

Cerebral Blood Flow Response to Posture Transition and Walking in Older Adults with Heart Failure

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Individuals with heart failure (HF) have lower cerebral blood flow (CBF) and oxygenation at rest, and lower cerebral oxygenation at peak exercise, likely due to insufficient cardiac output and poor respiratory function; however, no studies have examined the effects of low intensity activity such as are common of activities of daily living, on cerebral hemodynamics in individuals with HF. We recruited 10 individuals with HF (aged 78 ± 4 years, 7 men, LVEF 20-61%), and 13 healthy age-matched controls (aged 79 ± 8 years, 4 men, LVEF 52-73%) to examine the cerebral hemodynamic response to quiet standing and walking. Participants completed 3 transitions; 1) supine to 3-minutes standing, 2) sitting to 3-minutes walking at a self-selected slow pace, 3) sitting to 3-minutes walking at a self-selected normal pace. Portable finger plethysmography measured central hemodynamics, portable capnography measured partial pressure end-tidal carