K. *et al.* 2014). However, the link between vascular stiffness and balance strategies has yet to be determined.

Slower gait speeds have been associated with reduced resting CBF (Ezzati A. *et al.* 2017), but it is unknown whether cerebral hypoperfusion is observed during walking in persons with slow gait speeds or those who employ adaptive strategies resulting in greater step-step variability. The purpose of the present investigation was to i) examine the posture-related reductions in tSO_2 and CBF during a transition from supine and seated rest to walking, ii) to examine the relationships between walking related reductions of tSO_2 with step-step variability and features of gait, iii) to examine whether reduced tSO_2 and CBF are related to stiffer arteries and features of gait (including slower gait speed).

It is hypothesized that, i) a sub-population of older adults will be at greater risk of low tSO_2 and CBF with walking, ii) older adults with reduced tSO_2 will have increased step-step variability and compromised gait features, iii) older adults with reduced tSO_2 and CBF will have stiffer arteries and altered gait features.

Methods

Participant Description

Twenty-seven older adults age 71-101 years old (17 females; age 86.8±5.3; height 162.3±8.5 cm; weight 70.7±12.8 kg) gave written and informed consent to volunteer in the present study which was reviewed and approved by the Office of Research Ethics at the University of Waterloo and the Schlegel-University of Waterloo Research Institute of Aging. Technical problems prevented the

analysis of 1 participant therefore all of the results and findings to follow are based on a sample size of 26 older adults.

All of the participants were previously part of a larger study (Chapter 3) which included 77 older adults who performed three active transitions to standing, including a supine-stand transition. From this previous study, approximately three quarter of the participants for the current study were identified as having relatively unchanged cerebral oxygenation and good stability on standing, while the other quarter had reductions in oxygenation and poorer stability.

All of the participants in the current study live in conjugate living at one of the Schlegel Villages in Ontario Canada. Participants arrived 2 h postprandial to testing where they completed a brief health questionnaire (past health, current health, physical activity levels, medications). The health questionnaire indicated that all participants were free of neuromuscular and neurological conditions as well as free of diabetes, stroke or any recent (within 3 months) myocardial infarctions.

Self-reported questionnaire

The self-reported health status questionnaire, modified from Robertson (Appendix A, (Robertson A.D. 2013)), was verbally administered to each participant upon arrival to the testing session. Participants reported on vision, past health behaviours such as smoking status and physical activity, past health conditions such as heart failure, kidneys or liver disease (listed in table 2), current health concerns such as irregular heart beats and pain with walking, current medications (prescribed and over-the-counter) and perceived balance (fear of falling).

Fall History Reports

Fall history reports encompassed a 104 item report completed by a Schlegel Village staff member where the participants resided. Fall reports included information regarding location and time

of day of falls as well as questions surrounding pre-existing medical conditions, medical explanation for fall or being pushed or bumped by someone. All 26 participants were included for fall analysis. The total number of fall reports recorded within 6-months before (3 fall reports pertaining to 2 individuals) and after testing (10 fall reports pertaining to 5 individuals). One fall prior to testing was remove from analysis as it was attributed to a person-to-person collision, resulting in 2 fall reports pertaining to 2 individuals.

Cardiovascular and Cerebrovascular Hemodynamics

Participants rested quietly on a bed for instrumentation of arterial finger BP by plethysmography (Portapres, Finapres Medical Systems, Amsterdam, The Netherlands), cerebral tissue near-infrared spectroscopy (NIRS; PortaLite, Artinis Medical Systems BV, Netherlands) and a portable transcranial Doppler ultrasound (TCD-X; Atys medical, Soucieu en Jarrest, France). The Portapres device was placed on a walker that was moved by the participant, the PortaLite and the TCD-X devices were light weight and were carried by the participant during the walking. A brachial return to flow calibration was used on the finger arterial BP waveform and beat-to-beat measures of systolic, diastolic, and mean BP (SBP, DBP, MAP) were adjusted to a manual BP. BP at the level of middle cerebral artery was calculated (BPmca = BP – (distance above heart in cm*0.78)). Estimates of stroke volume, cardiac output, and total peripheral resistance (Finometer Pro; Finapres Medical Systems, Arnheim, The Netherlands) were normalized to body surface area (DuBois D & DuBois EF 1916)(SVi, Qi and TPRi respectively). The NIRS device was used to collect relative changes in oxygenated, deoxygenated, and total hemoglobin content (OxHb, DeoxHb, and TotHb) as well as cerebral oxygenation (tSO_2=OxHb/TotHb). The NIRS device was also used to estimate heart rate (HR) which was derived from the beat-to-beat OxHb interval. The NIRS device was placed over the prefrontal lobe in accordance with the international 10-20 EEG land marking system (right: Fp2, F4, F8. left: Fp1, F7, F3)

(Perrey S. 2008). A source detector distance of 4 cm was used for the OxHb, DeoxHb and TotHb signals to reduce signal contamination from surrounding tissues (Kohri S. *et al.* 2002). The NIRS signal was later processed into beat-by-beat data points where the mean hemoglobin values were extracted from each beat. A 2 Mz Doppler probe was fastened to the TCD-X head set and the participants' glasses if they wore prescription glasses. The middle cerebral artery was then identified and the vessel signal was optimized (Aaslid R. *et al.* 1982). The TCD-X software was subsequently used to auto adjust the robotic arm and improve signal quality. Peak-systolic (SFV), end-diastolic (DFV) and mean (MFV) CBF velocities were used for beat-to-beat analysis, as well as CBFV pulse pressure (CBFVpp=SFV-DFV). A reliable CBFV signal with walking was acquired for 20 of the participants.

Dynamic Testing

All participants completed two active transitions to walking: i) supine-walk-with-walker (supine-walk) and ii) sit-walk-with-walker (sit-walk). Transitions were performed in a random order. The 2 transitions were preceded by a practice transition (sup-walker) to ensure all participants felt comfortable walking with the walker. All transitions began with 10 min of supine or seated rest, followed by an assisted transition into the standing position. Assistance from supine to a seated position was provided by the research team whereby one researcher placed hands behind the participant's left shoulder and left elbow while a second guided the participant's feet to the standing position. Participants walked at a self-selected usual pace on an oval track for 1-minute. At the different testing sites, the straightway of the track was 20.4±3.9 m and the radius was 0.8 m making the arc length approximately 2.5 m.

To capture gait variables, an accelerometer (16g accelerometer data logger x16-mini, Gulf Coast Data Concepts, LLC, Waveland, MS, USA) was placed on the lateral plane of the left ankle and sampled at 50 Hz. Technical problems prevented collection of right ankle accelerometer data on 4

participants (2 regulators). For this reason, all analyses are presented on the left ankle accelerometer data only. For those participants who had data from both ankles, Pearson's correlations were performed for all gait variables between the left and right ankle. Significant correlations ($p \leq 0.05$) were found for all supine-walk relationships other than two variables, one of which had a $p=0.067$ (out of 20 left and 20 right ankle variables). All but 2 of the total 20 left and 20 right ankle gait variables for sit-walk had a $p \leq 0.1$ where the other 2 p-values were 0.107 and 0.132.

A customized Matlab program (Matlab R2015a; The Mathworks Inc, Natick, MA, USA) was used for feature extraction (toe off, mid-heel swing and heel strike, figure 4-1), cropping of turns, computing gait variable and time aligning data to beat-to-beat measures (e.g. BP and CBF). To identify the timing of each gait feature the data were filtered at 100 Hz and the timing and amplitude of toe off, mid heel swing and heel strike were extracted from the raw signal and used for further analysis (Selles R.W. *et al.* 2005). Turns around the arc length of the track which demonstrated clear reductions of acceleration were cropped from further analysis (typically 4 steps). Indicators of gait variability (cadence, gait cycle, swing phase and stance phase) were computed from the end of the third step until the closest step 25-sec later (early walking). A second 25-sec interval was extracted from the last 25-sec of walking (late walking). The early and late walking intervals were then time aligned to the cardio- and cerebrovascular beat-to-beat data and the same 25-sec intervals were extracted.

Gait speed was calculated as the distance traveled during 1-minute, divided by time. Participants were also categorized as being slow (< 0.6 m/s), mildly abnormal (0.6->1.0 m/s), normal (1.0-<1.3 m/s) and fast (≥1.3 m/s) as per the Task Force of the International Academy on Nutrition and Aging (Abellan van Kan G. *et al.* 2010; Studenski S. *et al.* 2003; Quach L. *et al.* 2011). Aside from gait speed, all other temporal measures of gait were constructed from the toe-off, mid-heel swing and heel strike time intervals of early and late walking (Figure 4-1). Gait cycle time was calculated as the time between toe-off to the next toe-off gait feature (Figure 4-1A). Swing time represents the time

from toe-off to heel strike, stance time represents the time from heel strike to toe off, fractional mid-heel swing represents the fraction of time within a gait cycle that mid swing occurs, and fractional stance time is the percent of time within a gait cycle that represents stance time (Figure 4-1). Gait analysis from one participant from the regulator group, and one from the impaired-regulator group is shown in Figure 4-2. Mean and standard deviation values for gait cycle time, swing time, stance time, fractional stance time and fractional mid-heel swing time were calculated. The standard deviations represent variability of temporal measures and mean values represent gait features to complement the gait assessment. The standard deviation of gait cycle time represents step-step variability.

Time scale and averaging

Resting baseline values of beat-to-beat data were averaged over 30 sec of supine or seated rest (from -45 sec to -15 sec prior to a transition). Time at zero seconds indicates the beginning of the first step. Nadir signifies the single lowest tSO_2 beat value. With the introduction of walking there was greater beat-beat variability thus a single nadir beat was chosen over a 3-beat average used in the previous experiment. Positive time indicates time following the beginning of transition.

Arterial Measures

Following dynamic testing, participants were instrumented for continuous monitoring of HR (electrocardiogram, Finapres Medical Systems, Amsterdam, The Netherlands). Total body water (TBW) was then estimated using a body impedance analysis (MF-BIA QuadScan 4000: Bodystat LTD, Isle of Man, UK) with electrodes placed on the right wrist, middle finger, ankle and toe with the participant in a supine position and arms and legs abducted from the body (Sun S.S. *et al.* 2003).

Arterial stiffness was assessed by carotid pulse pressure (cPP) and compliance coefficient (cCC), carotid distensibility coefficient (cDC), intima media thickness (IMT), carotid-femoral pulse wave

velocity (cfPWV), and estimated augmentation index and PWV (AI, ePWV). cPP was measured in the left carotid artery by applanation tonometry for 15–20 beats (SPT-301, Millar Instruments, Houston, TX, USA). Brightness-mode (B-mode) ultrasound images (M5 system, Mindray Bio-Medical Electronics Co., Shenzhen, China) of the carotid artery were taken using an 8–12 MHz linear array transducer (L14-6s) to measure arterial diameter with manual electronic calipers in triplicates over three consecutive heart beats. The combination of cPP and arterial diameter from ultrasonic images were used to calculate cCC and cDC (van Bortel L.M *et al.* 2012; van Bortel L.M. *et al.* 2002; Reneman R.S. *et al.* 2005). The carotid diameter and IMT were measured from B-mode ultrasound images of the right carotid within 1–2 cm of the bifurcation. IMT was defined as the distance from the lumen-intimal interface to the media-adventitial interface of the far wall of the artery. A set of eight electronic calipers were manually placed over a 1 cm segment of images captured at the ECG R-peak over three consecutive beats for right carotid, and an average was computed to represent a single mean IMT value. Pulse waves from the right common carotid and femoral arteries were recorded for 20–30 beats by Doppler ultrasound (Doppler Box, Compumedics DWL, Singen DE). Pulse wave arrival times were calculated from the time difference between the ECG R-peak and the foot of the velocity wave. To clearly identify the foot of each pressure wave, a low-pass 5–30 Hz filter was applied (Robertson A.D. *et al.* 2010a) and the maximum 2^{nd} derivative of each waveform was calculated. cfPWV was calculated by dividing the difference in the measured superficial distances from the measurement sites to the suprasternal notch and the difference in pulse arrival times. Resting central SBP and DBP (cSBP and cDBP) as well as AI and ePWV were assessed in the supine resting position using the Mobil-O-Graph cuff placed over the brachialis artery (Mobil-O-Graph, I.E.M. GmbH, Strolberg, Germany). The Mobil-O-Graph detects the oscillometric waveform and uses customized software (ARCSolver software) to apply transfer function analysis that reconstructs the central waveform. Subsequently, the shape and timing of the central pulse wave are used to calculate AI, AI75 (augmentation index

adjusted for HR) and ePWV. The Mobil-O-Graph has been validated against a well-established non-invasive estimation of central BP known as SphymoCor for both central hemodynamics and arterial stiffness measurements (Weiss W. *et al.* 2012; Luzardo L. *et al.* 2012).

$cCC\ (mm^2/MPa) = [\pi \bullet \Delta D(mm) \bullet D(mm)] / [2 \bullet PPcar(MPa)]$

$cDC\ (10^{-3}/kPa) = [2 \bullet \Delta D(mm) \bullet D(mm) + \Delta D(mm)^2] / [D(mm)^2 \bullet PPcar(kPa)]$

(van Bortel L.M. *et al.* 2002; Reneman R.S. *et al.* 2005)

Statistical analysis

All statistical analysis was completed using IBM SPSS version 20 (IBM SPSS Statistics 20; IBM Corp, Armonk, NY, USA), and all tests were considered significant at $p \leq 0.05$ and trends were reported at $p \leq 0.1$.

Participant Grouping- The current study identified obvious differences between older adults during walking which demonstrate reflected abnormalities in tSO_2 (Figure 4-2 A), MFV (Figure 4-2 B), gait characteristics (Figure 4-2 C-D), step-step variability (Figure 4-2 E), stance time variability (Figure 4-2 F) and gait speeds (Figure 4-2 G). In the previous investigation (Chapter 3) participants also demonstrated varying abilities to recover tSO_2 upon standing (supine-walk condition) and therefore k-cluster analysis was used to separate participants into two groups (Chapter3). The small sample size (n=26) in the current investigation, combined with varying tSO_2 responses in the older adults did not allow for any strong cluster groups to be formed. Karkow et al (2002) identified that signs of pre-syncope mainly occur when oxygenation and perfusion are less than tSO_2 of 60% (Krakow K. *et al.* 2000). Therefore, during the supine-walk condition of early walking, a cut off value of $tSO_2 \leq 60\%$ was used to classify participants into two groups, high-tSO_2 (n=18) and low-tSO_2(n=8). Three quarters of

the low-tSO_2 group from the current investigation also had a $tSO_2 \leq 60\%$ during initial standing of the supine-stand experiment (Chapter 3). Thus, participants classified as having low cerebral oxygenation appear to have a relatively low tSO_2 while upright standing or walking.

Effects of group, condition and time - A two-way mixed ANOVA (general linear model in SPSS) was used to assess the main effect of condition and group for gait speed and all hemodynamic and mean gait variables. Two levels of repeated measures were used for within-subject evaluation for the condition (supine-walk, sit-walk) and two levels of between-subject factors were used to evaluate group effects (high-tSO_2 vs. low-tSO_2). For all ANOVAs if Mauchly's test of Sphericity was significant the Greenhouse-Geisser correction was used. If a significant interaction was found, Tukey's honest significant difference (HSD) test was used to further evaluate significant levels.

For high-tSO_2 vs. low-tSO_2, a Mann-Whitney U Test and a Levene's Test for equality of variance was performed on all gait variability data. Corrections for multiple tests were not applied, thus not all variables with a $p \leq 0.05$ are truly significant. A correction was not applied as this is an exploratory study requiring additional power to accurately assess multiple comparisons on non-continuous data. A Friedman's Test was used to analyze differences in conditions between the supine-walk and sit-walk transitions.

Group characteristics comparisons – All data were analyzed using an ANOVA in SPSS version 20.0. All nominal data were tested using a Chi-square test with the Fisher's Exact Test correction factor (Phi was used to estimate the effect size when significance was found).

Relationships comparisons - Pearson Product-moment correlations were used to assess the relationships between i) experiments (supine-stand vs. supine-walk) at baseline, nadir and during

initial standing/early walking, ii) TCD and tSO_2 signals during both early and late walking of both conditions, iii) cerebrovascular hemodynamics (tSO_2, TotHb, OxHb, DeoxHb, PSV, EDV and MFV) and all mean and standard deviation gait characteristic as well as gait speed during the supine-walk condition, iv) gait speed and gait characteristics (all mean and standard deviation measures), v) vascular stiffness and cerebrovascular hemodynamics (all NIRS and TCD signals during baseline, early-walk and late-walk) and vi) vascular stiffness measures and gait characteristics and gait speed.

Results

Experiment comparisons (Figure 4-3)

The tSO_2 measurements for the same persons on two different occasions (supine-walk test of the current study and supine-stand test in Chapter 3) were not significantly correlated during baseline, nadir or early-walking or standing values. The baseline correlation is not significant however there is not much variation surrounding the line of identify.

Group characteristics (Table 4-1)

There were no significant differences between groups for age, sex, BMI, BSA, or TBW. However, there were trends for lower brachial DBP and MAP ($p=0.085$ and $p=0.071$), as well as significantly ($p=0.039$ and $p=0.042$) lower central SBP and DBP in the low-tSO_2 group. There was a higher cfPWV ($p=0.057$) in the high-tSO_2 group, and higher self-reported incidence rates of emphysema/pneumonia ($p=0.086$). Although not significant, the majority of participants in the low-tSO_2 group were considered sedentary. There were no significant differences between groups for physical activity, current health or medications.

Beat-to-beat hemodynamic responses (Figures 4-4 and 4-5)

During the transitions to walking HR slowly but steadily increased. During late-walking HR was higher ($p=0.059$) during the sit-walk condition compared to the supine-walk condition. There were differences ($p<0.05$) in condition for baseline values of SVi, Qi and TPRi estimated from the pulse contour analysis ; whereby SVi and TPRi were higher at baseline during the sit-walk condition and Qi was higher at baseline during the supine-walk condition. During late-walking SVi and Qi were higher during the supine-walk vs. sit-walk condition. A trend for an interaction for TPRi late walking was found but Tukey's HSD did not identify any significant comparisons. Beat-to-beat SBP, DBP and MAP was lower ($p<0.05$) during supine-walk versus sit-walk baseline. As mentioned above (Table 4-1), the low-tSO_2 group had a lower DBP and MAP at baseline compared to thehigh-tSO_2 group.

Cerebrovascular responses demonstrated a higher baseline EDV and MFV during the supine-walk compared to the sit-walk condition ($p=0.021$ and $p=0.073$). An interaction ($p=0.012$) was found for baseline CVRi, where the high-tSO_2 group had a higher CVRi at baseline compared to the low-tSO_2 group during the sit-walk condition. CVRi was also found to be higher in the sit-walk condition compared to the supine-walk condition during early walking. Both RI and PI were higher ($p<0.01$) at baseline during the sit-walk condition compared to the supine-walk condition. The low-tSO_2 group had lower ($p<0.001$) tSO_2 at baseline, nadir, early-walk and late-walk compared to high-tSO_2 group. The low-tSO_2 group also had higher TotHb and higher DeoxHb at nadir, early-walking and late walking ($p<0.1$). Trends for OxHb suggest that the supine-walk nadir is lower than the sit-walk nadir and during early and late walking the low-tSO_2 group have higher OxHb.

Relationships between CBFV and tSO_2 (Figure 4-2 and 4-6)

Although there were no significant correlations between tSO_2 and PSV or EDV (Figure 4-6) a participant with a higher tSO_2 typically had a higher PSV, EDV or MFV value. As seen in figure 4-2 the

trends between tSO_2 and MFV from supine rest to walking, generally align. Likewise, the low-tSO_2 participant has a lower tSO_2 and MFV compared to the high--tSO_2 participant (Figure 4-2).

Gait variability relative to cerebrovascular hemodynamics (Figures 4-7 to 4-8)

Gait cycle variability and stance time variability were significantly greater in the low-tSO_2 group compared to the high-tSO_2 group (Figure 4-7). Correlations were run between cerebrovascular hemodynamics (tSO2, TotHb, OxHb, DeoxHb, PSV, EDV and MFV) and all mean and standard deviation gait characteristic as well as gait speed. Correlations were run for the supine-walk condition only as group differences in cerebrovascular hemodynamics were most prominent during this condition. It was found that as relative changes in OxHb increased, from supine rest to early walking, mean stance time also increased. Likewise, as relative changes in OxHb increased, from supine rest to late walking, mean gait cycle time also increased. During the supine-stand late walking interval, as DeoxHb increased mean fractional stance time decreased.

Relationships between gait speed and gait characteristics (Table 4-2)

Although gait speed was not directly associated to cerebrovascular hemodynamics, it is associated with gait characteristics that were related to cerebrovascular responses during walking. Gait speeds (supine-walk and sit-walk) were negatively correlated ($p<0.05$) to mean gait cycle time, mean stance time and mean fractional stance time. Gait speed during the sup-walk was significantly and positively correlated to cadence, swing variability, variability of fractional stance time.

Cerebrovascular hemodynamics relative to vascular stiffness (Figure 4-9 and Table 4-3)

Significant relationships between reduced CBF and increased vascular stiffness as well as increased cerebrovascular resistance and increased vascular stiffness were found. As EDV increased,

cPP decreased and cDC increased (Figure 4-9). As cerebrovascular resistance index increased so did central diastolic blood pressure (Figure 4-9). The only NIRS signal correlated to vascular stiffness was DeoxHb (Table 4-3). As a relative change in DeoxHb increased from baseline to walking cfPWV decreased. However, these results are highly dependent on the baseline resting values as DeoxHb represents relative changes only.

Gait speed and gait characteristics relative to vascular stiffness (Figure 4-10)

Increased central arterial stiffness, marked by increased cPP with the Mobil-O-Graph, was associated with reduced gait speed for both the supine-walk and sit-walk conditions. As noted above, increased carotid PP was significantly correlated to reduced EDV (Figure 4-9).

As mentioned previously, participants in the low-tSO_2 group had higher relative OxHb upon walking (Figure 4-5) which was associated with increased mean stance and gait cycle times (Figure 4-8). Increased mean stance and gait times were associated with slower gait speed (Table 4-2). Furthermore, increased vascular stiffness as associated with reduced CBF (Figure 4-9 and Table 4-3) and increased reduced gait speed (Figure 4-10).

Discussion

The current study is the first to relate changes in cerebral perfusion and oxygenation to gait characteristics in older adults who transitioned from supine or seated positions to walking. Consistent with the study's hypotheses, we observed that there is a sub-population of older adults who have low tSO_2 and CBF during walking. These older adults with cerebral hypoperfusion have increased step-step variability. The participants with greater arterial stiffness also had lower CBF and altered cerebrovascular hemodynamics, as well as slower gait speeds. Although these data were derived from a relatively small population of older adults, the observed relationships between cardio- and

cerebrovascular health, and the slower gait speed and altered gait strategies point to an increased risk for falls that might be detected with longer follow up.

Cerebral oxygenation and blood flow

Previous research has shown that approximately 1 in 5 older adults has an impaired blood pressure response on transition from supine to standing positions (Romero-ortuno R. *et al.* 2011; Finucane C. *et al.* 2014). This impaired response might lead to cerebral hypoperfusion that could cause dizziness and unexplained falls (Finucane C. *et al.* 2017) as considered in Chapter 3. In the current study design, we recruited individuals from a previous investigation (Chapter 3) who had good regulation of cerebral oxygenation and more stable posture on standing, as well as those with poorer regulation of cerebral oxygenation and less stable posture. The previous study (Chapter 3) identified three quarters of participants to have relatively unchanged tSO_2 and good stability whereas the current study identified approximately 65% of participants to have higher tSO_2, higher BP, and reduced step-step variability. The grouping between experiments differed because the performance of the task (stand versus walk) resulted in different cardio- and cerebrovascular hemodynamic responses. Thus, the new grouping for the current study was based on $tSO_2 \leq 60\%$ during walking versus the previous experiment that grouped participants based on hypoperfusion with a static stand (large postural reductions from baseline and sustained static stand reductions in tSO_2).

The supine-stand and supine-walk responses of TotHb, OxHb and DeoxHb between high- and low-tSO_2 groups were consistent between experiments. Larger reductions in TotHb, OxHb and larger increases in DeoxHb were observed in the high-tSO_2 group (Figure 4-5). These findings are in line with Mehagnoul-Schipper et al. 2003 where following an active stand healthy older adults had a larger reduction ($p<0.05$) in OxHb and TotHb than older adults with diastolic dysfunction (Mehagnoul-Schipper D.J. *et al.* 2003). The posture related reductions in TotHb and OxHb of the high-tSO_2 group

from the current investigation are consistent with the age-related trends observed by Edlow et al. in a younger population (Edlow B.L. *et al.* 2010).

Recent studies have investigated cerebral oxygenation during walking in older adults, but this research did not include postural transitions and focused on challenges such as dual tasking (Nieuwhof F. *et al.* 2016; Maidan I. *et al.* 2016). This is the first study to demonstrate the response of both tSO_2 and CBF during transitions from supine or seated postures into over-ground walking in older adults. At first glance of the cerebrovascular responses to walking (Figure 4-5) there is not a clear coupling between CBF and tSO_2 this is due to the low sample size of participants with acquired TCD signals (n=11 high-tSO_2 and n=5 low-tSO_2). The CBF values of the low-tSO_2 group are low (as seen by a typical low--tSO_2 participant in Figure 4-2) however one of the 5 participants in this group had a high CBFV response, leading to a high group average. High CBFV in older adults might reflect a high CBF, or it might be a consequence of a smaller diameter middle cerebral artery, or minor cerebral artery stenosis that had not been previously diagnosed (Baumgartner R.W. *et al.* 1999). As mentioned, when looking at the individual responses (Figure 4-2) the trends in the tSO_2 response aligns with the trends in the MFV response for both the low- and high-tSO_2 participants. Generally speaking, participants with a low tSO_2 also have low CBF (Figure 4-2 and 4-6). Previous reports of combined tSO_2 and CBFV recordings have found changes in tSO_2 with acetazolamide injections (known to increase CBF) to not be as large as changes seen in the CBFV signals (Tachtsdis I. *et al.* 2008). However overall changes in tSO_2 were correlated to changes in percent MFV ($r=0.77$, $p<0.01$) (Tachtsdis I. *et al.* 2008).

Observed differences between individuals (tSO_2 of high- vs. low-tSO_2 groups) were anticipated yet still disconcerting to see a sub-population of older adults experience some degree of hypoperfusion when walking. In order for the low-tSO_2 group to have increased CBF and tSO_2, an increase in Qi would be required (Bronzwaer A.G.T. *et al.* 2017), this could be derived from either an increase in HR or more likely an increase in SVi via the muscle pump (O'Hare C. *et al.* 2017). The

muscle pump is capable of propelling blood towards the heart and increasing venous return despite large pressure gradients (Halliwill J.R. *et al.* 2014; Stegall H.F. 1966), however this mechanism may be failing in some manner for some older adults. During muscle activation, such as with the dynamic movement of walking, the cardiovascular system must meet the metabolic demands of the active muscle and the brain (Ichinose M. *et al.* 2014). During high-intensity dynamic exercise in young adults, BP is tightly regulated by alterations in arterial baroreflex controls to ensure that slight changes in TPRi do not impact the Qi and oxygen delivery to the working muscle and the delivery of blood to the brain (Ichinose M. *et al.* 2014). In the older adults who have reduced tSO_2 during walking, failure of one or more of these mechanisms may be contributing to the reduced tSO_2.

Syncope has been associated with both low BP and CBFV during tilt-test (Novak P. 2016). However, in light of a relatively maintained BP, CBFV has also been show to decrease during a tilt-test (Novak P. 2016) and OxHb has been shown to decrease during an active stand (Mehagnoul-Schipper D.J. *et al.* 2001). This suggests that although posture related reductions in BP can likely indicate cerebral hypoperfusion some older adults may experience cerebral hypoperfusion despite a relatively maintained BP.

Considering the signs of hypoperfusion during late walking in the low-tSO_2 group it is uncertain how cerebral perfusion responds beyond the 1-minute of walking observed in the current study. The trends of the oxygenated and deoxygenated hemoglobin signals recorded by near infrared spectroscopy (Figure 4-5) indicate that cerebral hypoperfusion might persist. Future longer-term studies should investigate cerebral oxygenation over longer periods and assess any relationships to incidence rates of future falls in the high- vs. low-tSO_2 populations.

Cerebrovascular hemodynamics and gait strategies

In the previous larger study presented in Chapter 3, higher tSO_2 was associated with better postural stability. The current study has identified differences in tSO_2 among older adults during walking (Figure 4-2), which were associated with abnormalities in gait strategies (Figure 4-7). Gait cycle variability, also referred to as step-step variability, is a predictor of multiple falls in older adults (Callisaya M.L. *et al.* 2011) and has previously been correlated to CBFV in young adults on a treadmill while performing a cognitive task (Gatouillat A. *et al.* 2015). The current study is the first to evaluate gait variability during over-ground walking in older adults while simultaneously recording cerebrovascular hemodynamics. Step-step variability (gait variability), was significantly greater in the low-tSO_2 group during early walking compared to the high-tSO_2 group during the supine-walk condition (Figure 4-7). Additionally, stance time variability was greater in the low-tSO_2 group during the supine-walk condition for early walking (Figures 4-7). Although the low-tSO_2 group had a lower group effect of tSO_2 and higher group effect of TotHb, OxHb and DeoxHb compared to the high-tSO_2 group, it appears as though most of the group differences are driven by the changes observed in the supine-walk condition (Figure 4-5). Likewise, the group differences in gait variability are most predominant and only significant during the supine-condition as well (Figure 4-7). Additionally, other compromised gait characteristics marked by increased stance time and gait cycle time during the supine-walk condition were significantly associated with increased OxHb (Figure 4-8). It is important to note that OxHb was also significantly higher in the low-tSO_2 group suggesting participants with lower tSO_2 during walking are also more likely to have increased mean stance time and mean gait cycle time.

Slower gait speed at usual pace is a risk factor for falls, mortality, institutionalization, disability and cognitive impairment in older adults (Abellan van Kan G. *et al.* 2010). Although there were no direct relationships between gait speed and tSO_2, gait speed was significantly correlated to the gait

variables which were found to be associated with tSO_2 (Table 4-2). As mentioned above, an increase in OxHb (found in the low-tSO_2 group) was associated with increased mean stance time and gait cycle time (Figure 4-8), and increased gait cycle time and mean stance time were also significantly ($p<0.05$) correlated (-0.553 and -0.597) to reduced gait speed (Table 4-2). Therefore, older adults with lower tSO_2 have higher OxHb which is associated with compromised gait features (increased mean gait cycle time and stance time) which are also associated with reduced gait speed. Low CBF (Ezzati A. *et al.* 2017; Robertson A.D. *et al.* 2010b) and impaired endothelial function, marked by sVCAM-1 and cerebrovascular reactivity to carbon dioxide (Tchalla A.E. *et al.* 2015; Sorond F.A. *et al.* 2010), have been reported to be associated with slow gait speed. It is speculated that the areas of the brain which control motor function may be exposed to cerebral hypoperfusion or dysregulation, thus contributing to reduced gait speed. As mentioned above, a decrease in Qi would contribute to decreased CBF in older adults (Bronzwaer A.G.T. *et al.* 2017). With age, greater oxygen consumption is required to perform activities of daily living (Avlund K. 2010) and measures of perceived fatigability have been associated with increased cost of oxygen during walking (Barbosa J.F. *et al.* 2016). It has been suggested that older adults attempt to maintain their fatigue within a comfortable range by modulating their levels of physical activity (Alexander N.B. *et al.* 2010; Eldadah B.A. 2010). Therefore, an older adult with a reduced Qi and cerebral hypoperfusion would likely feel fatigued and consequently modulate their self-selected gait speed to return to a comfortable range of exertion.

Slower gait speed is also a predictor of frailty (Abellan van Kan G. *et al.* 2010). Various definitions of frailty exist which include the assessment of physical (ex. inactivity, gait speed, weight loss, exhaustion, grip strength) (Fried L.P. *et al.* 2001), psychological and social attributes (Uchmanowicz I. *et al.* 2017; Fried L.P. *et al.* 2001); however all frailty indexes and definitions agree that frailty consists of the cumulative deficits of multiple systems which result in vulnerability to adverse outcomes (Uchmanowicz I. *et al.* 2017; Fried L.P. *et al.* 2001). Although frailty was not assessed in the current

thesis it has been associated with age related changes in BP, such as orthostatic hypotension (Ooi W.L. *et al.* 1997) and thus could likely be an underlying condition which contributes to the observed cerebral hypoperfusion and poor dynamic postural control during walking in the low-tSO_2 participants.

Vascular stiffness and its associations to cerebrovascular hemodynamics and gait strategies

Central arteries are structurally built to be highly elastic allowing for distension and recoiling of the vessel wall to reduce the pulsatile pressures ejected from the heart. Arterial stiffening is a natural consequence of aging, but the rate of increase in stiffness does vary between individuals (Gepner A.D. *et al.* 2014). Increased arterial stiffness lowers the cushioning effect of the arterial waveform and increases pulsatility, exposing cerebral tissue to excessive pressures, and consequently impacting cerebrovascular hemodynamics (Mitchell GF 2008; Webb A.J. *et al.* 2012). The current study found various measures of reduced CBF at rest and during walking to be significantly correlated with increased vascular stiffness (Figure 4-9 and Table 4-3). Increased EDV at rest was correlated to reduced carotid pulse pressure ($r= -0.527$, $p=0.03$), as well increased EDV while walking was correlated to increased carotid distensibility coefficient ($r=0.511$, $p=0.036$). Increased CVRi while walking was correlated to increased central diastolic blood pressure ($r=0.582$, $p=0.037$, Figure 4-9 and Table 4-3). These relationships suggest stiffer arteries are associated with reduced CBF (EDV) and altered cerebrovascular hemodynamics (CVRi) during over-ground walking. These findings are supported by Robertson et al. 2010 who reported increased vascular stiffness to be associated with lower resting CBF and higher resting CVRi (Robertson A.D. *et al.* 2010a). Increased vascular stiffness, marked by increased central pulse pressure by the Mobil-O-Graph, was associated with reduced gait speed during the supine-walk ($r= -0.386$, $p=0.069$) and the sit-walk ($r= -0.446$, $p=0.033$) conditions (Figure 4-10). Cumulatively, these results suggest increased vascular stiffness is associated with low CBF while walking, altered cerebrovascular hemodynamics while walking and reduced gait speed in older adults

Limitations

Some limitations must be mentioned. This is an exploratory study whereby statistical power was low, meaning the probability of making a type II error (suggesting something is not there when it is) is high. Not only was there a low sample size but there were large inter-individual variations in response to walking. The sub-sample of participants in the current study had too small of a sample size which lacked a natural spread of data to allow for k-cluster analyses.

The relationship between the two experiments lacked consistency between baselines, nadir and upright posture values of tSO_2. The baseline tSO_2 values had similar ranges between experiments but were not significantly associated with one another. Effects of circadian rhythm on tSO_2 in young adults have been shown to impact intra-individual variations of tSO_2 as much as 4.32±1.76% ($p<0.001$ between evening and morning (Metz A.J. *et al.* 2013). It has also been found that tSO_2 absolute values separated by 5-months have a cross correlation coefficient of 0.8 in older adults (Hallacoglu B. *et al.* 2012). The differences in time between the two experiments was on average 7.3 months and thus the differences observed in baseline tSO_2 between experiments could be attributed to changes in medication (3 participants went off a BP lowering medication and 4 participants went on a BP lowering medication between experiments). The observed differences in tSO_2 values at nadir and initial standing vs. early-walking would inherently differ because of the task at hand. The muscle pump with walking would likely impact both the nadir and early walking tSO_2 values compared to a static stand.

It was not possible to monitor arterial or end-tidal CO_2 during the older adult studies. As CO_2 plays a major role in regulation of CBF, this is an important limitation, and it is not known how hyperventilation might have contributed to cerebral hypoperfusion.

The estimated SV and subsequently Q derived from the Modelflow contour analysis demonstrates reliable beat-to-beat representation of SV at rest (Harms M *et al.* 1999). However, it

has been recently reported that the Modelflow method does not accurately estimate SV during dynamic changes in SV, particularly during orthostatic stress (Gibbons T. 2017).

The prevalence of fallers reported (retrospectively 15%, prospectively 26%) are lower than population studies report (33.3%) (Tromp *et al.* 2001), therefore falls may be underestimated or the population selected may not be representative of a typical older adult population.

Conclusions

The novelty of this study lies in the simultaneous collection of cerebrovascular hemodynamics and gait variables during over-ground walking in older adults. It can now be reported that a sub-population of older adults are at increased risk of low tSO_2 with walking and that individuals with reduced tSO_2 have increased step-step variability, a predictor of future falls. Complementary to these findings are the fact that older adults with stiffer arteries also have reduced CBF during walking, altered cerebrovascular hemodynamics while walking and slower gait speeds. These results describe a condition wherein some older adults are repeatedly exposed to cerebral hypoperfusion during 1-minute of walking which is a constant act of daily living. Therefore, older adults with cerebral hypoperfusion are at increased risk of instability and future falls on a regular day-to-day basis

Tables and Figures

Table 4-1: Subject Characteristics

Characteristic	High-tSO_2 (n=18)	Low-tSO_2 (n=8)	p-value
Age, years	87.5±5.0	84.7±5.6	N.S.
Sex (women), % (n)	67 (12)	50 (4)	N.S.
BMI (kg/m^2)	27.3±4.4	25.1±4.1	N.S.
Height (cm)	161.4±8.4	165.4±8.4	N.S.
Weight (kg)	71.4±12.9	69.0±14.3	N.S.
BSA (m^2)	1.75±0.19	1.76±0.21	N.S.
Limb length (cm)	74.1±3.5	75.6±3.4	N.S.
TBW (L), (n=13, n=6)	28.3±5.4	28.7±4.7	N.S.
Brachial SBP (mmHg)	141±24	132±18	N.S.
Brachial DBP (mmHg)	69±11	59±17	0.085
Brachial MAP (mmHg)	93±13	83±11	0.071
Current self-reported fear of falling (scale 0 to 10) (n=16, n=8)	3.06±3.04	2.13±2.17	N.S.
Current self-reported balance confidence (scale 0-10) (n=16, n=8)	5.13±2.94	4.88±2.95	N.S.
Retrospective fallers within 6-months before data collection (past falls), % within group (n)	6 (1)	13 (1)	N.S.
Prospective fallers within 6-months after data collection (future falls), % within group (n)	11 (2)	25 (2)	N.S.
Combined gait speed slow: <0.6 m/s, % (n)	11 (2)	13 (1)	N.S.
Combined gait speed mildly abnormal: 0.6 – >1.0 m/s, % (n)	50 (9)	75 (6)	N.S.
Combined gait speed normal: 1.0 - > 1.3 m/s, % (n)	39 (7)	13 (1)	N.S.
Combined gait speed fast: ≥1.3 m/s, % (n)	0 (0)	0 (0)	N.S.
Mobil-O-Graph Data			
Central SBP, mmHg (n=16, n=7)	129±20	110±16	0.039
Central DBP, mmHg (n=16, n=7)	85±13	72±14	0.042
Central PP, mmHg (n=16, n=7)	44±11	38±12	N.S.
Augmentation Index @75 [90%CI], %, (n=16, n=7)	36.0±13.9	28.1±17.4	N.S.
Augmentation Pressure, mmHg, (n=16, n=7)	20.1±10.7	16.3±6.4	N.S.
Reflection Magnitude, (n=16, n=7)	65.7±8.7	65.3±7.3	N.S.
ePWV, (n=16, n=7)	13.9±1.7	12.8±1.5	N.S.
Vascular Stiffness			
cfPWV, (n=18, n=7)	9.48±1.68	8.00±1.58	0.057
Carotid pulse pressure (mmHg), (n=16, n=7)	53.5±15.5	56.9±19.9	N.S.
Compliance Coeff (mm^2/Kpa), (n=16, n=7)	0.466±0.160	0.646±0.531	N.S.
Distensibility Coeff (10^-3/Kpa), (n=16, n=7)	18.3±6.3	24.6±19.7	N.S.
Intimal-medial thickness (cm), (n=17, n=8)	0.086±0.020	0.093±0.025	N.S.
Physical Activity (Self-report questionnaire)			
Sedentary, % (n)	33 (6)	63 (5)	N.S.
Active, % (n)	50 (9)	38 (3)	N.S.
Highly Active, % (n)	17 (3)	0 (0)	N.S.

Past Health (Self-report questionnaire)			
Heart attack, % (n)	17 (3)	13 (1)	N.S.
Heart failure, % (n)	0 (0)	13 (1)	N.S.
Open heart surgery, % (n)	6 (1)	0 (0)	N.S.
Congenital heart disease, % (n)	0 (0)	0 (0)	N.S.
Atrial Fibrillation, % (n)	22 (4)	25 (2)	N.S.
Carotid stenosis, % (n)	6 (1)	0 (0)	N.S.
COPD, % (n)	11 (2)	0 (0)	N.S.
Hypertension, % (n)	39 (7)	25 (2)	N.S.
High cholesterol, % (n)	33 (6)	13 (1)	N.S.
Sleep Apnea, % (n)	6 (1)	0 (0)	N.S.
Emphysema/pneumonia, % (n)	0 (0)	25 (2)	0.086
Asthma/bronchitis, % (n)	0 (0)	13 (1)	N.S.
Kidney/liver disease, % (n)	6 (1)	38 (3)	N.S.
Smoking (never), % (n)	67 (12)	50 (4)	N.S.
Smoking (ex-smoker), % (n)	28 (5)	38 (3)	N.S.
Current Health (Self-report questionnaire)			
Irregular heart beat, % (n)	17 (3)	13 (1)	N.S.
Chest pain, % (n)	6 (1)	0 (0)	N.S.
Persistent cough, % (n)	0 (0)	13 (1)	N.S.
Wheezing/shortness of breath, % (n)	22 (4)	13 (1)	N.S.
Memory complaints, % (n)	17 (3)	0 (0)	N.S.
Fatigue (general) , % (n)	17 (3)	13 (1)	N.S.
Headaches, % (n)	0 (0)	0 (0)	N.S.
Dizziness/light-headedness, % (n)	28 (5)	13 (1)	N.S.
Any pain (all recorded lower back pain other than one person in poor group reported leg pain), % (n)	17 (3)	25 (2)	N.S.
Medications			
Aldosterone antagonist % (n)	6 (1)	25 (2)	N.S.
Alpha adrenoreceptor antagonist % (n)	6 (1)	25 (2)	N.S.
Angiotensin receptor blocker % (n)	11 (2)	25 (2)	N.S.
ACE inhibitor % (n)	17 (3)	13 (1)	N.S.
Beta blocker % (n)	28 (5)	25 (2)	N.S.
Calcium channel blocker % (n)	33 (6)	25 (2)	N.S.
Proton pump inhibitor % (n)	44 (8)	38 (3)	N.S.
Polypharmacy (≥ 3 different types of BP lowering meds) % (n)	11 (2)	25 (2)	N.S.

BMI body mass index, *BSA* body surface area, *TBW* total body water, *BP* blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *MAP* mean arterial pressure, *combined gait speed* equals the average of supine-walk and sit-walk gait speeds, *PWV* pulse wave velocity, *cfPWV* carotid-femoral PWV, *CPOD* chronic obstructive pulmonary disease, *ACE* angiotensin-converting enzyme, *N.S.* not significant (p≥0.1)

Table 4-2: Pearson Product-moment correlations between gait speed and gait characteristics

Gait Characteristic	Time	Supine-walk: r	Supine-walk: p-value	Sit-walk: r	Sit-walk: p-value
Mean gait cycle time	early	-0.553	0.003	-0.514	0.007
Mean stance time	early	-0.597	0.001	-0.561	0.003
Mean fractional stance time	early	-0.569	0.002	-0.595	0.001
Mean gait cycle time	late	-0.522	0.006	-0.638	0.000
Swing variability	late	0.419	0.037		N.S.
Mean stance time	late	-0.528	0.006	-0.688	0.000
Mean fractional stance time	late	-0.522	0.006	-0.574	0.002
SD fractional stance time	late	0.437	0.029		N.S.

SD standard deviation, *N.S.* not significant p>0.05.

Table 4-3: Correlations between vascular stiffness and cerebrovascular hemodynamics

Vascular Stiffness Characteristic	Cerebrovascular characteristic	Condition	Time	r-value	p-value	n
carotidPP	EDV	Supine-walk	Baseline	-0.527	0.030	17
cDC	MFV	Supine-walk	Baseline	0.503	0.040	17
cDC	EDV	Supine-walk	Early walk	0.511	0.036	17
cDBP	CVRi	Supine-walk	Early walk	0.582	0.037	13
cfPWV	Deox	Supine-walk	Early walk	-0.613	0.001	25
cDC	EDV	Supine-walk	Late walk	0.511	0.036	17
cfPWV	Deox	Supine-walk	Late walk	-0.663	0.000	25

EDV end diastolic velocity, *MFV* mean flow velocity, uration, *DeoxHb* deoxygenated hemoglobin, *PP* pulse pressure, *cDC* carotid distensibility coefficient, *cfPWV* carotid-femoral pulse wave velocity.

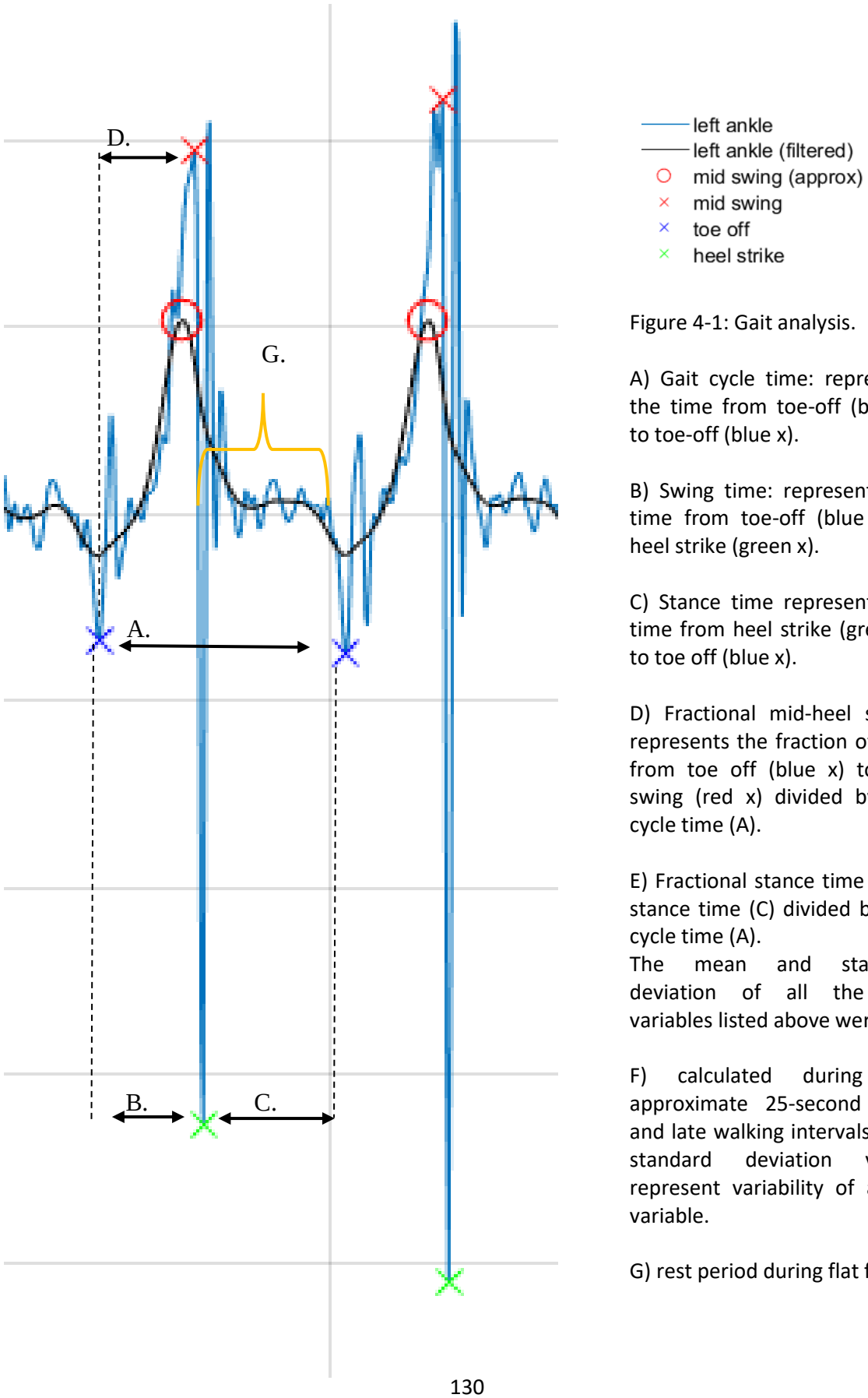


Figure 4-1: Gait analysis.

A) Gait cycle time: represents the time from toe-off (blue x) to toe-off (blue x).

B) Swing time: represents the time from toe-off (blue x) to heel strike (green x).

C) Stance time represents the time from heel strike (green x) to toe off (blue x).

D) Fractional mid-heel swing: represents the fraction of time from toe off (blue x) to mid swing (red x) divided by gait cycle time (A).

E) Fractional stance time is the stance time (C) divided by gait cycle time (A).
The mean and standard deviation of all the gait variables listed above were

F) calculated during the approximate 25-second early and late walking intervals. The standard deviation values represent variability of a gait variable.

G) rest period during flat foot

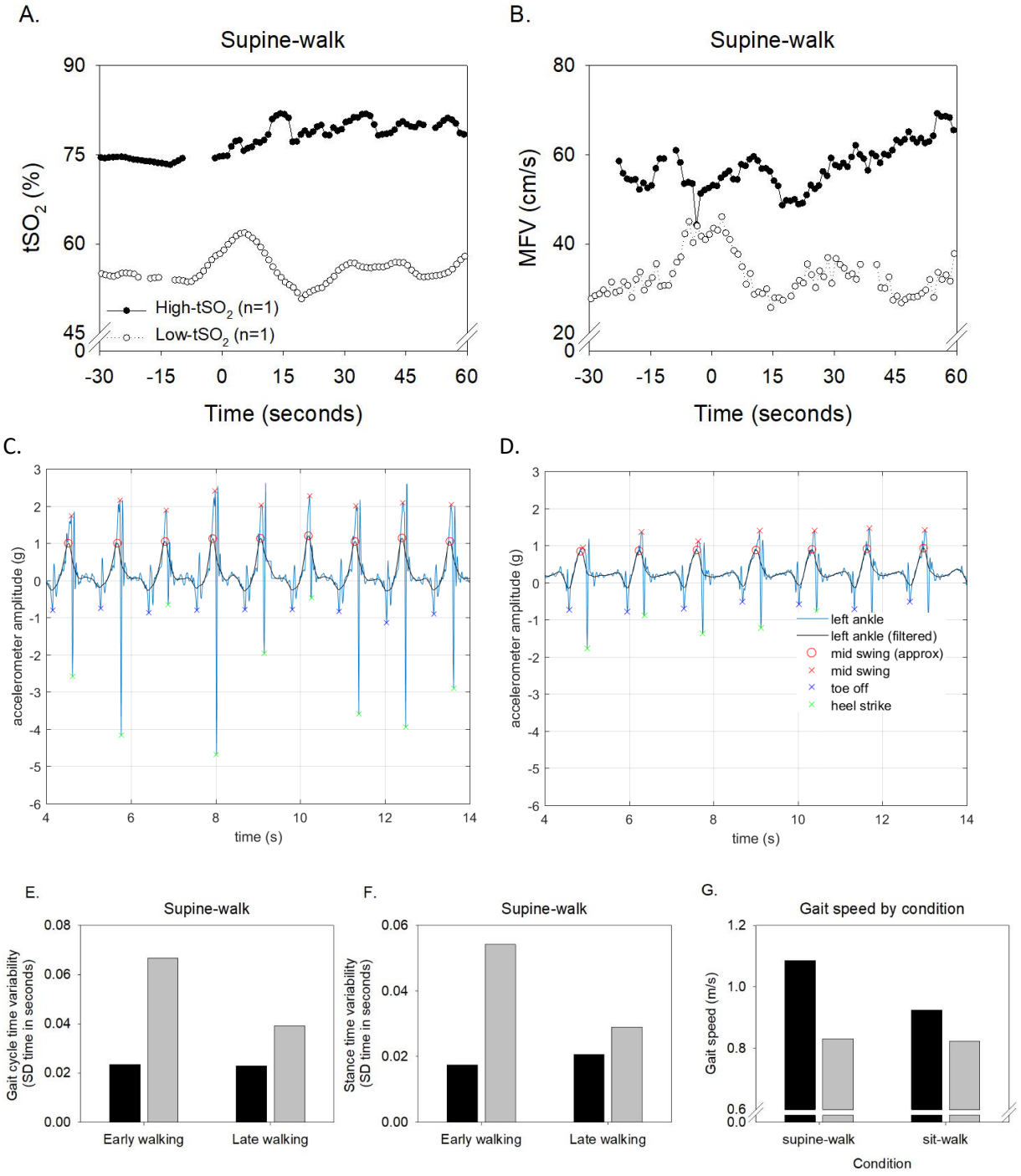


Figure 4-2: Cerebrovascular hemodynamics and gait dynamics in a single high- and low-tSO_2 participant. Cerebrovascular response, accelerometer monitored walking response, and calculated gait cycle time variability, stance time variability, and gait speed in a single high-tSO_2 participant and a single low-tSO_2 participant. Cerebral oxygenation (tSO_2, A) and cerebral mean flow velocity (MFV, B) responses to a supine-walk transition in a typical regulator and impaired-regulator. Raw summation and filtered data from the 3-axis accelerometer are shown for individuals in the high-tSO_2 group (C) and low-tSO_2 group (D) during the late period walking for the supine-walk transition. Resulting values for these two individuals (high-tSO_2 group, black bars and low-tSO_2 group, grey bars) are shown for

gait cycle time variability (E) and stance time variability (F) during the supine-walk condition for both early and late walking, as well as gait speed (G) during the two difference conditions.

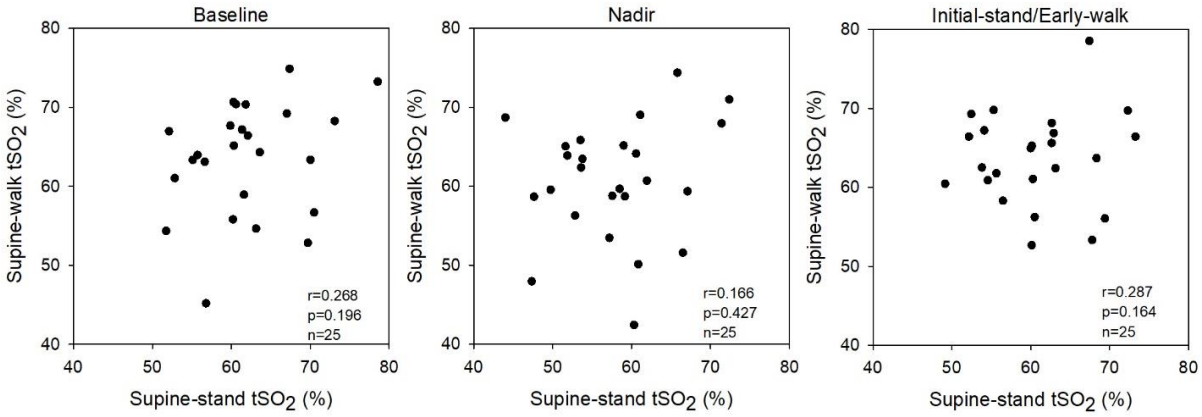
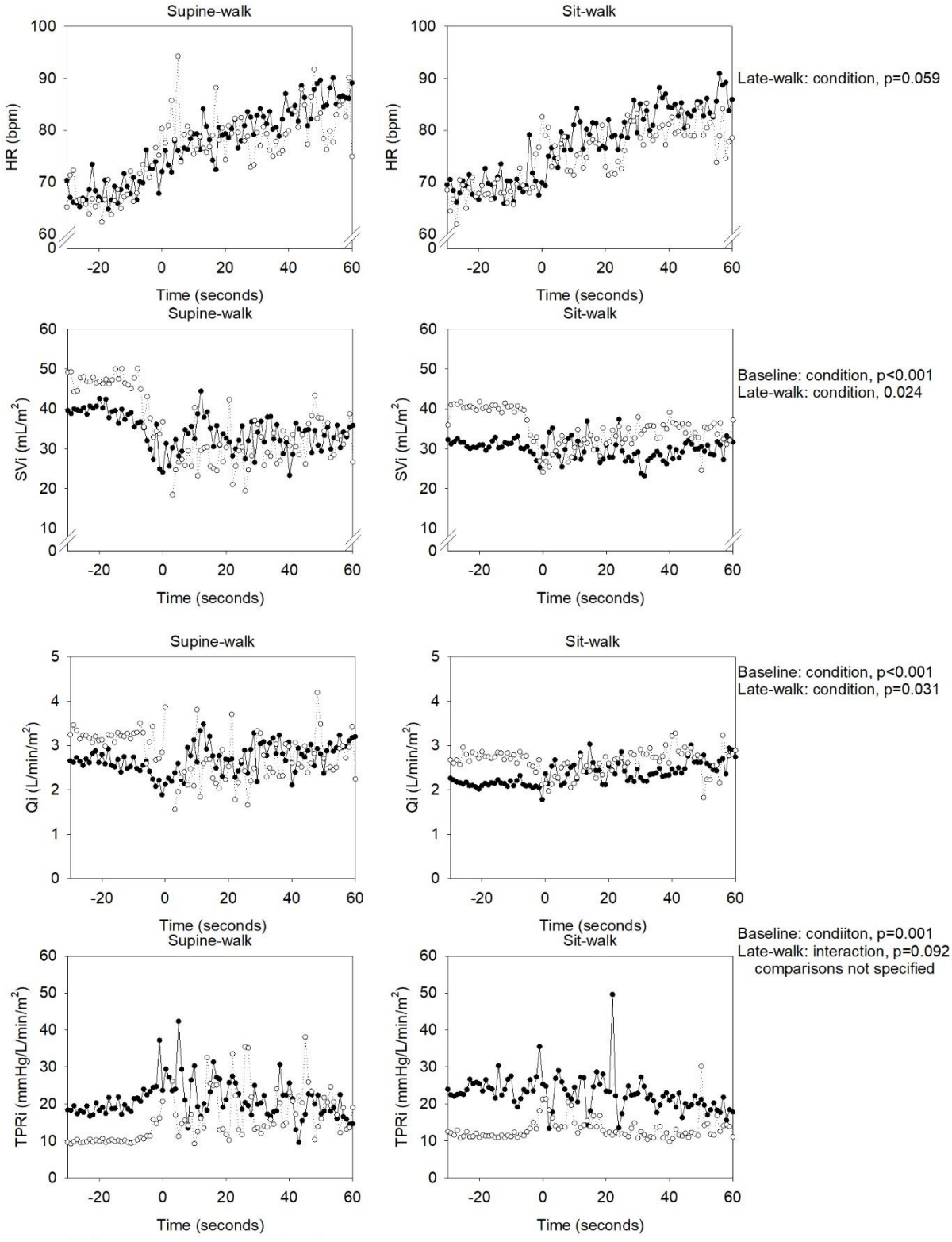


Figure 4-3: Between experiment comparisons of cerebral oxygenation. Pearson Product-moment correlations were run between two experiments, the supine-stand for these same individuals measured during the previous study (Chapter 3) and the supine-walk. Baseline value represents a 30-second supine resting average, nadir marks the lowest 3-beat (supine-stand) or 1-beat (supine-walk) value following the posture transitions, initial stand is a 20-second average from 2 to 22 seconds after upright posture (supine-stand), early walk is ~25-second average starting from the beginning of the fourth step (supine-walk). One participant was removed from the between experiment correlation analysis as they were an extreme outlier from switching off of 2 different blood pressure lowering medications.


Supine-walk
Sit-walk
HR (bpm)
Time (seconds)
Late-walk: condition, p=0.059
SVi (mL/m2)
Baseline: condition, p<0.001
Late-walk: condition, 0.024
Qi (L/min/m2)
Baseline: condition, p<0.001
Late-walk: condition, p=0.031
TPRi (mmHg/L/min/m2)
Baseline: condiiton, p=0.001
Late-walk: interaction, p=0.092
comparisons not specified

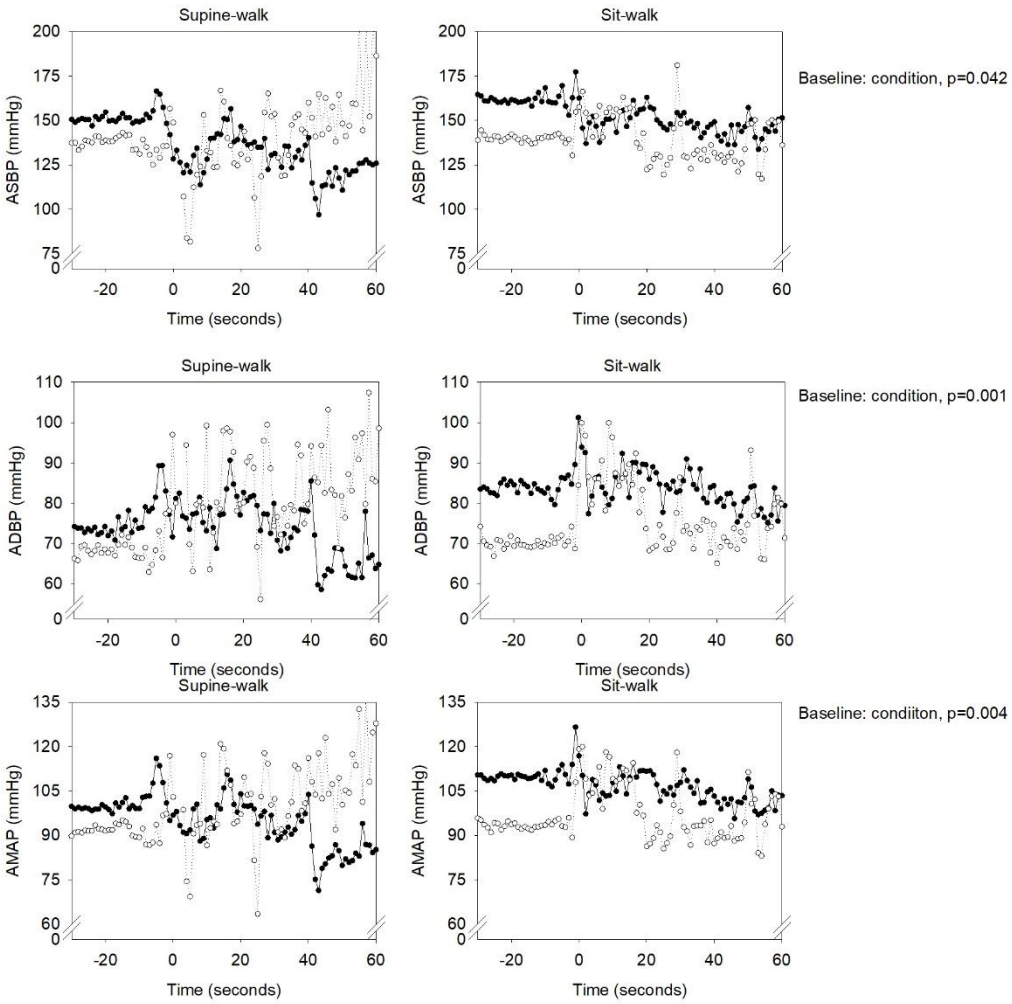
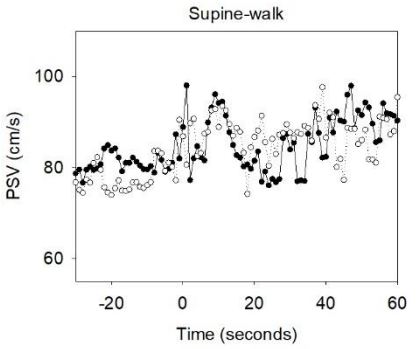
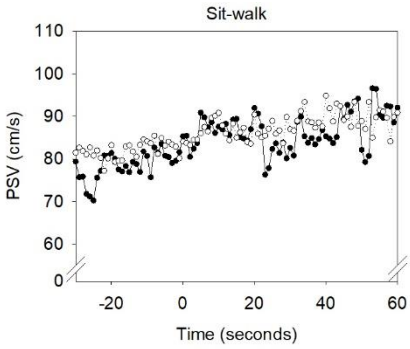
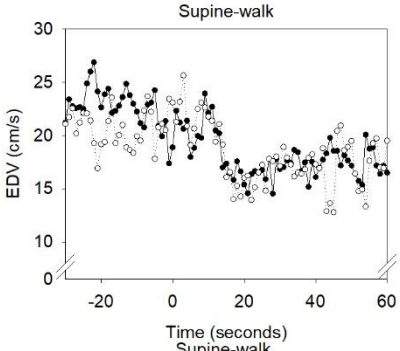
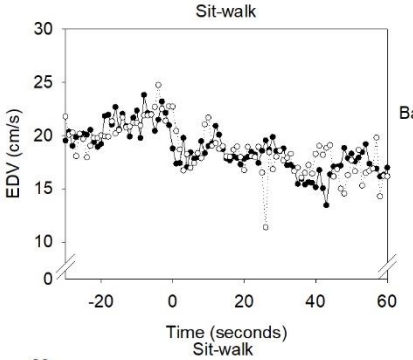


Figure 4-4: Cardiovascular responses to a supine-walk and sit-walk transition. Time at zero marks the first toe-off ankle movement, negative time represents rest and active transition. Black filled circles mark mean values of second-by-second data of high-tSO_2 group (HR: n=18; SVi, Qi, TPRi: baseline n=13, nadir n=4, early and late walk n=13, BP: baseline n=14, nadir n=5, early and late walking n=14); white circles mark the postural response of the low-tSO_2 group (HR: n=8; SVi, Qi, TPRi, BP: baseline n=7, nadir n=2, early and late walk n=5). *MAP* mean arterial pressure, *Qi* cardiac output index, *SVi* stroke volume index, *TPRi* total peripheral resistance index, *N.S.* not significant p>0.1

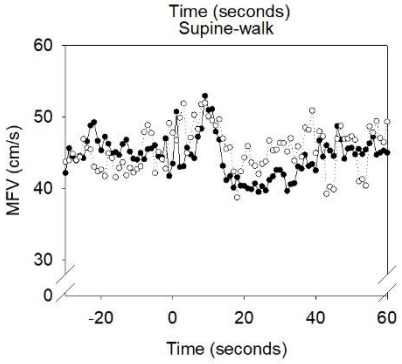


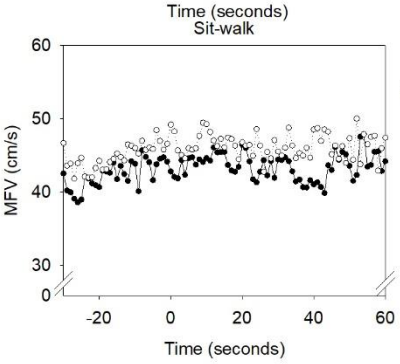




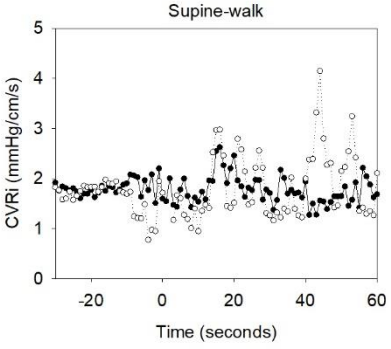


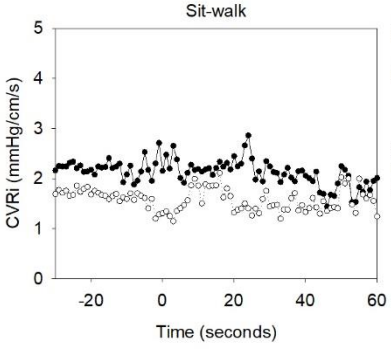
Baseline: condition, p=0.021





Baseline: condition, p=0.073





Baseline: interaction, p=0.012
sit-walk: regulators vs. impaired-regulators
Early-walk: condition, p=0.097

NOTE:
PI - Baseline: condition, p<0.001
RI - Baselien: condition, p=0.002

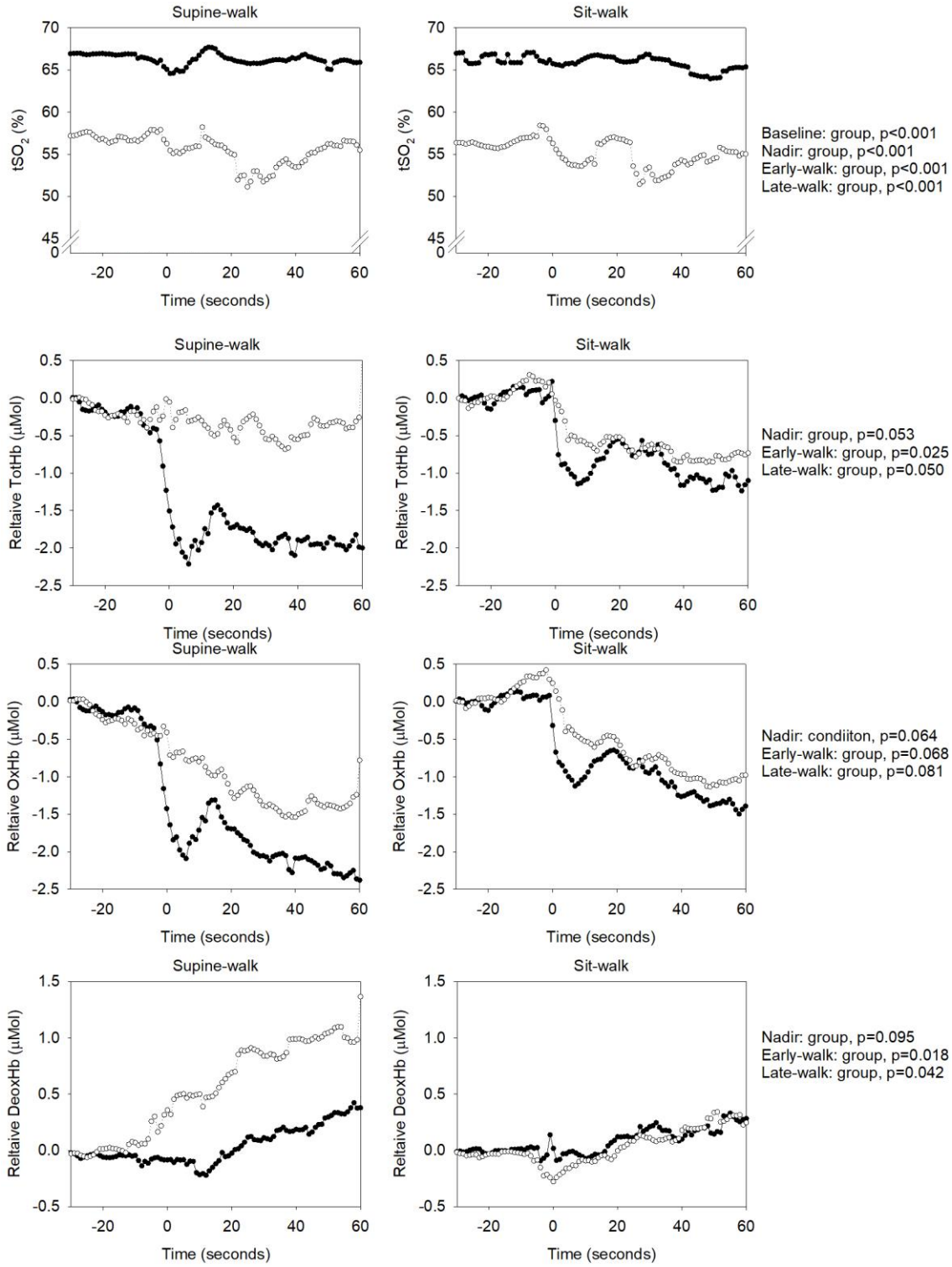


Figure: 4-5: Cerebrovascular responses to a supine-walk and sit-walk transition. Time at zero marks the first toe-off ankle movement, negative time represents rest and active transition, positive time represents walking. Black filled circles mark mean values of second-by-second data of high-tSO_2 group (NIRS data n=18, CBF data: baseline n=10, nadir n=5, early and late walking n= 11); white circles mark the postural response of the low-tSO_2 group (NIRS data n=8, CBF data: baseline n=6, nadir n=2, early and late walking n=5. *PSV* peak systolic velocity, *EDV* end diastolic velocity, *MFV* mean flow velocity,

CVRi cerebrovascular resistance index, *tSO_2* cerebral tissue saturation, *TotHb* total hemoglobin, *OxHb* oxygenated hemoglobin, *DeoxHb* deoxygenated hemoglobin

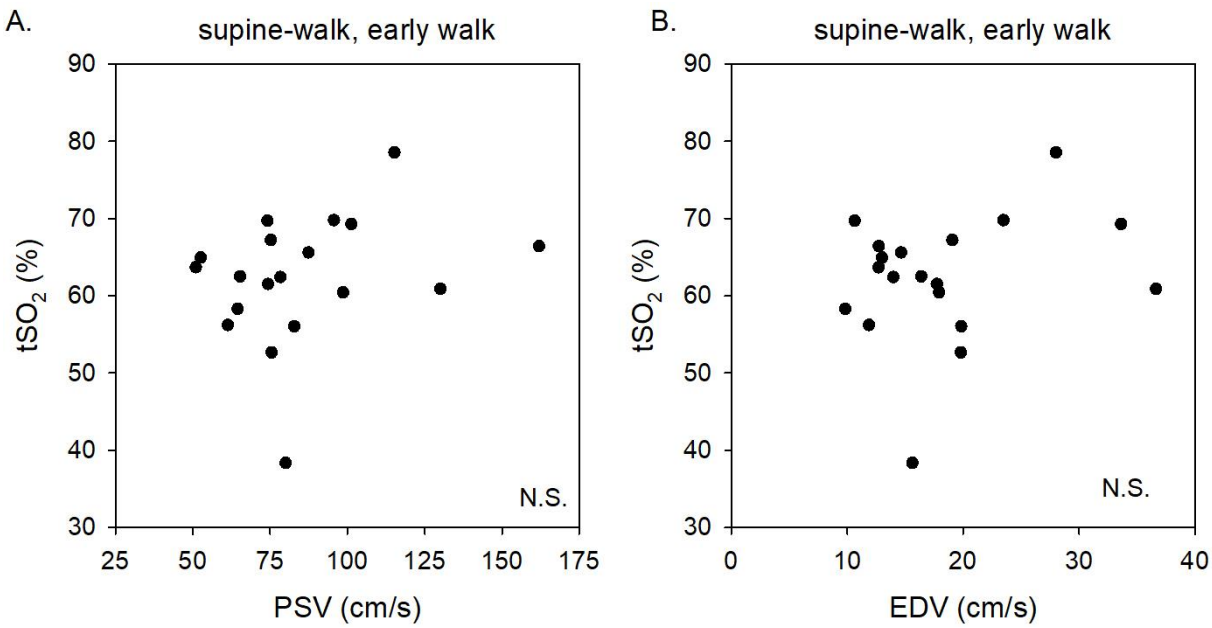


Figure 4-6: Cerebral blood flow and oxygenation. Pearson Product-moment correlations between TCD and cerebral oxygenation (tSO_2) during supine-walk condition. *PSV* peak-systolic velocity, *EDV* end-diastolic velocity,

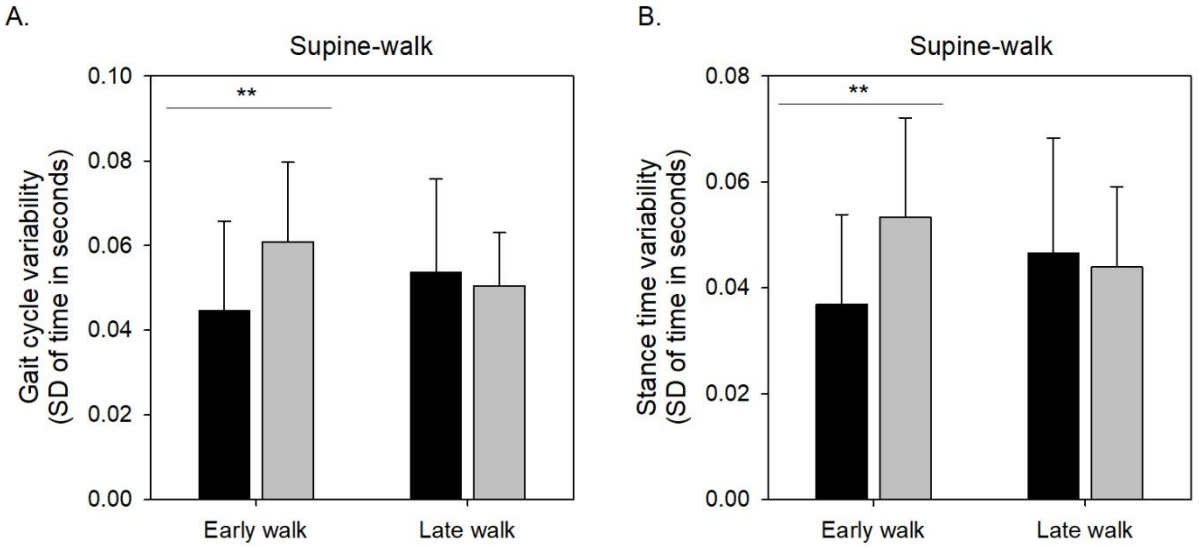


Figure 4-7: Gait variability between groups. Gait cycle variability (A) and stance time variability (B) during early and late walking of a supine-walk transition (p=0.037 and p=0.008 respectively). Black filled bars mark mean values and standard deviation data of the high-tSO_2 group (n=17); grey bars mark mean values and standard deviation data of the low-tSO_2 group (n=7).

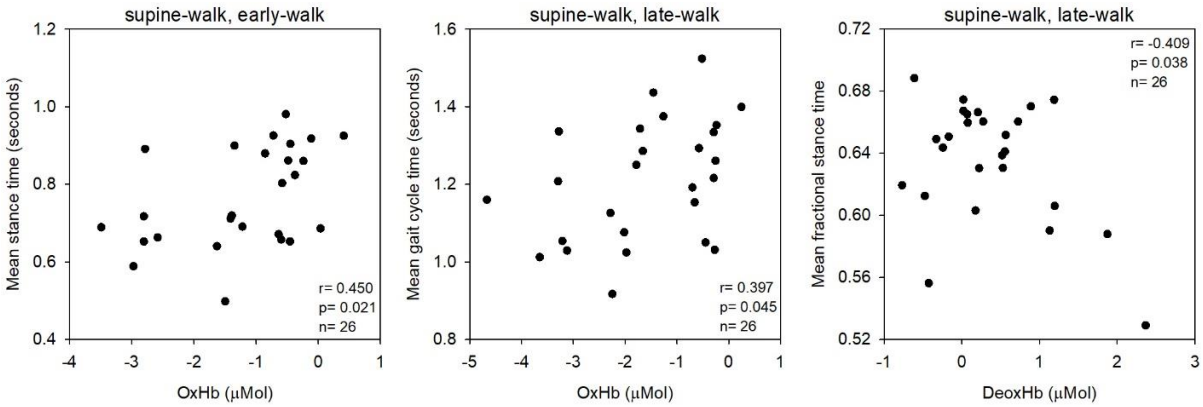


Figure 4-8: Cerebral oxygenation and gait dynamics. Pearson Product-moment correlations between cerebrovascular hemodynamics and gait characteristics during the supine-walk condition. *OxHb* oxygenated hemoglobin, *DeoxHb* deoxygenated hemoglobin

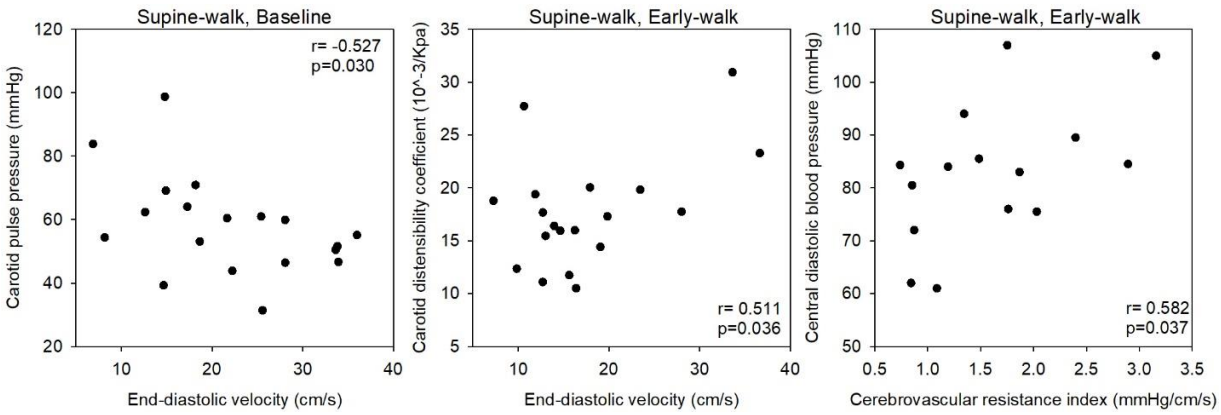


Figure 4-9: Cerebrovascular hemodynamics and vascular stiffness. Pearson Product-moment correlations between vascular stiffness and cerebrovascular hemodynamics.

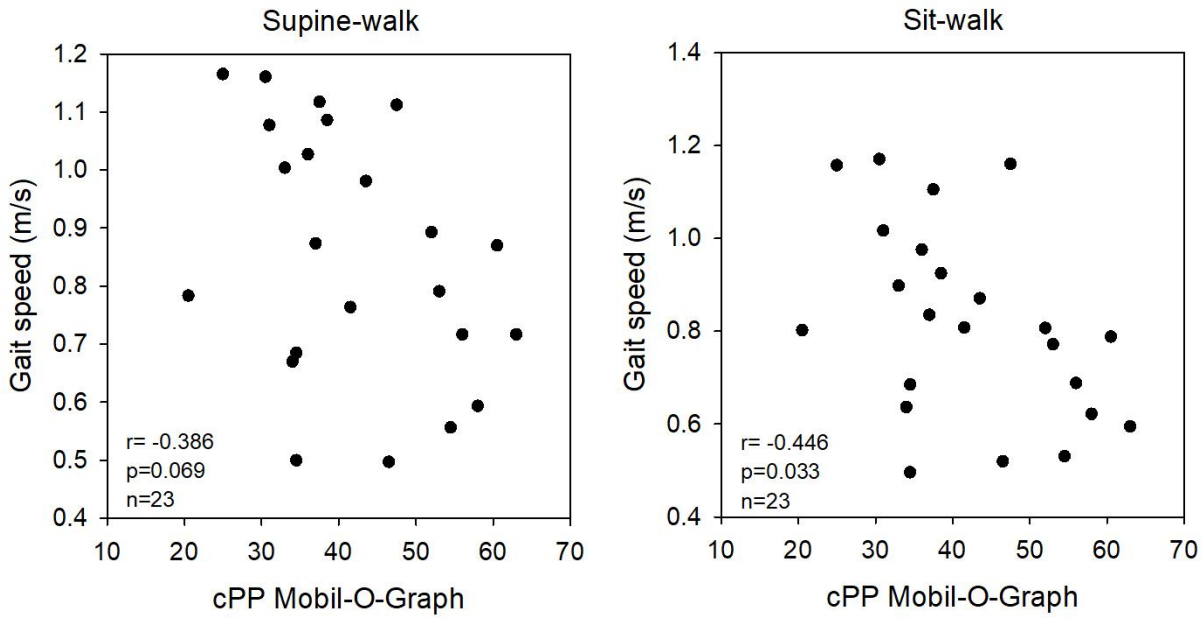


Figure 4-10: Vascular stiffness and gait speed. Pearson Product-moment correlations between gait speed (supine-walk and sit-walk conditions) and central pulse pressure (cPP, units mmHg) from the Mobil-O-Graph.

CHAPTER 5. GENERAL DISCUSSION

It is estimated that a third of older adults fall each year (Tromp *et al.* 2001), having devastating impacts on a person's quality of life (Statistics Canada 2011b) (Cumming R.G. *et al.* 2000). Although the causes of falls are multifactorial, orthostatic hypotension is considered an independent risk factor for future falls, unexplained falls and injurious falls (Finucane C. *et al.* 2017). Posture related reductions in BP and CBF typically recover in a supine to stand maneuver within 30-s however in some older adults BP does not fully recover (Romero-ortuno R. *et al.* 2011) and thus cerebral perfusion may not be maintained. Yet the relationships between CBF and oxygenation (tSO_2) to postural control, gait dynamics and fall history have not previously been investigated. This thesis examined i) the cerebrovascular response to various posture transitions while simultaneously recording measures of postural stability as well as ii) the relationships between cerebrovascular hemodynamics and gait strategies during different transitions into walking. Measures of vascular stiffness were a part of this thesis to identify if stiffer vessels, indicative of vascular aging (Laurent S. 2012; Mitchell GF 2008; Webb A.J. *et al.* 2012), are related to cerebral hypoperfusion and compromised gait characteristics. Retrospective and prospective fall history reports were also collected for both studies to identify any relationships between cerebral hypoperfusion and falls in older adults. A supplementary component of this thesis was a proof of principle study in young adults whereby manipulating both arterial blood pressure and CBF velocity (CBFV) allowed the quantitative assessment of changes in postural stability as a function of tSO_2.

Primary Findings

Posture related reduction of tSO_2 during a supine-stand transition in older adults (69-100 years old) resulted in varied responses (Chapter 3). A sub-population of older adults (impaired-regulators) demonstrated greater posture related reduction of tSO_2 and reduced postural stability

compared to older adults (regulators) with higher levels of tSO_2 upon standing (Figure 3-4). It was also found that when going from supine to standing, a 10-s sitting pause time was enough time to improve tSO_2 and postural stability in older adults from the sub-population with hypoperfusion (Figure 3-4). The prospective 6-month falls follow-up revealed that older adults with lower tSO_2 upon standing had a trend for increased risk of a future fall (4 of 15 participants had a fall) compared to older adults with a higher tSO_2 (6 out of 62 participants had a fall).

When transitioning from a supine position into walking (Chapter 4) older adults (71-101 years old) demonstrated varied tSO_2 recovery responses. A sub-population of older adults was identified to have lower tSO_2 (Figures 4-2 and 4-5) during walking and these same individuals had increased step-step variability (Figures 4-7), a predictor of falls in older adults (Callisaya M.L. *et al.* 2011). Associations between increased arterial stiffness with reduced CBF and slower gait speeds were established.

Rationale for intervention study in young adults

The associations reported in Chapters 3 and 4 between cerebral oxygenation, postural stability and gait characteristics suggested that reduced delivery of oxygen to the brain was associated with poorer stability and gait patterns. It was not possible to manipulate cerebral oxygen delivery in these older adults, so a supplementary study (Supplement) was conducted to test this association. With the application of a double-thigh cuff occlusion and hyperventilation, CBFV was quantifiably reduced in young adults (20-33 years old) during a transition to standing posture. The magnitude of change of CBFV was assessed alongside changes in postural stability. Not all participants responded to the stimulus in the same way which allowed for a group comparison. Individuals who had significantly and progressively lower CBF (marked by increased CBFV deficit) across conditions, also had significantly and progressively poorer measures of postural stability across conditions (Figure S-5). The

findings from the supplementary study in young adults can be extended to the results involving older adults (Chapters 3 and 4). Quantifiable reductions in CBF follow the same time course and magnitude of reduced postural stability in young adults. Therefore, data obtained from the young adults can be used to interpret the associations made between cerebral hypoperfusion with reduced postural stability and compromised gait patterns in older adults.

Significance

The causes of falls are multifactorial however the associations of cerebral hypoperfusion to postural instability and increased step-step variability is a novel finding and the literature implicates poor balance control to an increased risk of having a future fall in older adults (Muir S.W. *et al.* 2010; Berg K.O. *et al.* 1992; Callisaya M.L. *et al.* 2011). Falls in older adults can contribute up to 85% of all injury-related hospitalizations, 40% of nursing home admissions and approximately 20% of deaths due to injury (Statistics Canada 2011b). Falls also impact balance confidence and fear of falling leading to reduced involvement in activities, further reducing strength and flexibility and increasing fall risk and lowering quality of life (Cumming R.G. *et al.* 2000).

A secondary consequence of cerebral hypoperfusion is its impact on cognition. Young adults (29±7 years old) with hypotension have demonstrated longer execution times during attentional tasks, reductions in accuracy during sustained attention tasks and working memory tasks compared to normotensives (Duschek S. *et al.* 2005). Hypotensive older adults who additively experience orthostatic hypotension demonstrate increased odds of having a cognitive impairment (Yap P.L. *et al.* 2008). Mild cognitive impairment and dementia have been shown to predict reduced quality of life in older adults (Kuo L.M. *et al.* 2017). Thus, older adults with cerebral hypoperfusion, such as the participants in the sub-population of the current investigations, may be at risk of cognitive impairment and compromised quality of life.

It is noteworthy to point out that although not significant, when separating participants based on a cut off of $tSO_2 \leq 60\%$ while walking, the low-tSO_2 group had a lower tSO_2 at baseline, nadir and during initial standing and late walking (Figure 5-1). Similarly, there were trends for reduced cSBP and significantly reduced cDBP in the low-tSO_2 group (Figure 5-2). This suggests that even though the criteria to split participants between experiments differed and regressions between experiments were not significant (Figure 4-3), both experiments yielded similar results of a reduced tSO_2 in one of the groups.

Finally, during the supine-walk experiment (Chapter 4) older adults with reduced tSO_2 had increased step-step variability (Figure 4-7) and had increased OxHb (Figure 4-5). Older adults with increased OxHb also had increased mean stance time and mean gait cycle time (Figure 4-8). Increased gait cycle time and mean stance time were significantly correlated to slower gait speed (Table 4-2). It was also found that older adults with stiffer arteries had lower CBF while walking and slower gait speeds. Increased vascular stiffness has been associated with reduced CBFV, increased vascular resistance (Robertson A.D. *et al.* 2010a), cerebral small vessel disease (Henskens L.H. *et al.* 2008) as well as cognitive impairment and cognitive decline (Zeki Al Hazzouri A. *et al.* 2013). Although the relationship between reduced CBF and tSO_2 were not directly linked to reduced gait speed, these findings suggests older adults with lower tSO_2 are more likely to have compromised gait strategies which is associated with increased likelihood of having a future fall. Furthermore, older adults who have reduced tSO_2 and higher OxHb with walking are more likely to have advanced vascular aging which is associated with reduced CBF, slower gait speed, and according to the literature an increased likelihood of cognitive impairment and a decline in quality of life (Zeki Al Hazzouri A. *et al.* 2013).

Limitations

Some limitations to this thesis are:

i) The studies involving older adults were under powered and this was in part due to the large variation in cerebrovascular and cardiovascular responses to a posture transition in older adults. Despite including n=77 and n=27 participants the low sample sizes increased the likelihood of making a type II error.

ii) The nature of a cross-sectional study design prevents conclusions to be made on causal relationships. Therefore, it cannot be established that cerebral hypoperfusion is causing impaired stability or increased gait variability but rather associations are made.

iii) The exclusion criteria rejected any participants who had a stroke, diabetes, neurological or neuromuscular disorder. These boundaries limit the generalizability of the results as the participant sample included no longer represents population norms.

iv) The prevalence of fallers reported (Chapter 3: 10% retrospectively, 13% prospectively, Chapter 4: retrospectively 15%, prospectively 26%) are lower than population studies report (33.3%) (Tromp *et al.* 2001), therefore falls may be underestimated or the population that volunteered to participate in this study was a generally healthier group of older adults than previously reported.

v) The study protocols involved only a single performance of each condition all taken on a single day/time of day, where the orthostatic responses are known to be variable; this suggests a different response could be rendered on a different day/time (Vara-Gonzalez L. *et al.* 2006).

vi) Cerebral blood flow velocity was not collected on the n=77 participants (Chapter 3); this limited conclusions to be made on tSO_2 among experiments. Cerebral blood flow velocity

is a qualitative indicator of cerebral blood flow that can be affected by variations in diameter of the middle cerebral artery.

vii) It was not possible to monitor arterial or end-tidal CO_2 during the older adult studies. As CO_2 plays a major role in regulation of CBF, this is an important limitation, and it is not known how hyperventilation might have contributed to cerebral hypoperfusion.

viii) Potential neuromuscular contributions to gait speed and variability were not measured in the current study; it is possible that these factors contributed independently to between group differences. The low tSO_2 observed in some participants in this study might have reflected a chronic cerebral hypoperfusion which could have independently affected neural gait control.

ix) Other mechanisms, such as i) an insufficient muscle pump and thus reduced SV ii) impaired baroreflex regulation and iii) monitoring of CBF in areas of the brain not fed by the middle or anterior cerebral artery, were not evaluated and could influence cerebral hypoperfusion data.

x) The estimated SV calculated by the Modelflow algorithm of the plethysmography devices integrates a three-element model of arterial impedance with the arterial pressure wave to reliably track beat-to-beat differences in stroke volume during rest (Harms M *et al.* 1999). However, recent data suggests the Modelflow method does not accurately estimate SV during dynamic fluctuations in SV, such as during orthostatic stress (Gibbons T. 2017).

Future directions

The supine-stand and supine-walk experiments (Chapters 3 and 4) could be extended to include a larger sample size, $P_{ET}CO_2$ collection, as well as CBFV for the supine-stand experiment. By collecting a larger sample size more relationships among cardio- and cerebrovascular measures could

be better understood; For example, a larger sample size in Chapter 4 would allow further investigation of changes in BP and SV. Gathering additional information of SV to the current walking results (Figure 4-4) would lend further insight about muscle pump activity and BP regulation. The gained knowledge by adding $P_{ET}CO_2$ would help identify why some participants experienced hypoperfusion. Providing a second measure of cerebral perfusion (CBFV) to the supine-stand experiment would allow for supplementary comparisons between experiments and assist in strengthening any current findings as CBFV is widely used and is a highly studied marker of CBF in the literature. New technologies such as three-dimensional ultrasound imaging could be added to assist in diagnosis of vascular abnormalities associated with aging (ex. Stenosis and turbulent flow patterns). These additions to the current thesis would confirm the tentative conclusions already established and expand on understanding the underlying mechanisms associated with cerebral hypoperfusion.

The sit-stand and sit-walk conditions (Chapters 3 and 4) appear to be somewhat protective to tSO_2 reductions in comparison to the supine to stand or walk tests (Figures 3-3 and 4-5). Tukey's HSD test indicated that the sit-stand condition was the only condition which did not have group differences in delta tSO_2 (Figure 3-4). Although not significant, the sit-walk condition demonstrate similar NIRS signal responses between groups and group differences in gait variability were only evident during the supine-walk condition. A future direction of work would be to i) investigate the mechanism for increased tSO_2 during the sit conditions, ii) investigate if the lower tSO_2 impacts cognition, and iii) investigate other modalities to increase tSO_2 in a similar fashion (e.g. apply external leg compression or provide a hyperoxic environment). These latter experiments could extend into the study of younger adults in the Supplement to determine if acute changes in cerebral oxygenation could impact postural stability.

The older adults with low tSO_2 in Chapter 3 had a significantly higher prevalence of HF. HF has been associated with lower levels of CBF velocity (Loncar G. *et al.* 2011) and significantly greater

reductions in CBF velocity while upright compared to age and sex matched controls (Fraser K.S. *et al.* 2015). Therefore, this may be a sub-population of participants who are at increased risk of cerebral hypoperfusion with upright posture (both standing and walking) and at increased risk of postural instability and/or increased step-step variability. Therefore, future work should be directed towards investigating the relationships between cerebral hyoperfusion, gait strategies, falls and cognition in individuals with HF.

Analysis on the supine-walk experiment could be extended to investigate delta responses between early and late walking (cerebrovascular hemodynamics and gait strategies) as well as using functional data analysis to compare i) CBFV and tSO_2 and ii) cerebral perfusion and step-step variability on a continuum versus using discrete data points seen in the current thesis.

Future studies could also be extended to testing stability once a participant has already invoked cerebral hypoperfusion; for example, during a double thigh cuff plus hyperventilation condition a perturbation could be exerted 2-s after upright posture has occur. This would test the ability of a participant to maintain postural stability in light of cerebral hypoperfuion. Likewise, for an older adult following 1-minute of walking a stand test could be performed to evaluate postural stability following extended upright posture experience cerebral hypoperfusion.

General Conclusions

When transitioning to standing or walking, older adults demonstrated varied cerebrovascular responses. Older adults with significantly lower cerebral oxygenation had poorer postural stability, increased step-step variability and an increased likelihood of having a future fall. A brief sitting-pause time before standing can improve cerebral oxygenation and postural stability. Older adults with stiffer arteries have lower CBF and altered cerebrovascular hemodynamics while walking as well as reduced gait speed. In a supplementary study, intentional manipulation of CBFV in the young healthy adults

provided evidence of a link between tSO_2 and postural instability providing supportive evidence that postural instability in the older adults might have been caused by the lower tSO_2 and CBFV. In conclusion, this research found significant relationships between cerebral hypoperfusion, postural instability and compromised gait strategies. These changes might be placing some older adults at an increased risk of a future fall.

Tables and Figures

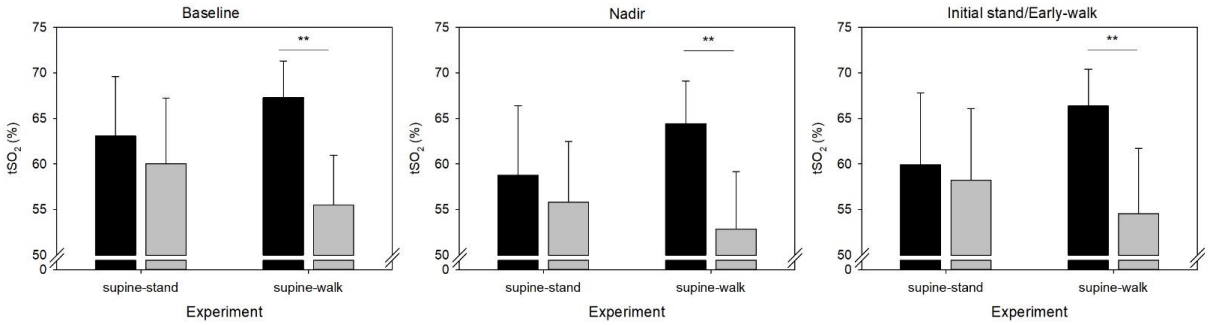


Figure 5-1: Comparison between experiments for cerebral oxygenation (tSO_2) values at baseline, nadir and upright standing/walking. Participants in the current graph are from the supine-walk experiment (Chapter 4). However, the tSO_2 values are from baseline, nadir and initial-standing of the supine-stand condition (Chapter 3) and the baseline, nadir and early-walking tSO_2 values form the supine-walk condition (Chapter 4). The classification of high- and low-tSO_2 groups used in the supine-walk experiment (Chapter 4) was used again here for between experiment comparisons. Black filled bars mark mean values and standard deviation data of high-tSO_2 group (baseline and nadir: n=17, initial stand/early-walk n=18); grey bars mark mean values and standard deviation data of the low-tSO_2 group (n=8). Mixed model repeated measures ANOVA revealed a significant interaction for baseline, nadir and initial stand/early-walk ($p=0.012$, $p=0.034$ and $p=0.009$ respectively). Tukey's HSD identified significant ($p<0.05$) differences are between the high- and low-tSO_2 groups during the supine-walk condition (marked by **).

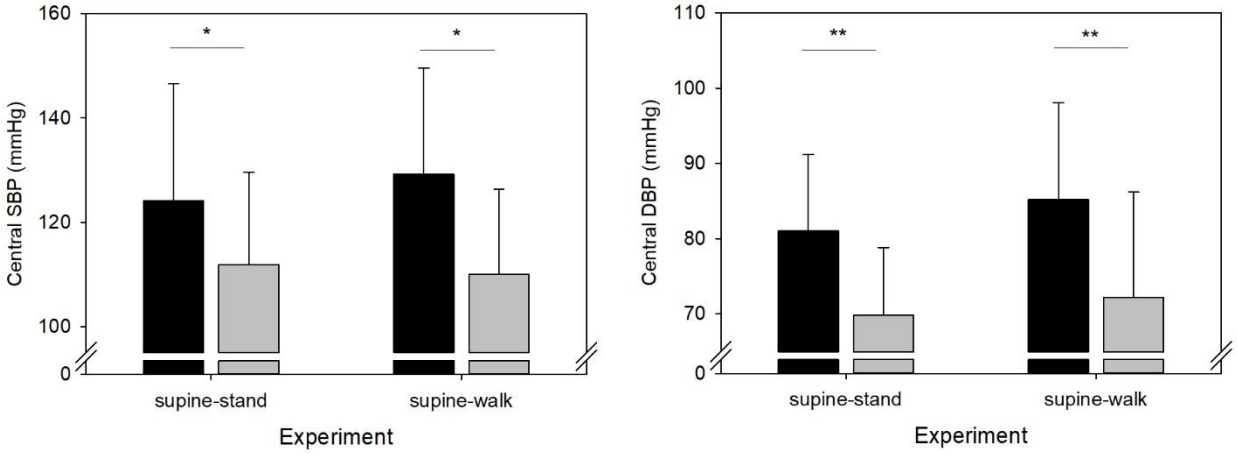


Figure 5-2: Between experiment comparisons for central blood pressure. Central systolic and diastolic blood pressure (cSBP, cDBP) during supine rest of the supine-stand (Chapter 3) and supine-walk (Chapter 4) experiments. Participants in the current graph are from the supine-walk experiment (Chapter 4). However, the tSO_2 values are from baseline, nadir and initial-standing of the supine-stand condition (Chapter 3) and the baseline, nadir and early-walking tSO_2 values form the supine-walk condition (Chapter 4). The classification of high- and low-tSO_2 groups used in the supine-walk experiment (Chapter 4) was used again here for between experiment comparisons. Black filled bars mark mean values and standard deviation data of high-tSO_2 group (n=15); grey bars mark mean values and standard deviation data of the low-tSO_2 group (n=7). Mixed model repeated measures ANOVA revealed a trend for cSBP to have group differences (p=0.067, marked as*) and cDBP to have a significant group difference (p=0.017, marked as **).

SUPPLEMENT. Acute reductions in cerebral blood flow affect postural stability in young adults

Introduction

The transition from supine to standing posture causes a transient, sometimes substantial, reduction in blood pressure (BP) (Franke W.D. *et al.* 2006). In the Irish Longitudinal Study on Aging with 4475 adults over 50 years of age, initial orthostatic hypotension was found in 33% of the population, and orthostatic hypotension increased in prevalence from 7 – 18% as the population aged (Finucane C. *et al.* 2014) Importantly, impaired BP stabilization, requiring longer than 30s, also increased with age to over 40% (Finucane C. *et al.* 2014). Although cerebrovascular autoregulation is largely effective in restoring cerebral blood flow (CBF) with transitions from supine to upright posture (Lipsitz L.A. *et al.* 2000), acute and prolonged reductions in BP on standing might be associated with cerebral hypoperfusion (Edlow B.L. *et al.* 2010; Mehagnoul-Schipper D.J. *et al.* 2000b; Gutkin M. & Stewart J.M. 2016). A reduction in CBF large enough to cause postural instability is alluded to in the literature (Shaw B.H. & Claydon V.E. 2014; van Wijnen V.K. *et al.* 2017; Lipsitz L.A. 1985; Hossain M. *et al.* 2001; Shaw B.H. *et al.* 2015) yet the direct link between changes in cerebral oxygenation and changes in postural control have not been investigated.

Impaired postural control might be related to regulation of BP and CBF as suggested by the observation that both elevated and low levels of resting supine systolic BP are independent risk factors for postural instability during quiet standing (Maciaszek J. *et al.* 2011). A period of hyperventilation increased postural sway (Sakellari V. & Bronstein A.M. 1997); this observation was probably related to reduced CBF, but no measurements were made of CBF or oxygenation (Sakellari V. & Bronstein A.M. 1997).

To test a direct link between cerebral perfusion and postural stability, a repeated measures design was employed in the current study where three transitions from supine rest to standing were

compared. The control condition had a rest to standing with no intervention. An additional challenge to BP regulation on standing was provided by 3-min bilateral thigh cuff deflation during the transition to standing. A third challenge added a period of hyperventilation during the supine period with thigh cuff occlusion, both of these interventions were stopped with standing. It was hypothesized that CBF would decrease on standing with greater reductions after the thigh cuff manipulation and the thigh cuff plus hyperventilation, and that a critical level of CBF deficit would be associated with increases in postural instability.

Materials and methods

Participant Description

Nineteen healthy young adults (10 females; age 26±4 years; height 172±6 cm; weight 71±13 kg) gave written and informed consent to volunteer in the present study which was reviewed and approved by the Office of Research Ethics at the University of Waterloo. Participants were asked to refrain from exhaustive exercise and alcohol for 24 h before testing and caffeinated beverages for 12 h before testing. Participants arrived 2 h postprandial to testing where they completed a brief health questionnaire. The health questionnaire indicated that all participants were free of cardiovascular disease, 18 participants had never smoked (1 participant smoked 2 cigarettes/week) and 17 of the participants were active on a regular basis (minimum of 1-2 days/week). Total body water (TBW) was estimated using a body impedance analysis (MF-BIA QuadScan 4000: Bodystat LTD, Isle of Man, UK) with electrodes placed on the right wrist, middle finger, ankle and toe with the participant in a supine position and arms and legs abducted from the body (Sun S.S. *et al.* 2003).

General Protocol

All participants randomly completed three supine-stand transitions: i) control (CON), ii) thigh cuff deflation (TC), iii) thigh cuff deflation with hyperventilation (TC-Hyp). The three transitions were preceded by a practice transition (condition iii) to ensure tolerance of the test. All transitions began with 10 min of supine rest, followed by a transition into the standing position with an assist to place the feet correctly for measurement of stability. Participants stood with feet together for 90 sec. Upon completion of the standing protocol participants were asked to rate their perceived pre-syncopal symptoms, if any, during the first 30 sec of standing. The pre-syncope symptoms were presented on a visual analog scale of 1 to 10 (1: no symptoms, 10: intolerable) for dizziness, visual or hearing disturbances, sweating, nausea, neck, back or precordial discomfort, palpitations, and fatigue (Lewis N.C. *et al.* 2013; Thomas K.N. *et al.* 2009). Cerebrovascular reactivity to carbon dioxide (CrCO2) was randomly conducted either before or after the completion of the posture transitions and the order of hypercapnic versus hypocapnic conditions was randomized.

Double thigh cuff condition - The bladders of the thigh cuffs were placed over top of the femoral artery and inflated to 20mmHg above resting supine systolic BP for 3 min (Kaya S. *et al.* 2011; Tiecks F.P. *et al.* 1995). At the end of the 3 min inflation, during the transition from supine to standing, rapid deflation was achieved by a quick release valve.

Double thigh cuff and hyperventilation condition - In addition to a double thigh cuff inflation/deflation protocol (above), participants were asked to hyperventilate for the final 90 sec of the supine thigh cuff inflation. Participants were asked to hyperventilate at 30 breaths/min and they were coached to alter the depth of their breaths to achieve a reduction in $P_{ET}CO_2$ of approximately 10 mmHg (Coverdale N.S.

et al. 2014). Participants were asked to breathe normally upon the commencement of the posture transition.

Hemodynamics

Continuous monitoring of heart rate (HR; electrocardiogram, Finapres Medical Systems, Amsterdam, The Netherlands), beat-beat arterial finger BP by plethysmography (Finometer Pro; Finapres Medical Systems, Arnheim, The Netherlands), and exhaled peak carbon dioxide ($P_{ET}CO_2$; Roxon Medi-tech Ltd, St-Leonard QC, Canada) were recorded (1kHz) (PowerLab, ADInsturments, Colorado Springs, CO, USA) and processed (LabChart 7, ADInsturuments, Colorado Springs CO). Estimates of stroke volume, cardiac output, and total peripheral resistance (Finometer Pro; Finapres Medical Systems, Arnheim, The Netherlands) were normalized to body surface area (DuBois D & DuBois EF 1916)(SVi, Qi and TPRi respectively).

Cerebral blood flow was assessed by transcranial Doppler ultrasound (TCD) and near-infrared spectroscopy (NIRS). The TCD device with a 2-MHz transducer (TCD; Multigon Industries, Elmsford, NY, USA) continuously monitored CBF velocity (CBFV) in the middle cerebral artery. Offline analysis of CBFV included beat-to-beat averaging, gated to the ECG R-wave, where mean flow velocity (MFV), peak velocity (PSV), and minimum velocity (MV) for each beat were extracted for further analysis. Mean arterial pressure at the level of the middle cerebral artery (MAPmca=MAP – (distance above heart*0.78)) and the TCD velocity signal were utilized in the following calculations; cerebrovascular resistance index (CVRi=MAPmca/MFV)), resistance index (RI=[PSV-MV]/PSV), pulsatility index (PI=[PSV-MV]/MFV), and dynamic cerebral autoregulation (dCA= $[(MFV(t_2) – MFV(t_1)) / MFV(t_1)] / [(MAP(t_2) – MAP(t_1)) / MAP(t_1)]$), where t_1 = nadir value and t_2 = resting supine baseline.

A NIRS device (NIRS; PortaLite, Artinis Medical Systems BV, Netherlands) was used to collect relative changes in oxygenated, deoxygenated, and total hemoglobin content (OxHb, DeoxHb, and

TotHb respectively) as well as cerebral oxygenation (tSO_2=OxHb/TotHb). The NIRS device was placed over the prefrontal lobe in accordance with the international 10-20 EEG land marking system (right: Fp2, F4, F8. left: Fp1, F7, F3) (Perrey S. 2008). A source detector distance of 4 cm was used for the OxHb, DeoxHb and TotHb signals to reduce signal contamination from surrounding tissues (Kohri S. *et al.* 2002). The NIRS signal was later processed into beat-by-beat data points where the mean, maximum, and minimum hemoglobin values were extracted from each beat.

Time scale and averaging

Resting baseline values were averaged over 30 sec of supine rest (from -45 sec to -15 sec prior to a transition or any cuff inflation). Time at zero seconds indicates upright posture. Nadir signifies the single lowest MV beat following upright posture. Initial standing is characterized by a 10 sec average starting at nadir. Prolonged standing represents a 10 sec average from 50 sec to 60 sec after nadir (Fig. S-1).

Cerebral blood flow deficit

A cerebral blood flow deficit (Eq. 1) represents the amount of CBF which falls short of resting supine levels during a posture change. The CBF deficit is defined as the area above the curve from nadir (single lowest CBF MV beat following upright posture) to resting baseline values (along the y-axis) and from nadir to recovery (first MV beat which exceeded resting baseline values or was no longer increasing) (along the x-axis). A larger area above the curve suggests a larger CBF deficit. A delta CBF MV was also used to characterize the change in CBF from supine resting conditions (30 sec average) to prolonged standing (10 sec average).

Eq. S-1 – Area above the curve: $\text{CBF deficit} = 1/2 \sum_{n=1}^{N-1}(t_{n+1} - t_n)\big(\text{CBF}(t_{n+1}) + \text{CBF}(t_n)\big)$

where t_1 corresponds to the time point at nadir, t_N corresponds to the time point where the curve reached the resting baseline (i.e. recovery), and $(t_{n+1} - t_n)$ corresponds to the spacing between consecutive time points.

Cerebrovascular reactivity to carbon dioxide

Cerebrovascular reactivity to carbon dioxide was assessed in the seated position during steady-state hypocapnia (hyperventilation) and hypercapnia (inhalation of a gas mixture: 5% CO_2, 21% O_2 and balanced nitrogen). Hyperventilation was achieved by increasing breathing rate (20 breaths/min) and coaching participants to reduce exhaled CO_2 (-10mmHg). Participants were asked to breathe normally for 3 min prior to and following hypo- and hypercapnic conditions. A three-way valve (Three-way T-shape Stopcock Type, Hans Rudolph) was secured to a 5-liter non-diffusing reservoir bag (Series 6000, Hans Rudolph, Shawnee, KS, USA) to allow for manual switching between the delivery of the gas mixture and room air. The gas sampling line from the CO_2 analyzing device was secured to a disposable facemask covering the participant's nose and mouth. Total $CRCO_2$ (hypercapnia – hypocapnia) was calculated by dividing the percentage change in CBF by the absolute change in $P_{ET}CO_2$ [$CRCO_2 = [\ (MFV(t_2) – MFV(t_1)) / MFV(t_1) \cdot 100\%] / (P_{ET}CO_2(t_2) – P_{ET}CO_2(t_1))]$

Postural Stability

A single Nintendo Wii Balance Board (Nintendo, Koyoto, Japan) was used to collect (100Hz) center of pressure (COP) displacement. Bluetooth technology was used to wirelessly transmit the data from the Nintendo Wii Balance Board to a customized nearby software program (LabView, National Instruments, Austin TX USA). Postural stability measures were later analyzed alongside cardio- and cerebrovascular variables by means of a customized Matlab program (Matlab R2012a; The Mathworks

Inc, Natick, MA, USA). Stability data were analyzed in the anterior-posterior (AP), medial-lateral (ML) and combined AP + ML directions. Measures of postural stability were calculated as the root mean square (RMS; Eq. 2), total path length (TPL; Eq. 3c), TPL AP and ML (Eq. 3a and 3b), sway vector average (SV avg; Eq. 4), and SV standard deviation (SV SD; Eq. 5). Postural stability was calculated over a 10 sec average during initial standing (from nadir to 10 sec after nadir) and prolonged standing (from 50 sec to 60 sec). The initial standing was chosen to start at nadir as this aligns with the CBF deficit and eliminates any initial overshoot responses in postural stability.

Eq 2: $\text{Root Mean Square (RMS)} = \sqrt{1/N \sum_{n=1}^{N} RD_n{}^2}$

where the resultant distance (RD) is the vector distance from mean COP to each point in either the ML or AP plane (Prieto T.E. *et al.* 1996)

Eq 3a: $\text{Total AP Length (TPL AP)} = \sum_{n=1}^{N-1} \sqrt{(\text{AP}_{n+1} - \text{AP}_n)^2}$

Eq 3b: $\text{Total ML Length (TPL ML)} = \sum_{n=1}^{N-1} \sqrt{(\text{ML}_{n+1} - \text{ML}_n)^2}$

Eq 3c: $\text{Total Path Length (TPL)} = \sum_{n=1}^{N-1} \sqrt{(\text{AP}_{n+1} - \text{AP}_n)^2 + (\text{ML}_{n+1} - \text{ML}_n)^2}$

Eq 4: $\text{COP Vector Average (COPV avg)} = \mu = 1/N \sum_{n=1}^{N} \sqrt{(\text{AP}_n - \text{AP}_{mean})^2 + (\text{ML}_n - \text{ML}_{mean})^2}$

Statistical analysis

Regressions were run in Sigmaplot version 12.5 (Systat Software Inc., San Jose, CA, USA), all other statistical analyses were completed using IBM SPSS version 20 (IBM SPSS Statistics 20; IBM Corp, Armonk, NY, USA), and all tests were considered significant at $p \leq 0.05$.

Participant Grouping- Not all participants responded to the manipulations by having a marked reduction of CBF. Therefore, participants were split into two groups (non-responders and responders). The non-responders group had a constant CBF deficit across conditions. Comparatively the responders group progressively increased their CBF deficit across CON, TC, and TC-Hyp conditions. A TwoStep cluster analysis (k-cluster) was used to automatically create the number of clusters (participant groups) and only a good cluster quality (silhouette measure of cohesion and separation of 0.5 to 1.0) was considered acceptable. The change in CBF deficit observed from the CON to the TC-Hyp condition was used as the continuous k-clustering variable (Romero et al 2011) to separate participants into the two groups: those who did not demonstrate a greater decrease in CBF, whereby rendering the TC-Hyp manipulation to be unsuccessful in lowering CBF (non-responders' deficit group, n=12) and those who demonstrated a marked decrease in CBF, suggesting the TC-Hyp manipulation significantly lowered CBF and increased the CBF deficit (responders' group, n=7).

Transition by grouping main effects – A two-way mixed ANOVA (general linear model in SPSS) was used to evaluate the main effects of transition type and group. Three levels of repeated measures were used for within-subject evaluation for the type of transition (transition: CON, TC, and TC-Hyp) and two levels of between-subject factors were used to evaluate group effects (group: non-responders vs. responders). If Mauchly's test of Sphericity was significant the Greenhouse-Geisser correction was used. In cases where a main effect for transition was found, pairwise comparisons (adjusted for multiple comparisons) were conducted. The two-way mixed ANOVA was performed to investigate the impact of transitions and CBF deficit grouping on measures of CBF (CBF deficit, MF, OxHb, DeoxHb, TotHb, and tSO_2), cardiovascular hemodynamics (HR, SVi, Qi, MAPmca, and TPRi), and postural stability (RMS AP, RMS ML, TPL, TPL AP, TPL ML, SV). Interaction effects were tested by Tukey's HSD analysis to identify where the significant ($p \leq 0.05$) differences lay.

Cerebral blood flow deficit and postural stability - Pearson product correlations and regression analysis were used to examine relationships between measures of cerebrovascular hemodynamics (CBF deficit and ΔMV from baseline to prolonged standing) and postural stability (RMS ML, RMS AP, and SV SD).

Symptoms analysis – A proportional odds regression was used to assess differences between groups and conditions.

Results

General orthostatic response (Control condition)

There were no significant differences between groups for age, BMI, BSA, TBW or CrCO2 (Table S-1). Approximately half of all participants in the CON condition demonstrated initial orthostatic hypotension for diastolic BP (DBP drop ≥20 mmHg). Only a small proportion (11%) of participants demonstrated initial orthostatic hypotension for systolic BP (SBP drop ≥ 40 mmHg) but all participants with an SBP drop ≥ 40mmHg also had a DBP drop ≥ 20 mmHg (Table S-2).

Cardio- and cerebrovascular hemodynamics – at nadir of MFV

Compared to the control condition, the two conditions with a thigh cuff deflation (TC and TC-Hyp) had higher HR and SVi and lower MAPmca at nadir (Figure S-2, main effect: condition all p=<0.05). Cardiac output was not different between conditions as the reduction in SVi was countered by the increase in HR. There were no interactions or group effects observed for cardiovascular hemodynamics at nadir.

Cerebral blood flow MV was reduced ($p<0.05$) across transitions (CON to TC to TC-Hyp) and a trend ($p=0.089$) for group differences indicates that responders had a lower CBF at nadir (Fig S-3). Expectedly, $PETCO_2$ at nadir was lower during the TC-Hyp condition compared to the CON or TC condition ($P<0.001$, Fig. S-2). These mentioned results suggest that the thigh cuff deflation method

was effective in lowering MAPmca for both the TC and TC-Hyp condition and the hyperventilation task was effective in further lowering CBF MV as it was significantly lower than the CON and TC conditions. The trend to group differences in CBF MV at nadir (p=0.085) suggests the responders group are driving the lower nadir values in the TC and TC-Hyp conditions (table S-2).

CBF deficit

The CBF deficit progressively grew from CON to TC because the thigh cuff deflation caused a greater reduction in both BP and MV during the TC and TC-Hyp conditions. Subsequently, the CBF deficit increased further from TC to TC-Hyp because the addition of hyperventilating reduced MV even further. Group differences in MV at nadir (Fig. S-3 p=0.089) suggest significant differences between conditions were driven primarily by the responders group. The lower MV nadir values in the responders group combined with the significant interaction for the duration of CBF deficit (time from nadir to recovery) suggests responders had a lower MV for a longer duration during the TC and TC-hyp conditions lending to a larger CBF deficit value (table S-2).

Cardio- and cerebrovascular hemodynamics – Prolonged standing

Heart rate and SVi had an interaction effect (transition*group, p<0.01) whereby HR was significantly higher during the TC-Hyp condition at 1-min compared to the Con and TC conditions; furthermore, the responders had a significantly higher HR compared to non-responders during the TC-Hyp condition (Fig. S-2). Comparatively, SVI was significantly lower in the responders group compared to the non-responders group during the TC-Hyp condition (Fig. S-2).

During prolonged standing CBF MV was reduced (p=0.061) between the CON and TC-Hyp conditions (Fig. S-3). The reduction in CBF MV can be attributed to the reduction (P<0.001) in $P_{ET}CO_2$ between the CON and TC-Hyp conditions (Fig. S-3).

Effects on postural instability – Initial standing

When examining the relationship between CBF deficit and postural stability between groups (group*condition $p<0.001$, Fig. S-5 left panel), it is clear that the non-responders group had a relatively constant CBF deficit across conditions and comparatively the responders group progressively and significantly increased their CBF deficit across CON, TC and TC-Hyp conditions (Tukey's HSD identified significant differences between all conditions for the responders group only, $p\leq0.05$, Fig. S-5). Identical trends between groups and conditions were observed during the initial standing phase for COPV-avg, RMS AP, and RMS ML measures of postural stability (group*condition, $p=0.005$, $p=0.007$, $p=0.09$ respectively, Fig S-5 left panel). Specifically, Tukeys HSD analysis revealed that for COPV-avg significant differences exist between the CON condition and both TC and TC-Hyp for only the responders group. Furthermore, there was a group effect in the TC-Hyp condition for COPV-avg. For RMS AP significant differences were present between the CON condition and TC-Hyp as well as between groups during the TC-Hyp condition. For RMS ML there were differences between groups during the TC-Hyp condition. Thus, when the CBF deficit was unchanged (non-responders group) postural stability upon standing was also unchanged, however when the CBF deficit became progressively larger (responders group) postural stability also became progressively poorer (Fig. S-5 left panel).

Postural stability showed considerable variability between participants as evident by examples of the first 10-sec of standing after nadir for a non-responder and a responder in figure S-4. Due to the angular momentum generated from a supine-stand transition, greater RMS AP movement was observed compared to RMS ML movement during initial standing (Fig. S-4 and S-5), for this reason the SV avg is also larger during initial standing compared to quiet standing (Fig S-5).

Effects of CBF during prolonged standing and postural instability – Prolonged standing

During prolonged standing (50-60s after transition), there were no differences in CBF MV between the responder and non-responder groups, but there was a trend to a lower value in the TC-Hyp condition (p=0.061, Fig S-5, right panel). Condition by group interactions reveal similar patterns for COPV-avg (p=0.07) and RMS ML (p=0.013); whereby, Tukey's HSD analysis identified significant differences in COPV-avg between the CON and TC-Hyp conditions for responders only, and group differences for RMS ML during the TC-Hyp condition. These data demonstrate that the non-responders had relatively unchanging measures of stability and the responders group had progressively poorer COPV-avg and RMS ML from the CON to the TC-Hyp condition (Fig. S-5 right panel). These results suggest that reductions in CBF even 1-min post-transition are linked with postural instability.

Perceived Symptoms

Across conditions the percent of participants with symptoms increased as well as the severity of the symptom (Fig. S-6). The only symptoms evident during the CON condition were dizziness/light-headedness and unsteadiness. The proportional odds regression identified that relative to the reference group (TC-Hyp Responders) all other conditions and the non-responders group had a substantially lower response to dizziness/light-headedness. The order in which the severity of dizziness/light-headedness regressed is as follows: TC-Hyp non-responders, TC responders, TC non-responders, CON responders, CON non-responders. Although, TC-Hyp non-responders had a lower severity of dizziness/light-headedness compared to the reference group it was the only condition which was not significantly lower. Likewise, the symptom of unsteadiness was markedly lower during all other conditions as well as in the non-responders groups. The order in which the severity of unsteadiness regressed is as follows: TC-responders, TC-Hyp non-responders, TC non-responders, CON

non-responders, CON responders. Only the TC responders group had a trend to be lower than the reference group (TC-Hyp responders), all other comparisons were significantly lower.

Discussion

In this study, we progressively reduced CBF and measured postural instability following a unique combination of standing plus thigh cuff release, and standing plus thigh cuff release with hyperventilation in young healthy adults. Consistent with the hypothesis, accumulation of a larger CBF deficit was associated with greater postural instability (a well-known risk factor for future falls) (Muir S.W. *et al.* 2010) observed in the early phase after standing, and persisting for up to 1-min. These data provide an experimental basis for the proposed links between cerebral hypoperfusion, dizziness and falls (Edlow B.L. *et al.* 2010; Mehagnoul-Schipper D.J. *et al.* 2000b; Gutkin M. & Stewart J.M. 2016).

Previous research has employed supine or sitting to standing transitions to challenge arterial BP and CBF regulation (Lipsitz L.A. *et al.* 2000; Demura *et al.* 2008; Demura *et al.* 2010). Likewise, rapid release of double thigh cuff occlusion has been used in supine (Aaslid R. *et al.* 1989) and seated (Lind-Holst M. *et al.* 2011) postures. To the best of our knowledge, this is the first time that standing and leg cuff deflation have been combined. An unexpected finding was the observation of participants whom we called responders and non-responders according to their CBF deficit responses to these additive stimuli during posture transition. In the CON condition, there were no differences in CBF deficit between the groups. However, a highly significant interaction effect showed that responders progressively increased the CBF deficit from CON to the TC and further to the TC-Hyp conditions. The non-responder group increased CBF deficit from CON to TC, but there was no further change in TC-Hyp.

Potential explanations for the differences in CBF deficit between include the tendencies for smaller changes in $P_{ET}CO_2$ with the hyperventilation maneuver in the non-responder group. All

participants were encouraged to reduce $P_{ET}CO_2$ and were given visual and verbal encouragement to accomplish the reduction. The absence of statistically significant interaction effects between condition and group for $P_{ET}CO_2$ suggested that each group hyperventilated to the same extent. There were, however, some differences as the non-responder group had a slightly smaller reduction in $P_{ET}CO_2$ from the TC to the TC-Hyp condition (35.3 to 30.3 mmHg at nadir compared to 34.1 to 26.8 mmHg). With the lower $P_{ET}CO_2$, the non-responders did have lower MFV at nadir in TC-Hyp than TC, but CBF deficit was not different between conditions. The small differences in $P_{ET}CO_2$ in the TC-Hyp between groups might have contributed to the relatively greater indicator of cerebrovascular resistance, RI, which could have been reflected in the greater CBF deficit in the responder group. The two groups had similar cerebrovascular response to CO_2 so this was unlikely to be related to the difference. A longer duration from nadir to CBF deficit recovery in the responder group might reflect differences in cerebrovascular autoregulation, but autoregulation is expected to be enhanced with lower $P_{ET}CO_2$ (Aaslid R. *et al.* 1989; Edwards M.R. *et al.* 2004). The larger CBF deficit from CON to TC-Hyp in the responders group (199±62(cm/s)*s) versus non-responders (18±32(cm/s)*s) was a combination of differences in $P_{ET}CO_2$, a lower MV value at nadir combined with a longer time to reach recovery values (baseline average) lending to the larger CBF deficit during the TC-Hyp condition of non-responders.

The combination of manipulations were successful in driving a greater reduction of arterial BP ($p=0.017$) at nadir. The reductions in artieral BP can be attributed to reduced SVi ($p<0.001$) and TPRi (not significant) during the TC and TC-Hyp conditions. The reduction in BP likely triggered the baroreflex thus increasing HR and resulting in an unchanged Qi between conditions. The combination of standing with a thigh cuff occlusion method did not demonstrate any group differences in BP (Fig. S-2). The addition of hyperventilation (commonly used to reduce CBF (Coverdale N.S. *et al.* 2014)) to standing with a thigh cuff deflation did not cause a greater drop in BP but it did reduce CBF. Across

conditions and among groups the average supine MFV was 66 cm/s and $P_{ET}CO_2$ was 39 mmHg (Table. S-2).

Cerebral blood flow and postural instability

This is the first study to demonstrate measured reductions in CBF alongside increases of postural instability (responders, left panel Fig. S-5). Elevated and low resting seated SBP values have been indicated to negatively affect postural stability (COP 95% area) during quiet standing in older adult males (Maciaszek J. *et al.* 2011). However, the current study ascertains that CBF and more specifically CBF deficit are more closely linked to postural instabilities than indices of BP. In consideration of the Romero-Ortuno et al. 2011 study which has reported a wide-range of postural BP responses in older adults (Romero-ortuno R. *et al.* 2011), the current study findings would suggest a wide-range of CBF deficits in young adults are possible (attributed to both changes in BP and CBF) and that the impact of varied responses are reflected in different degrees of postural instability.

The current study also found similar transition trends and group differences in TotHb (Fig. S-3) to MV. Demura et al. 2008 and 2010 reported measures of TotHb within the cerebral tissue alongside body sway parameters during a supine-stand and sit-stand transition at varied room temperatures (Demura *et al.* 2008; Demura *et al.* 2010). The authors suggest that in young healthy adults a relationship exists between TotHb recovery time and postural sway patterns following a posture transition. They also state that the starting position (sitting vs. supine) influences the delay of BP regulation which may impact TotHb recovery time and thus COP (Demura *et al.* 2008). The current study findings agree that a relationship clearly exists between sway parameters and measures of cerebral flow but we have taken this one step further by maintaining a consistent transition movement pattern (supine-stand) yet manipulating CBF and measuring its relationship to COP sway; furthermore, we have two different groups of young adults who respond differently to the imposed

manipulations of CBF and we found that as the CBF deficit either remains unchanged (non-responders) or as it increases (responders) postural stability also remains unchanged (non-responders) or increases (responders).

Hyperventilation during standing has also been shown to impact postural sway because of both the mechanical movement of hyperventilating (rib cage and thoracic movement) and changes in respiratory centers in the brain which may modulate postural control (David P. *et al.* 2012). David et al. 2012 suggest postural control while hyperventilating may be compromised as the voluntary effort of hyperventilating bypasses automatic centers of the forebrain and compromises postural control. The current investigation evaluated postural control following hyperventilation in an effort to minimize the effects of voluntary hyperventilation on postural stability. Similar to the current study, Sakillari and Bronstein 1997 evaluated postural stability following bouts of hyperventilation. The authors assessed unsteadiness following varied degrees of hyperventilation (0 sec, 30 sec, 60 sec and 90 sec when breathing as deeply and quickly as possible) preceding an eyes closed quiet stand task (Sakellari V. & Bronstein A.M. 1997); whereby hyperventilating for 30 sec significantly increased postural sway (RMS AP and ML). However, as the percent of transcutaneous partial carbon dioxide pressure decreased from 30 sec to 90 sec of hyperventilation, a progressive increase in body sway was not observed. Sakillari and Bronstein 1997 suggest unsteadiness associated with hyperventilating may be due to a disruption in proprioception although they did not consider effects of $P_{ET}CO_2$ on CBF and cerebral hypoperfusion.

Standing CBF MV and postural instability at 1-min standing

The relationships between CBF and postural stability were maintained 1-min post-transition. Cerebral blood flow MV was lower in the TC-Hyp versus CON condition ($p=0.061$), and although not significant, the MV appears lower in the responders group compared to the non-responders group

(Fig. S-5). The responders group also had significantly lower SVi during the TC-Hyp condition versus the TC condition (Fig. S-1) and they had significantly higher HR during the TC-Hyp condition (Fig. S-2). During prolonged standing both COPV-avg and RMS ML demonstrate interactions (p=0.07 and p=0.013) where COPV-avg is significantly greater in the responders group during the TC-Hyp condition compared to the CON condition and RMS ML is significantly greater in the responders compared to the non-responders during the TC-Hyp condition. These findings identify that between the CON and TC-Hyp conditions MV is lower and for responders they also have increased HR and COPV-avg. The aforementioned results are the first to demonstrate a maintained relationship between BP and CBF regulation (SVi and MV) to postural instability (COPV-avg and RMS ML) 1-min post-transition.

Conclusions

Orthostatic hypotension and blood pressure disturbances have been proposed as a cause or primary contributor for falls in older adults because of its theoretical link to cerebral hypoperfusion (Shaw B.H. & Claydon V.E. 2014; van Wijnen V.K. *et al.* 2017) yet this is the first study to report concurrent reductions in CBF with increasing measures of postural unsteadiness. Although not all participants responded to the stimulus (thigh cuff deflation or hyperventilation) in the same fashion the individual responses allowed us to group participants and evaluate the effects of CBF (unchanged or reduced) relative to differed responses in postural stability (unchanged or increased). We found that individuals who had significantly lower CBF (marked by increased CBF deficit) had significantly poorer postural stability upon standing and during prolonged standing. The CBF decrease appears to impact measures of quiet standing in a young healthy adult population even up to 1-min post transition. These findings provide support to proposed mechanisms suggesting that older adults who experience cerebral hypoperfusion upon standing may also exhibit greater initial and prolonged

postural instability which may place them at increased risk of unsteadiness and potentially having a future fall.

Tables and Figures

Table S-1. Participant characteristics separated by cerebral blood flow deficit group

Characteristic	All (N=19)	Non-responders (n=12)	Responders (n=7)	P value
Age, years	25.8±3.5	26.7±2.5	24.1±4.5	N.S.
Sex (women), % (n)	52.6 (10)	58.3 (7)	42.9 (3)	-
BMI (kg/m^2)	24±3.5	24.7±3.7	22.8±2.9	N.S.
Height (cm)	171.7±6.3	172±7.3	171.2±4.7	N.S.
Weight (kg)	71.1±13.4	73.4±14.4	67.1±11.5	N.S.
BSA (m^2)	1.83±0.18	1.86±0.19	1.78±0.16	N.S.
TBW (L)	38.7±11.3	36.6±10.3	42.5±13.4	N.S.
$CrCO_2$ (%/mmHg)	2.159±0.363	2.178±0.448	2.126±0.159	N.S.
Smoking (never), % (n)	94.7 (18)	91.7 (11)	100 (7)	-
Smoking (current), % (n)	5.3 (1)	83.3 (1)	-	-
Physical Activity (Self-report questionnaire)				
Activity level, % (n)				
Regular Exercise (3d/wk 50% mod)	89.5 (17)	83.3 (10)	100 (7)	-
Sedentary, % (n)	15.8 (3)	25.0 (3)	-	-
Active, % (n)	52.6 (10)	66.7 (8)	28.6 (2)	-
Highly Active, % (n)	31.6 (6)	8.3 (1)	71.4 (5)	-
Frequency of activity, % (n)				
0 days/week, % (n)				
1-2 days/week, % (n)	10.5 (2)	16.7 (2)	-	-
3-4 days/week, % (n)	57.9(11)	66.7 (8)	42.9 (3)	-
5 or more days/week, % (n)	26.3 (5)	-	71.4 (5)	-
Intensity (%) of total activity				
Light, mean±SD (median)	18.9±22.3 (10)	21.3±26.1 (15)	15.0±14.4 (10)	-
Moderate , mean±SD (median)	46.3±29.9 (50)	42.1±35.3 (35)	53.6±17.5 (60)	-
Hard , mean±SD (median)	24.2±25.4 (20)	20.0±28.8 (2.5)	31.4±17.7 (30)	-

BMI body mass index, *BSA* body surface area, *TBW* total body water, *CrCO2* Cerebrovascular reactivity to carbon dioxide

Table S-2. Cardio- and cerebrovascular hemodynamics separated by condition and cerebral blood flow deficit group

Characteristic	Control Condition (CON)			Thigh Cuff Deflation Condition (TC)			Thigh Cuff Deflation and Hyperventilation Condition (TC-Hyp)			p-value
	All N=19	Non-responders n=12	Responders n=7	All N=19	Non-responders n=12	Responders n=7	All N=19	Non-responders n=12	Responders n=7	
CBF deficit, (cm/s)*s	119.3±52.7	125.4±56.7	108.8±47.3	168.6±90.3	151.6±74.2	197.7±113.2	204.1±112.2	143.4±66.4	308.2±98.3	** p<0.001
dCA ratio, cm/s	0.736±0.823	0.685±0.551	0.823±1.209	0.867±0.732	0.649±0.621	1.240±0.801	1.246±1.495	1.545±1.633	0.732±1.154	N.S.
dCA ratio, mmHg/cm/s	-1.366±1.533	-1.366±0.922	-1.367±2.344	-1.364±1.279	-1.032±0.807	-1.932±1.766	-1.723±2.226	-2.117±2.409	-0.945±1.763	N.S.
Time at nadir (s)	3.22±0.96	3.26±0.76	3.15±1.31	3.85±1.65	3.85±1.77	3.83±1.56	3.45±1.98	4.37±1.63	1.87±1.53	**
Duration of CBF deficit - nadir to recovery (s)	6.65±1.64	6.82±1.54	6.35±1.89	8.03±2.34	7.67±1.90	8.66±3.01	8.24±2.21	7.32±1.89	9.81±1.89	**
Initial OH: DBP, n (%)	10 (53)	7 (58)	3 (43)	13 (68)	9 (75)	4 (57)	13 (68)	8 (67)	5 (71)	-
Initial OH: SBP & DBP, n (%)	2 (11)	1 (8)	1 (14)	4 (21)	2 (17)	2 (29)	7 (37)	4 (33)	3 (43)	-
Supine										
HR, bpm	59.3±6.3	58.0±6.3	61.4±6.1	59.9±7.9	58.8±7.6	61.8±8.5	60.1±9.8	58.3±9.3	63.2±10.6	N.S.
SBP, mmHg	116.6±8.3	116.4±9.7	117.0±6.0	116.8±8.2	115.2±9.0	119.5±6.2	116.3±8.6	114.0±9.5	120.3±5.4	N.S.
DBP, mmHg	69.0±5.6	71.0±5.5	65.7±4.1	69.0±4.9	70.4±4.6	66.5±4.7	68.8±4.8	69.2±5.8	68.0±2.8	N.S.
MAP, mmHg	84.9±5.5	86.1±6.0	82.8±4.0	84.9±4.8	85.3±5.1	84.2±4.7	84.6±5.3	84.1±6.5	85.5±6.5	N.S.
PP,mmHg	47.6±7.9	45.4±8.4	51.3±5.9	47.8±8.2	44.8±8.3	52.9±5.1	47.6±7.3	44.8±6.5	52.3±6.4	†† P=0.042
Qi, L/min/m^2	2.87±0.44	2.82±0.42	2.96±0.49	2.88±0.53	2.77±0.37	3.08±0.72	2.86±0.56	2.79±0.42	2.96±0.77	N.S.
SVi, mL/m^2	48.6±5.8	48.9±6.3	48.3±5.2	48.8±6.2	48.2±6.6	49.7±5.6	47.8±6.5	48.5±7.3	46.6±5.3	* p=0.062, c
TPRi, mHg/L/min/m^2	9.28±2.36	9.37±2.66	9.13±1.94	9.26±2.23	9.43±2.57	8.98±1.64	9.37±2.40	9.26±2.69	9.56±2.01	N.S.
PSV, cm/s	100.9±19.5	98.8±19.3	104.5±20.8	102.3±19.2	101.7±19.3	103.3±20.6	101.1±18.7	99.2±19.9	104.4±17.2	N.S.
MV, cm/s	44.6±9.3	45.1±9.8	43.8±9.1	44.2±9.0	44.8±10.0	43.1±7.5	43.2±8.5	42.1±9.6	45.1±6.5	N.S.
MFV, cm/s	66.0±14.2	65.8±14.8	66.4±14.3	65.9±14.0	66.3±15.0	65.1±13.2	64.7±13.2	63.3±15.0	66.9±10.0	N.S.
PPcbfv,cm/s	56.3±11.8	53.7±10.9	60.6±12.8	58.2±11.9	57.0±11.2	60.2±13.8	57.9±12.2	57.1±10.9	59.4±14.9	N.S.

CVRi, mmHg/cm/s	0.898±0.212	0.940±0.225	0.828±0.183	0.897±0.187	0.914±0.192	0.868±0.190	0.915±0.235	0.954±0.273	0.848±0.145	N.S.
RI,	0.56±0.04	0.54±0.04	0.58±0.033	0.57±0.04	0.56±0.04	0.58±0.03	0.57±0.04	0.58±0.03	0.56±0.06	** p=0.021
PI,	0.86±0.01	0.83±0.10	0.92±0.10	0.89±.011	0.87±0.1	0.93±0.09	0.90±0.12	0.91±0.08	0.89±0.18	* p=0.06
$P_{ET}CO_2$, mmHg	39.1±4.2	39.2±3.9	38.9±5.0	39.0±4.3	39.3±4.3	38.5±4.6	38.7±3.9	38.6±3.9	38.9±4.1	N.S.
tSO_2, percent	65.4±5.2	66.3±6.3	63.7±2.2	63.3±3.8	63.2±3.6	63.6±4.4	64.7±5.0	65.6±5.8	63.0±2.8	N.S.
TotHb, µMol	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	-
PPTotHb, µMol	0.581±0.125	0.614±0.128	0.529±0.110	0.583±0.098	0.631±0.089	0.507±0.055	0.573±0.146	0.628±0.118	0.488±0.153	†† p=0.02
OxHb,µMol	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	-
PP OxHb, µMol	0.490±0.100	0.515±0.098	0.450±0.095	0.494±0.084	0.535±0.080	0.429±0.038	0.488±0.118	0.534±0.098	0.416±0.116	†† p=0.017
DeoxHb, µMol	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	-
PP DeoxHb, µMol	0.100±0.031	0.105±0.031	0.092±0.031	0.097±0.019	0.103±0.011	0.088±0.026	0.094±0.032	0.099±0.021	0.086±0.046	N.S.
Nadir										
HR, bpm	84.2±12.6	83.3±13.1	85.8±12.6	90.9±1.2	90.0±10.9	92.5±21.6	93.6±17.4	93.5±14.2	93.7±23.2	‡‡ p<0.001, a,b
SBPmca, mmHg	96.5±18.1	95.1±20.4	99.0±14.4	87.8±18.7	86.5±21.7	89.9±13.6	85.5±18.6	81.5±17.9	92.3±19.0	‡‡ p=0.004, a,b
DBPmca, mmHg	51.7±14.1	52.2±14.8	51.0±14.1	46.7±12.9	47.9±13.2	44.8±13.0	47.3±16.3	46.6±13.4	48.6±21.6	‡‡ p=0.046, a
MAPmca, mmHg	66.7±14.8	66.5±16.3	67.0±13.1	60.4±13.9	60.8±15.6	59.8±11.6	60.1±16.3	58.2±14.5	63.1±19.9	‡‡ p=0.017, a, b
PPmca,mmHg	44.8±10.0	43.0±8.9	48.0±11.5	41.0±12.2	38.6±11.2	45.2±13.6	38.1±10.8	34.8±8.4	43.8±12.7	‡‡ p=0.001, a, b
Qi, L/min/m^2	3.85±0.80	3.71±0.91	4.09±0.55	3.80±0.93	3.60±1.07	4.14±0.55	3.56±0.92	3.33±0.95	3.95±0.79	N.S.
SVi, mL/m^2	46.0±8.7	44.5±7.9	48.6±9.9	42.4±11.2	39.9±10.6	46.7±11.6	38.8±11.0	35.6±8.6	44.2±13.1	‡‡ p<0.001, a,b
TPRi, mmHg/L/min/m^2	5.46±1.66	5.50±1.64	5.39±1.84	5.02±1.41	5.20±1.39	4.71±1.49	5.45±2.19	5.50±2.00	5.37±2.67	N.S.

PSV, cm/s	104.9±20.5	104.9±24.2	104.9±13.9	101.0±22.3	101.3±22.6	100.5±23.7	98.7±17.1	98.2±18.9	99.4±14.8	N.S.
MV, cm/s	14.6±7.7	15.8±8.5	12.6±6.0	10.0±6.9	12.5±6.3	5.6±5.7	5.8±6.5	7.4±6.9	3.0±5.1	‡‡ p<0.001, a,b,c, † p=0.089
MFV, cm/s	44.4±11.6	45.1±13.8	43.4±7.3	39.0±8.4	40.0±9.6	37.3±6.1	33.7±6.5	35.1±6.4	31.2±6.3	‡‡ p<0.001, a, b, c
PPcbfv,cm/s	90.3±17.3	89.1±19.5	92.3±13.9	91.0±22.7	88.7±21.2	94.9±26.3	92.9±18.1	90.8±20.1	96.4±14.8	N.S.
CVRi, mmHg/cm/s	0.931±0.497	0.950±0.537	0.899±0.458	0.868±0.447	0.881±0.484	0.846±0.410	1.009±0.644	0.901±0.419	1.195±0.927	N.S.
RI,	0.86±0.06	0.89±0.06	0.88±0.06	0.90±0.08	0.87±0.06	0.93±0.091	0.94±0.07	0.92±0.08	0.97±0.05	‡‡ p<0.001, b, c, † p=0.096
PI,	2.09±0.39	2.05±0.42	2.16±0.33	2.36±0.48	2.26±0.42	2.53±0.56	2.81±0.58	2.61±0.53	3.16±0.55	‡‡ p<0.001, a, b, c
$P_{ET}CO_2$, mmHg	35.6±4.5	35.9±4.7	35.3±4.3	34.9±4.7	35.3±5.0	34.1±4.5	29.0±4.3	30.3±4.8	26.8±2.2	‡‡ p<0.001, b, c
tSO_2, percent	62.5±5.5	63.5±6.7	60.8±2.1	59.6±4.0	59.1±3.7	60.3±5.0	59.4±5.7	60.6±6.5	57.3±3.3	‡ p=0.062, b
TotHb, µMol	-3.747±2.255	-3.762±2.603	-3.723±1.764	-3.668±2.193	-2.768±1.806	-5.083±2.091	-4.467±3.384	-4.202±2.331	-4.884±4.802	N.S.
PPTotHb, µMol	0.635±0.154	0.637±0.159	0.631±0.158	0.707±0.258	0.736±0.285	0.662±0.221	0.613±0.192	0.521±0.153	0.759±0.158	** p=0.028
OxHb,µMol	-3.762±1.881	-3.838±2.141	-3.644±1.535	-3.529±1.827	-2.985±1.835	-4.385±1.566	-4.182±2.714	-4.028±2.084	-4.424±3.677	N.S.
PP OxHb, µMol	0.598±0.141	0.598±0.156	0.598±0.126	0.649±0.229	0.675±0.268	0.606±0.162	0.559±0.170	0.476±0.137	0.690±0.133	** p=0.023
DeoxHb, µMol	0.024±0.557	0.083±0.622	-0.068±0.467	-0.128±0.854	0.227±0.735	-0.687±0.756	-0.290±1.082	-0.182±1.064	-0.459±1.173	N.S.
PP DeoxHb, µMol	0.100±0.046	0.099±0.053	0.100±0.036	0.104±0.044	0.105±0.048	0.101±0.041	0.075±0.038	0.059±0.036	0.100±0.029	‡ p=0.055 c, * p=0.075
Delta (supine to nadir)										

HR, bpm	25.0±8.8	25.3±9.0	24.4±9.1	31.0±11.6	31.2±8.9	30.8±16.0	33.4±13.1	35.2±11.0	30.4±16.7	‡‡ p=0.001, a, b
SBPmca, mmHg	-20.1±16.8	-21.2±16.5	-18.1±18.5	-29.0±17.2	-28.7±18.8	-29.5±15.4	-30.8±15.2	-32.5±12.5	-28.0±19.9	‡‡ p=0.003, a, b
DBPmca, mmHg	-17.3±14.8	-18.8±15.8	-14.8±13.6	-22.2±12.8	-22.5±13.7	-21.8±12.1	-21.4±14.4	-22.6±11.6	-19.5±19.2	‡ p=0.058 a, b
MAPmca, mmHg	-18.2±15.0	-19.6±15.7	-15.9±14.6	-24.5±13.8	-24.6±15.1	-24.4±12.5	-24.6±14.2	-25.9±11.5	-22.3±18.8	‡‡ p=0.015, a, b
PPmca,mmHg	-2.8±7.9	-2.4±6.5	-3.3±10.4	-6.8±8.9	-6.2±8.6	-7.8±9.9	-9.4±7.6	-10.0±6.3	-8.6±9.9	‡‡ p=0.003, a, b
Qi, L/min/m^2	0.976±0.682	0.890±0.607	1.124±0.823	0.918±0.765	0.833±0.793	1.063±0.751	0.703±0.796	0.537±0.810	0.988±0.740	‡‡ p=0.004, a, b
SVi, mL/m^2	-2.62±8.37	-4.35±6.44	0.35±10.86	-6.34±10.29	-8.29±8.92	-3.00±12.30	-9.01±11.74	-12.85±9.74	-2.42±12.63	N.S.
TPRi, mmHg/L/min/m^2	-3.83±1.66	-3.87±1.69	-3.74±1.73	-4.24±1.40	-4.23±1.63	-4.27±1.00	-3.92±1.71	-3.76±1.42	-4.19±2.22	N.S.
PSV, cm/s	4.0±10.2	6.0±8.7	0.4±12.3	-1.3±18.5	-0.5±15.0	-2.8±24.7	-2.5±7.6	-0.9±8.9	-5.1±3.8	N.S.
MV, cm/s	-30.0±7.2	-29.3±8.0	-31.3±5.9	-34.2±9.0	-32.2±9.8	-37.5±6.7	-37.4±9.3	-34.7±10.1	-42.1±5.7	‡‡ p<0.001, a, b, c
MFV, cm/s	-21.6±8.2	-20.8±8.2	-23.0±8.8	-26.9±11.1	-26.3±12.0	-27.8±10.2	-31.0±10.2	-28.2±11.0	-35.7±6.8	‡‡ p<0.001, a, b, c
PPcbfv,cm/s	34.0±12.1	35.3±12.8	31.7±11.5	32.8±18.8	31.8±14.4	34.7±26.0	34.9±10.7	33.7±13.1	37.0±4.2	N.S.
CVRi, mmHg/cm/s	0.032±0.396	0.010±0.435	0.071±0.357	-0.029±0.367	-0.033±0.400	-0.022±0.331	0.094±0.562	-0.053±0.323	0.347±0.799	N.S.
RI,	0.31±0.06	0.31±0.07	0.30±0.05	0.33±0.08	0.32±0.06	0.35±0.10	0.37±0.07	0.34±0.07	0.41±0.06	‡‡ p<0.001, a, c, *p=0.07
PI,	1.23±0.37	1.22±0.42	1.24±0.29	1.47±0.44	1.39±0.37	1.60±0.55	1.91±0.57	1.70±0.50	2.27±0.51	**p=0.043
$P_{ET}CO_2$, mmHg	-3.42±1.85	-3.30±2.06	-3.64±1.54	-4.08±2.62	-3.94±2.47	-4.33±3.04	-9.68±3.73	-8.28±3.08	-12.08±3.70	‡‡ p<0.001,

										b, c, † p=0.086
tSO_2, percent	-2.89±1.42	-2.87±1.22	-2.91±1.82	-3.78±1.67	-4.05±1.79	-3.32±1.46	-5.28±1.99	-5.04±2.32	-5.69±1.31	‡‡ p<0.001, a, c
TotHb, µMol	-3.747±2.255	-3.762±2.602	-3.723±1.764	-3.668±2.193	-2.767±1.806	-5.083±2.091	-4.467±3.384	-4.202±2.331	-4.884±4.802	N.S.
PPTotHb, µMol	0.054±0.194	0.024±0.224	0.102±0.135	0.124±0.259	0.105±0.275	0.155±0.249	0.040±0.265	-0.107±0.175	0.272±0.215	** p=0.01
OxHb,µMol	-3.762±1.880	-3.838±2.141	-3.644±1.535	-3.529±1.827	-2.984±1.834	-4.385±1.566	-4.182±2.714	-4.028±2.084	-4.424±3.677	
PP OxHb, µMol	0.109±0.170	0.083±0.207	0.148±0.087	0.155±0.224	0.140±0.258	0.177±0.172	0.071±0.224	-0.058±0.146	0.274±0.166	** p=0.007
DeoxHb, µMol	0.0153±0.553	0.076±0.614	-0.079±0.468	-0.139±0.849	0.217±0.733	-0.698±0.742	-0.285±1.079	-0.173±1.065	-0.460±1.160	N.S.
PP DeoxHb, µMol	-0.001±0.051	-0.006±0.059	0.008±0.035	0.006±0.051	0.002±0.056	0.014±0.045	-0.020±0.055	-0.040±0.041	0.013±0.062	N.S.
Prolonged Standing										N.S.
HR, bpm	75.6±11.1	75.8±13.1	75.2±7.6	78.1±12.9	79.7±14.0	75.4±11.1	77.8±12.9	74.3±12.5	83.9±12.0	** p=0.001
SBPmca, mmHg	124.1±14.7	121.6±16.4	128.3±11.2	126.7±15.9	124.1±18.3	131.0±10.3	127.7±14.9	126.7±16.3	129.5±13.0	N.S.
DBPmca, mmHg	79.3±10.1	79.4±10.1	79.2±10.8	80.1±9.7	80.5±10.0	79.4±9.9	81.7±10.2	81.8±10.0	81.5±11.4	N.S.
MAPmca, mmHg	94.2±10.9	93.4±11.5	95.6±10.6	95.6±11.1	95.0±12.3	96.6±9.5	97.0±11.1	96.8±11.3	97.5±11.6	N.S.
PPmca,mmHg	44.8±9.6	42.2±10.7	49.1±5.8	46.6±10.5	43.6±11.4	51.6±6.6	46.0±9.5	44.9±11.1	48.0±6.2	N.S.
Qi, L/min/m^2	2.59±0.53	2.59±0.54	2.58±0.55	2.67±0.57	2.62±0.40	2.74±0.82	2.55±0.48	2.51±0.34	2.62±0.62	N.S.
SVi, mL/m^2	34.7±7.2	34.9±7.7	34.5±6.9	34.6±7.0	33.7±6.9	36.2±7.4	33.5±7.5	34.7±8.4	31.4±5.7	** p=0.006
TPRi, mmHg/L/min/m^2	11.9±4.6	11.3±3.8	12.9±6.0	11.6±3.9	11.2±3.3	12.3±5.0	12.2±4.0	11.9±3.70	12.7±4.7	N.S.
PSV, cm/s	95.3±20.4	95.9±23.6	94.2±14.9	96.2±20.2	96.7±20.9	95.4±20.6	91.3±19.6	93.1±21.7	88.0±16.2	N.S.
MV, cm/s	42.3±9.5	43.1±11.2	40.9±6.2	42.7±8.62	43.8±9.5	40.9±7.3	39.3±11.0	41.1±11.4	36.4±10.6	‡ p=0.061, b
MFV, cm/s	60.2±14.4	60.9±16.6	58.9±10.6	60.1±13.3	61.1±14.5	58.4±11.6	56.0±14.7	58.0±15.3	52.7±14.1	‡ p=0.075, b

PPcbfv,cm/s	53.0±12.5	52.9±14.1	53.2±10.2	53.5±13.5	52.9±12.8	54.6±15.6	51.9±11.5	52.1±12.6	51.6±10.3	N.S.
CVRi, mmHg/cm/s	1.17±0.38	1.18±0.41	1.16±0.35	1.18±0.34	1.17±0.35	1.19±0.36	1.35±0.61	1.30±0.49	1.44±0.81	‡‡ p=0.032, b
RI,	0.56±0.05	0.55±0.05	0.56±0.04	0.55±0.05	0.55±0.43	0.57±0.68	0.57±0.07	0.56±0.06	0.59±0.09	‡ p=0.056, c
PI,	0.89±0.12	0.88±0.14	0.91±0.11	0.90±0.15	0.87±0.11	0.94±0.20	0.97±0.24	0.92±0.17	1.04±0.32	‡‡ p=0.031, c
$P_{ET}CO_2$, mmHg	37.0±4.7	37.2±4.7	36.8±5.0	37.3±4.6	37.7±4.5	36.7±5.0	33.2±5.0	34.3±4.0	31.3±6.2	‡‡ p<0.001, a, c
tSO_2, percent	63.3±5.6	64.4±6.4	61.2±3.1	61.3±4.5	60.6±4.8	62.5±4.0	62.6±4.9	63.8±5.7	60.6±2.1	N.S.
TotHb, µMol	-2.315±2.299	-2.525±2.348	-1.984±2.362	-1.873±2.315	-1.607±2.502	-2.291±2.103	-2.716±2.940	-2.345±2.263	-3.299±3.912	N.S.
PPTotHb, µMol	0.397±0.121	0.408±0.120	0.379±0.130	0.398±0.127	0.411±0.141	0.377±0.107	0.377±0.122	0.419±0.129	0.311±0.078	N.S.
OxHb,µMol	-3.210±2.660	-3.469±2.006	-2.804±2.252	-2.689±1.971	-2.692±2.217	-2.684±1.679	-3.460±2.692	-3.077±2.047	-4.062±3.585	N.S.
PP OxHb, µMol	0.344±0.098	0.350±0.097	0.335±0.107	0.352±0.128	0.367±0.150	0.328±0.089	0.327±0.104	0.359±0.119	0.276±0.066	N.S.
DeoxHb, µMol	0.895±0.721	0.943±0.666	0.820±0.849	0.816±0.953	1.085±1.012	0.392±0.722	0.744±0.735	0.732±0.612	0.763±0.951	N.S.
PP DeoxHb, µMol	0.067±0.023	0.072±0.022	0.060±0.025	0.081±0.059	0.092±0.073	0.063±0.021	0.063±0.017	0.068±0.016	0.054±0.017	N.S.

Supine -45 to -15sec average, *Nadir* single lowest MV beat, *Delta* nadir value minus supine average, *Prolonged Standing* 50 to 60sec, *CBF* cerebral blood flow, *dCA* dynamic cerebral autoregulation, *OH* orthostatic hypotension, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *PP* pulse pressure, *Qi* cardiac output, *SVi* stroke volume, *TPRi* total peripheral resistance, *PSV* peak systolic velocity, *MV* minimum velocity, *MFV* mean flow velocity, *PPcbfv* pulse pressure cerebral blood flow velocity, *CVRi* cerebrovascular resistance index, *RI* resistance index, *PI* pulsatility index, $P_{ET}CO_2$ end-tidal carbon dioxide, tSO_2 cerebral tissue saturation, *TotHb* total hemoglobin, *PPTotHb* pulse pressure total hemoglobin, *OxHb* oxygenated hemoglobin, *PPOxHb* pulse pressure oxygenated hemoglobin, *DexHb* deoxygenated hemoglobin, *PPDeoxHb* pulse pressure deoxygenated hemoglobin. **interaction (group by condition) p≤ 0.05, *interaction (group by condition) p≤ 0.1 >0.05, †† group effect p≤ 0.05, † group effect p≤ 0.1 >0.05, ‡‡ condition effect p≤ 0.05, ‡ condition effect p≤ 0.1 >0.05, *N.S.* not significant, '*a'* pairwise comparison between CON and TC conditions, '*b'* pairwise comparison between CON and TC-Hyp conditions, '*c'* pairwise comparison between TC and TC-Hyp conditions.

Table S-3. Measures of postural stability separated by condition and cerebral blood flow deficit group

Characteristic	Control Condition (CON)			Thigh Cuff Deflation Condition (TC)			Thigh Cuff Deflation and Hyperventilation Condition (TC-Hyp)			p-value
	All N=19	Non-responders n=12	Responders n=7	All N=19	Non-responders n=12	Responders n=7	All N=19	Non-responders n=12	Responders n=7	
Initial (nadir to 10s)										
RMS AP, cm	0.448±0.181	0.485±0.209	0.384±0.103	0.555±0.230	0.537±0.228	0.586±0.250	0.575±0.205	0.475±0.143	0.746±0.187	**p=0.007
RMS ML, cm	0.292±0.083	0.300±0.078	0.277±0.096	0.402±0.229	0.363±0.241	0.467±0.208	0.349±0.167	0.273±0.105	0.479±0.181	* p=0.09, ‡‡ p=0.048, a,b, † p=0.077
TPL ML+AP, cm	12.17±2.58	12.15±2.75	12.20±2.48	14.91±6.45	14.96±6.58	14.84±6.74	14.40±5.43	13.06±4.70	16.70±6.18	‡‡ p=0.047, b
TPL ML, cm	7.13±2.26	7.10±2.59	7.16±1.74	9.17±4.93	8.84±4.22	9.75±6.31	8.39±4.20	7.58±4.34	9.77±3.85	‡ p=0.077, a, b
TPL AP, cm	8.29±1.49	8.26±1.61	8.34±1.39	9.71±43.97	10.07±4.71	9.08±2.42	9.82±3.26	8.90±2.01	11.40±4.46	‡ p=0.105, b
COPV-avg, cm	0.468±0.157	0.505±0.177	0.405±0.096	0.614±0.218	0.578±0.215	0.676±0.224	0.560±0.195	0.494±0.127	0.754±0.187	** p=0.005
COPV-sd, cm	0.276±0.072	0.289±0.063	0.253±0.085	0.354±0.154	0.347±0.164	0.366±0.148	0.338±0.149	0.258±0.065	0.474±0.156	** p=0.006
Prolonged Standing (50 to 60s)										
RMS AP, cm	0.293±0.131	0.316±0.156	0.255±0.062	0.363±0.224	0.354±0.271	0.378±0.125	0.373±0.165	0.324±0.138	0.456±0.183	N.S.
RMS ML, cm	0.215±0.091	0.215±0.112	0.216±0.044	0.225±0.099	0.214±0.096	0.245±0.109	0.217±0.104	0.164±0.067	0.309±0.093	** p=0.013
TPL ML+AP, cm	7.78±1.74	8.12±2.03	7.19±0.93	8.55±2.22	8.45±2.66	8.71±1.33	8.26±2.05	7.87±1.49	8.94±2.78	N.S.
TPL ML, cm	4.10±1.31	4.17±1.53	3.98±0.93	4.67±1.63	4.65±1.93	4.70±1.05	4.08±1.26	3.83±1.06	4.50±1.54	N.S.

TPL AP, cm	5.65±1.48	5.98±1.7	5.07±0.73	6.12±1.53	5.99±1.80	6.33±1.03	6.28±1.60	6.04±1.18	6.70±2.20	N.S.
COPV-avg, cm	0.328±0.132	0.342±0.163	0.304±0.051	0.384±0.190	0.369±0.234	0.410±0.086	0.384±0.176	0.317±0.131	0.499±0.193	* p=0.07
COPV-sd, cm	0.165±0.074	0.179±0.086	0.141±0.042	0.215±0.110	0.209±0.137	0.226±0.039	0.200±0.072	0.177±0.079	0.240±0.033	‡‡ p=0.05, a, b

Initial nadir to 10 s, *Prolonged Standing* 50 to 60sec, *ML* medial-lateral plane, *AP* anterior-posterior plane, *RMS* root mean square, *TPL* total path length, *COPV* center of pressure vector, *Avg* average, *SD* standard deviation. ** and * interaction (group by condition), †† group effect and † group effect, ‡‡ and ‡ condition, *N.S.* not significant, post-hoc '*a'* pairwise comparison is between CON and TC conditions, post-hoc '*b'* pairwise comparison is between CON and TC-Hyp conditions, post-hoc '*c'* pairwise comparison is between TC and TC-Hyp conditions.

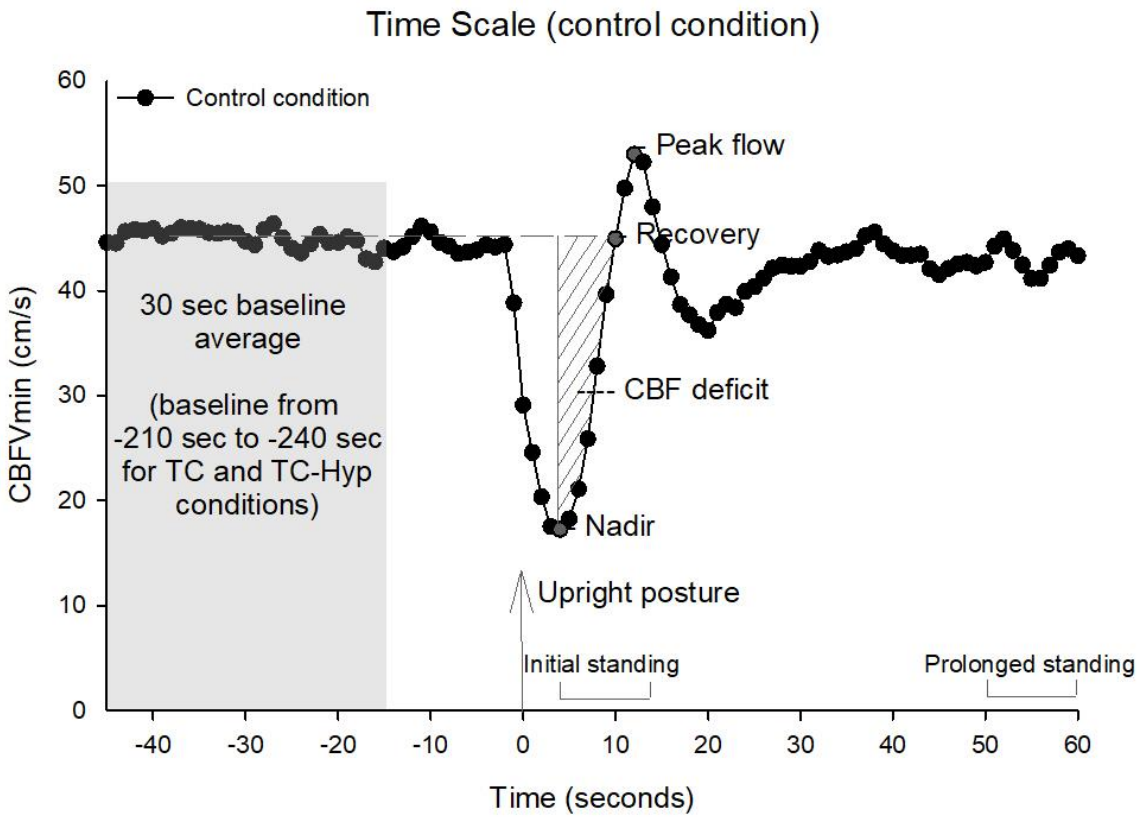


Figure S-1 Time scale: Negative time represents supine rest and active transition where time at zero marks up-right posture and positive time represents standing. A 30 sec baseline average was calculated from -45 sec to -15 sec during the control condition and from -210 sec to -240 sec for the thigh cuff inflation (TC) and thigh cuff inflation with hyperventilation (TC-Hyp) conditions. The nadir value signifies the lowest single CBFVmin beat, recovery marks the time at which CBFVmin reaches baseline average values and peak flow identifies the CBFVmin beat which no longer increases past upright posture. The cerebral blood flow (CBF) deficit is the area above the curve between nadir and recovery. Initial standing begins at the time of in which nadir occurs and continues for 10 sec and prolonged standing is from 50 sec to 60 sec of standing. During the TC and TC-Hyp conditions there was a 3 min double thigh cuff inflation which preceding upright posture. Additionally, during the TC-Hyp condition there were 90 sec of hyperventilation which began 90 sec into the double thigh cuff inflation and ended immediately prior to upright posture.

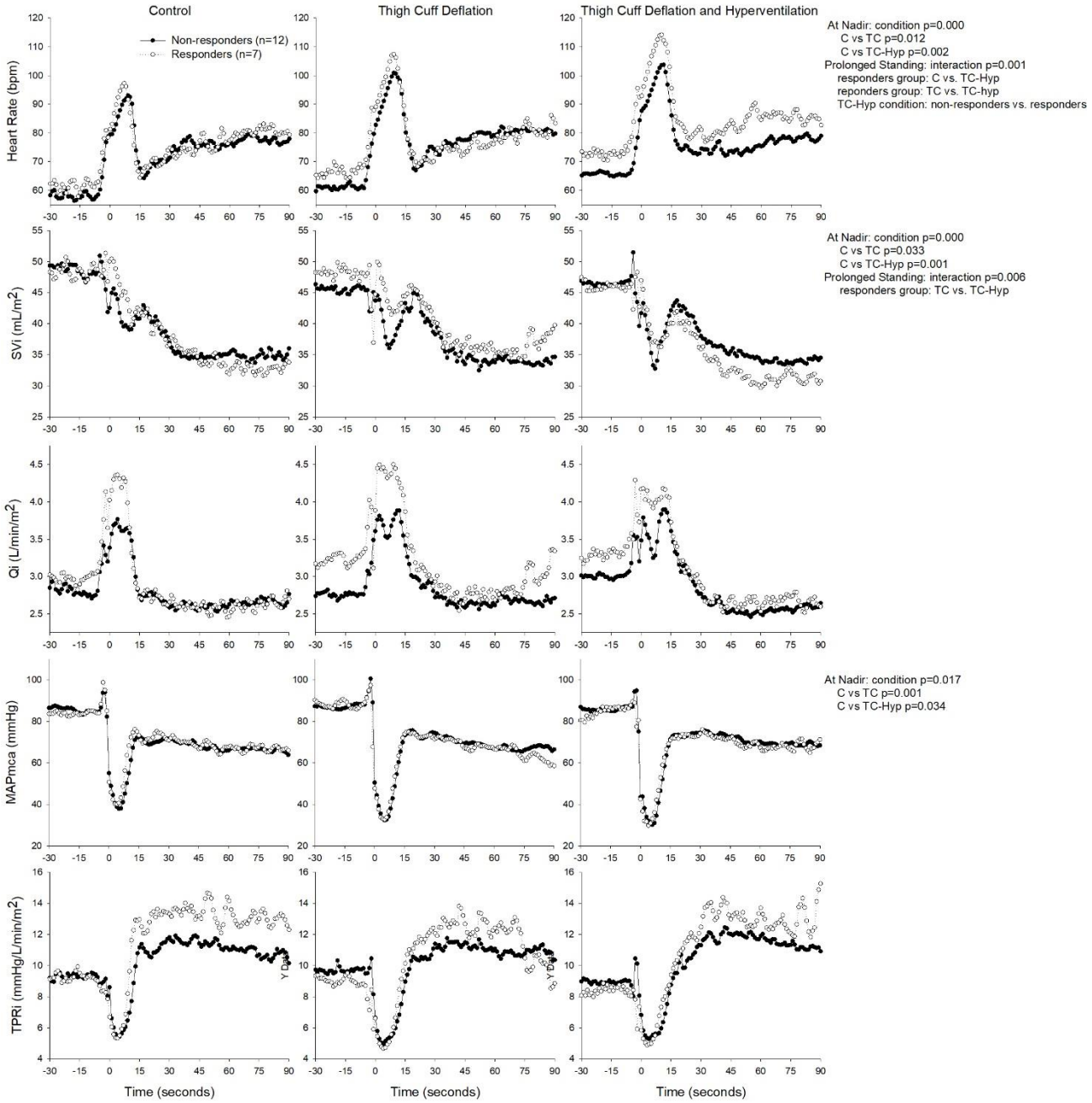


Figure S-2 Cardiovascular hemodynamics: A two way mixed ANOVA (condition by participant group) revealed significant main effects of condition at nadir for heart rate (HR), stroke volume (SVi) and mean arterial pressure at the level of the middle cerebral artery (MAPmca); whereby HR was significantly higher and SVi and MAPmca were significantly lower in the thigh cuff deflation and thigh cuff deflation and hyperventilation conditions. A significant interaction was observed during prolonged standing for HR and SVi where HR is elevated and SVi is lower in the responders group compared to the non-responders group during the thigh cuff deflation and hyperventilation condition. No significant relationships were found for cardiac output (Qi) or total peripheral resistance (TPRi).

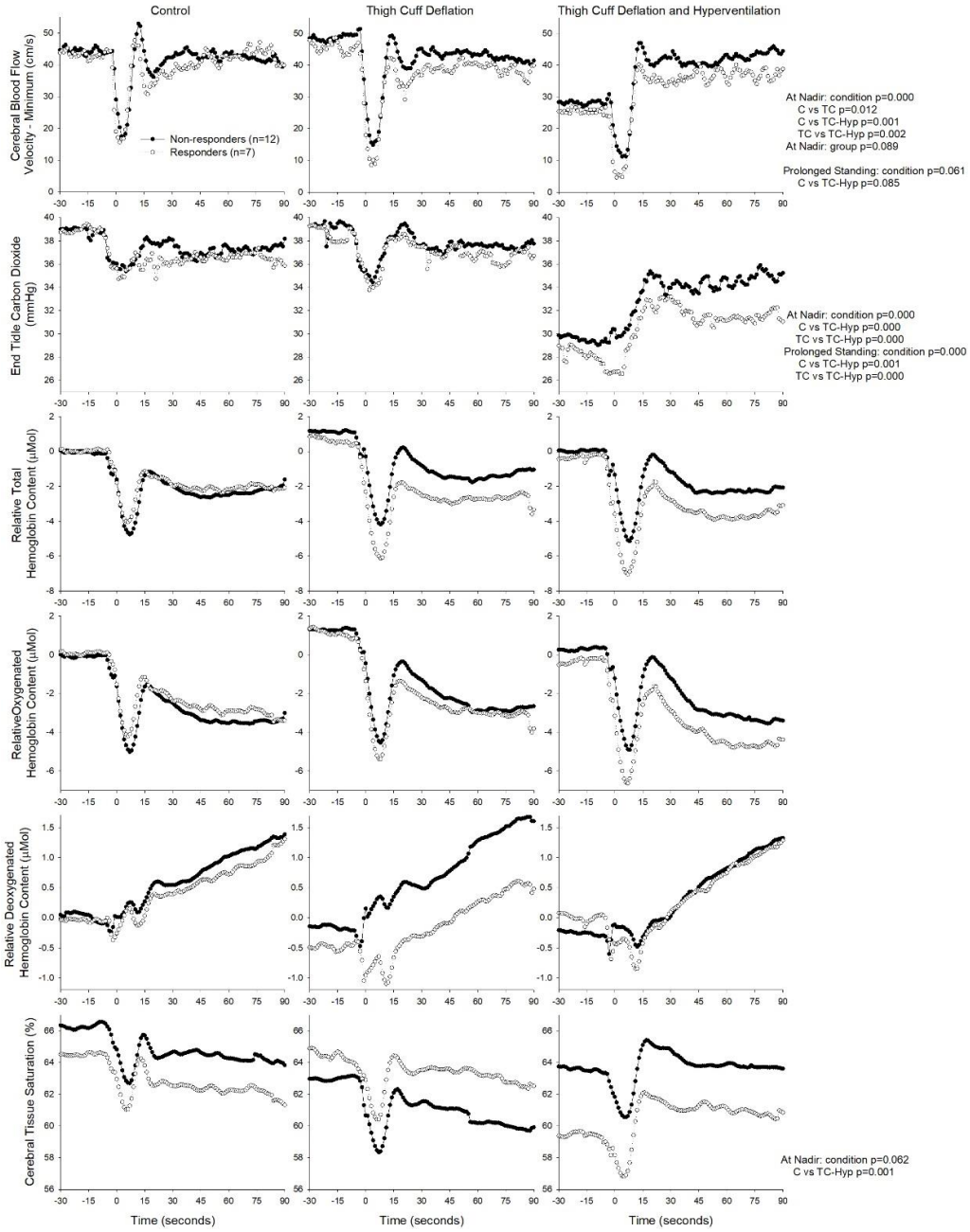


Figure S-3 Cerebrovascular hemodynamics: A two way mixed ANOVA (condition by participant group) revealed significant main effects of condition at nadir for cerebral blood flow velocity minimum (MV), end tidal carbon dioxide ($PETCO_2$) and cerebral tissue saturation (tSO_2); whereby MV was significantly different between all conditions and it progressively lowered from control to thigh cuff deflation to thigh cuff deflation and hyperventilation. There was also a trend for a main effect of grouping where the responders tended to have a lower MV versus non-responders. $PETCO_2$ was significantly lower in the thigh cuff deflation and hyperventilation condition compared to any other condition. A main effect of condition was also observed during prolonged standing for MV and $PETCO_2$ where the thigh cuff

deflation and hyperventilation condition had lower $PETCO_2$ compared to the other two condition and MV was lower compared to the control condition.

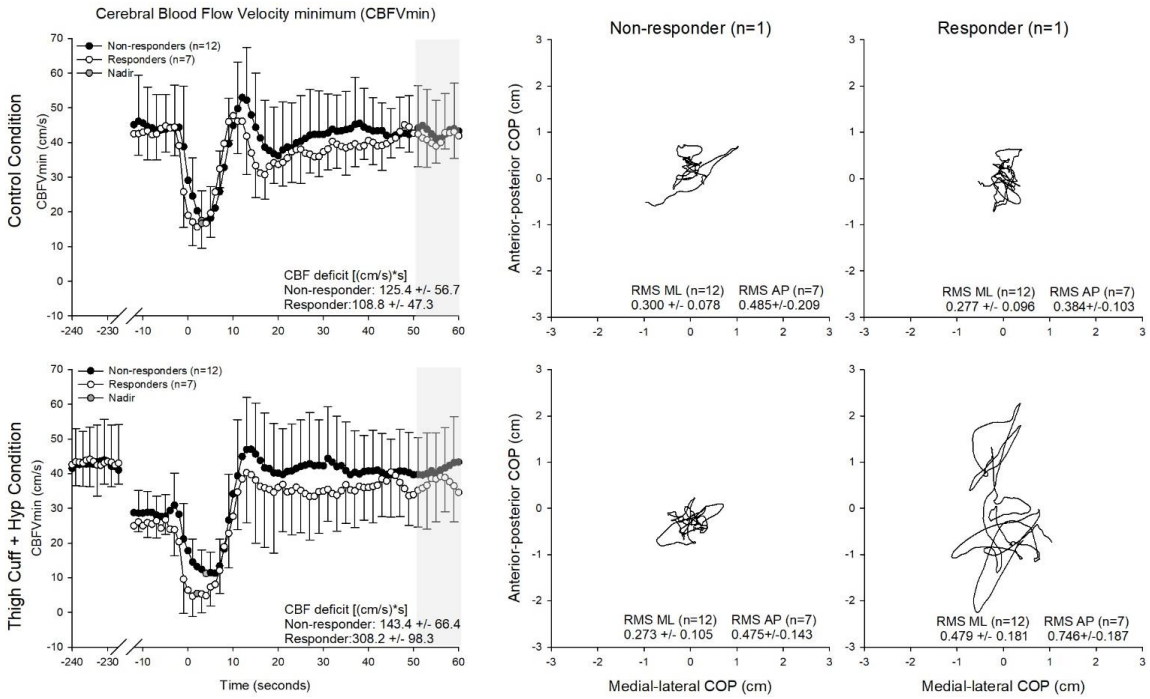


Figure S-4: Responders and non-responders cerebral blood flow velocity (CBFV) and stability. Top row of figures present the group mean (SD) during the control condition for CBFV minimum (supine to 60 s standing) and center of pressure (COP) postural stability tracing (nadir to 10 s) for a representative non-responder and non-responder. The lower row of figures show CBF velocity minimum during the thigh cuff and hyperventilation condition for the same non-responder and non-responder. CBF deficit and root mean square (RMS) medial-lateral (ML) and anterior-posterior (AP) shown on the panels are group by condition averages ± standard deviation. Responders had significantly larger CBF deficit during the thigh cuff and hyperventilation condition as well as significantly poorer postural stability.

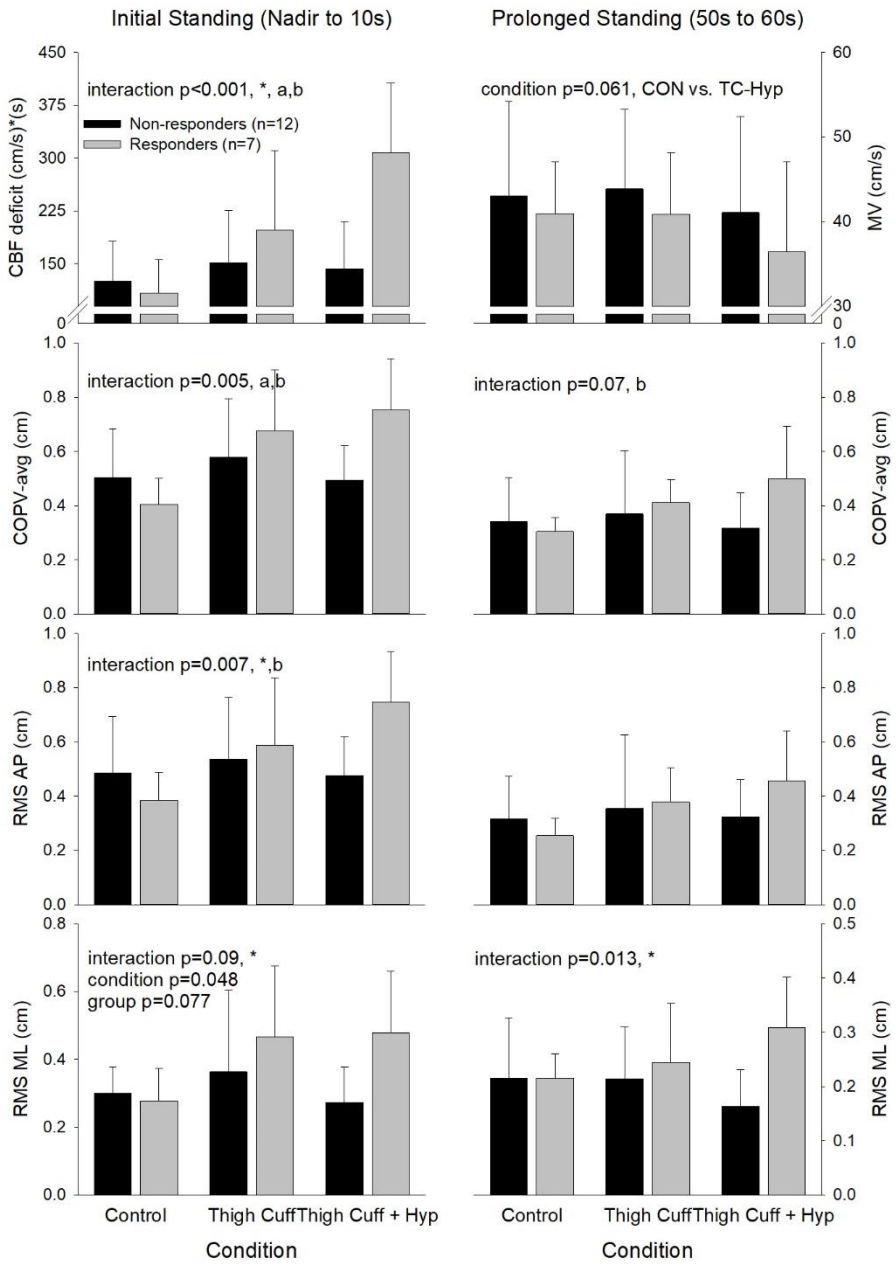


Figure S-5. Initial and prolonged standing cerebral blood flow (CBF) and stability. Initial and prolonged standing cerebral blood flow (CBF) deficit and postural stability (COPV-avg center of pressure vector average, RMS root mean square, AP anterior-posterior, and ML medial-lateral) are shown for the three conditions for the non-responder and responder groups. During initial standing significant interactions for CBF deficit, COPV-avg and a trend for an interaction for RMS ML reveals that as the CBF deficit increased across conditions for the responders group, postural instability also increased. Comparatively, the CBF deficit for the non-responders group remained relatively constant and so did their postural stability. Likewise, during prolonged standing CBF velocity minimum (MV) and RMS ML

demonstrate interactions (p=0.07 and p=0.013 respectively) depicting a relationship where responders have a lower MV during the thigh cuff and hyperventilation condition as well as a higher RMS ML compared to the relatively unchanging values of the non-responders group. Tukey's HSD analysis identified significant differences between: * TC-Hyp condition non-responders vs. responders, 'a' responders between CON and TC conditions, 'b' responders between CON and TC-Hyp conditions, 'c' responders between TC and TC-Hyp conditions.

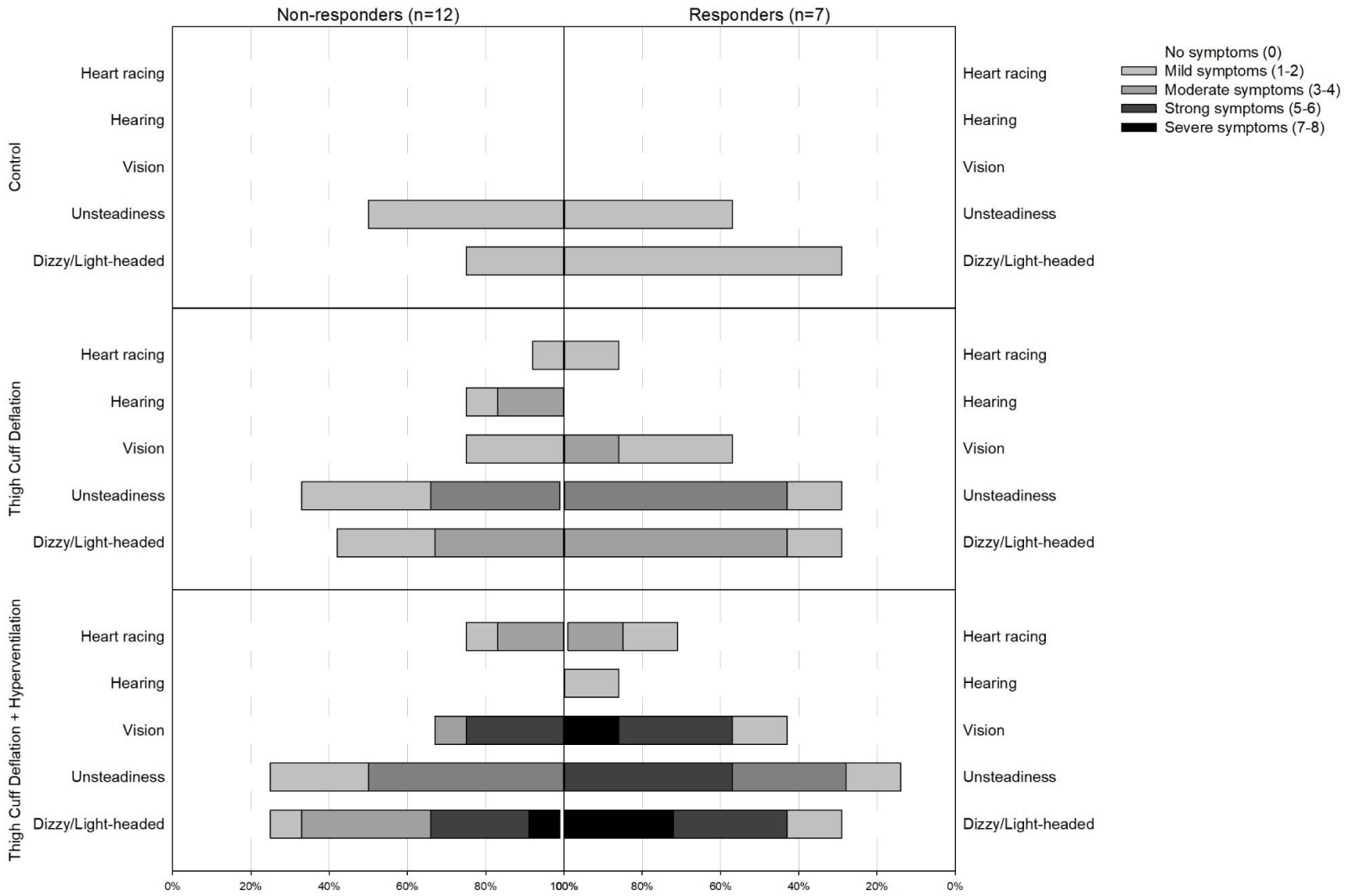


Figure S-6. Self-report symptoms of initially standing (scale 0-10). As the conditions progressively reduced the cerebral blood flow (Fig. S-5) the frequency and intensity of symptoms also increased.

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APPENDIX A – HEALTH STATUS QUESTIONNAIRES

HEALTH STATUS QUESTIONNAIRE – A – Chapter 4

Study Title: Brain blood flow and stability during standing after a change in posture

Researchers and Contact Information:

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Study ID: _____

Are you near sighted?
Do you wear corrective glasses or contacts?

Past Health

Check all that apply and **identify** approximate **date of diagnosis/event**

( ) Heart Attack
( ) Heart Failure
( ) Open Heart Surgery
( ) Congenital Heart Disease
( ) Atrial Fibrillation
( ) Stroke
( ) Transient Ischemic Attack
( ) Carotid Stenosis
( ) Peripheral Vascular Disease
( ) Blood Clots
( ) Chronic Obstructive Pulmonary Disease
( ) Hypertension
( ) High Cholesterol
( ) Diabetes (diet or insulin)
( ) Sleep Apnea
( ) Emphysema or Pneumonia
( ) Asthma or Bronchitis
( ) Kidney or Liver Disease
( ) Ulcers
( ) Chronic Inflammation: _____
( ) Other: _____

Current Health

Do you have a pacemaker? _____ If yes, when did you have it implanted?_____
Do you have arthritis? _____ If yes, what joints are affected?
_____
Do you experience moderate to severe pain while standing or walking?
_____

List any current (within the past 3 months) health issues (examples are listed under past health) and medications

Current health issues:	Current medications:	
1.	1.	7.
2.	2.	8.
3.	3.	9.
4.	4.	10.
5.	5.	11.
6.	6.	12.

Current Symptoms (within the past 3 months)

( ) Irregular Heart Beat
( ) Chest Pain
( ) Persistent Cough
( ) Wheezing/Shortness of Breath
( ) Memory Complaints
( ) Fatigue
( ) Headaches
( ) Dizziness/Light-Headedness
( ) Pain; If yes, where? _____
( ) Other: _____

Smoking

Never( ) Ex-smoker: quit year( ) Regular: # cigarettes/day( ) Years smoking( )

Current Activity Level

Please list the types of activities/exercises you have done in the past 3 months. Also, indicate how often (frequency) and how long (duration) you do these activities for.

Type of Activity	Frequency (how often)	Duration (for how long)

Balance Screening

Please select which number best represents your fear of falling and balance confidence.

	Not Afraid					Somewhat Afraid				Extremely Afraid
Fear of Falling	0	1	2	3	4	5	6	7	8	9	10

	Not Confident					Somewhat Confident				Extremely Confident
Balance Confidence	0	1	2	3	4	5	6	7	8	9	10

Identify if you have any known,
( ) Neurological Disorders (such as, Parkinson's Disease or Multiple Sclerosis)
( ) Neuromuscular Disorders (such as, Muscular Dystrophy, Adults Spinal Muscular Atrophy)

If so, please specify _____

Recent Nutritional Intake

Please list the time of your last meal, along with the type and quantity of food/beverages consumed during that last meal.

Time of last meal	Type of food/beverages consumed	Quantity consumed

Researcher Confirmation: _____ Date: _____

HEALTH STATUS QUESTIONNAIRE – B – Chapter 5

Study Title: Brain blood flow and balance during a transition to walking

Researchers and Contact Information:
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Richard Hughson, PhD phone: 519-888-4567 ext 32516 e-mail: hughson@uwaterloo.ca
Department of Kinesiology, Applied Health Sciences, University of Waterloo, Waterloo ON N2L 3G1

Study ID: _____

Exclusion Criteria: If any of the following apply, you should not participate in this study

- Diagnosis of dementia
- A history of cerebrovascular disease (ex. stroke or transient ischemic attack)
- An uncontrolled medical condition (ex. uncontrolled Diabetes)
- A cardiac event within the past 3 months (heart attack within the past 3 months)
- A neuromuscular disease affecting your balance or stability (ex. Muscular Dystrophy)
- A neurological disease affecting your balance or stability (ex. Parkinson's Disease)

SELF-REPORT CHECK LIST (check all that apply)

( ) Have you ever been diagnosed with dementia by a physician?
( ) Do you have a **pacemaker**? If yes, when did you have it implanted?_____.
( ) Do you have any known neurological disorders (e.g. Parkinson's Disease)?
( ) Do you have any known neuromuscular Disorders (ex. Muscular Dystrophy)?
( ) Do you have any allergies or sensitivities to water based gels or adhesives?
( ) Do you have arthritis? If yes, what joints are affected? _____
( ) Do you experience moderate to severe pain while standing or walking?
( ) Are you near sighted?
( ) Do you wear corrective glasses or contacts?

Past Health (identify approximate year of diagnosis/event)

( ) Heart Attack
( ) Heart Failure
( ) Open Heart Surgery
( ) Congenital Heart Disease
( ) Atrial Fibrillation
( ) Stroke
( ) Transient Ischemic Attack
( ) Carotid Stenosis
( ) Peripheral Vascular Disease
( ) Blood Clots
( ) Hypertension
( ) High Cholesterol
( ) Diabetes (diet or insulin)
( ) Sleep Apnea
( ) Emphysema or Pneumonia
( ) Asthma or Bronchitis
( ) Kidney or Liver Disease
( ) Ulcers
( ) Chronic Inflammation: _____
( ) Other: _____

( ) Chronic Obstructive Pulmonary Disease

Current Health (within the past 3 months)

List current health issues:

1.
2.
3.
4.
5.
6.
7.

List current medications:

1. 2.
3. 4.
5. 6.
7. 8.
9. 10.
11. 12.

Current Symptoms (within the past 3 months)

( ) Irregular Heart Beat
( ) Chest Pain
( ) Persistent Cough
( ) Wheezing/Shortness of Breath
( ) Memory Complaints
( ) Fatigue
( ) Headaches
( ) Dizziness/Light-Headedness
( ) Pain; If yes, where? _____
( ) Other: _____

Habits

Smoking: Never ( ) Ex-smoker: year ( ) Regular: # cigarettes/day ( )
Exercise: Never ( ) 1-3 times per week ( ) 3+ times per week ( )

Balance Screening

Please select which number best represents your fear of falling and balance confidence.

	Not Afraid/Confident				**Somewhat** Afraid/Confident						**Extremely** Afraid/Confident
Fear of Falling	0	1	2	3	4	5	6	7	8	9	10

Balance Confidence	0	1	2	3	4	5	6	7	8	9	10

Current Activity Level

Please list the types of activities/exercises you have done in the past 3 months. Also, indicate how often (frequency) and how long (duration) you do these activities for.

Type of Activity	Frequency (how often)	Duration (for how long)

What percentage of your total time spent performing physical activity is light, moderate and hard?

LIGHT:	2-4 on a scale from 0-10. No sweating, but faster breathing, e.g. walking.
MODERATE:	5-6 on a scale from 0-10. Some sweating and deeper breathing, but still able to talk comfortably, e.g. brisk walking or biking.
HARD:	7-8 on a scale from 0-10. Heavy sweating and heavy breathing with difficulty talking, e.g. running or swimming.

_____% Light
_____% Moderate
_____% Hard

Recent Nutritional Intake

Please list the time of your last meal, along with the type and quantity of food/beverages consumed during that last meal.

Time of last meal	Type of food/beverages consumed	Quantity consumed

Researcher Confirmation: _____ Date: _____

HEALTH STATUS QUESTIONNAIRE – C – Supplementary Study

Study Title: The influence of low cerebral blood flow on postural stability

Researchers and Contact Information:

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Department of Kinesiology, Applied Health Sciences, University of Waterloo, Waterloo ON N2L 3G1

Study ID: _____

Exclusion Criteria: If any of the following apply, you should not participate in this study

- Psychiatric illness or use of psychoactive drugs
- History of drug/alcohol abuse
- High blood pressure (≥ 140/90 mmHg)
- Medications which influence heart rate or blood pressure
- If you are or you think you may be pregnant
- Diabetes
- Resting heart rate > 110bpm
- Respiratory illness (ex. asthma)
- Peripheral vascular disease

Do one or more of these apply to you?: **Yes** or **No**

Do you have any allergies or sensitivities to water based gels or adhesives? **Yes** or **No**

Current Health (within the past 3 months)

List current health issues:
1.
2.
3.
4.

List current medications:
1.
2.
3.
4.
5.
6.
7.
8.

Smoking: Never ( ) Ex-smoker: year ( ) Regular: # cigarettes/day ( )

Physical Activity

How many days per week do you participate in at least 30 minutes of continuous physical activity? Circle one.

None 1-2 days 3-4 days 5+days

List the activities you have performed in the last 3 months and the frequency.
1.
2.
3.
4.
5.

What percentage of your total time spent performing physical activity is light, moderate and hard?

LIGHT:	2-4 on a scale from 0-10. No sweating, but faster breathing, e.g. walking.
MODERATE:	5-6 on a scale from 0-10. Some sweating and deeper breathing, but still able to talk comfortably, e.g. brisk walking or biking.
HARD:	7-8 on a scale from 0-10. Heavy sweating and heavy breathing with difficulty talking, e.g. running or swimming.

_____% Light
_____% Moderate
_____% Hard

Recent Nutritional Intake

Please list the time of your last meal, along with the type and quantity of food/beverages consumed during that last meal.

Time of last meal	Type of food/beverages consumed	Quantity consumed

Researcher Confirmation: _____ Date: _____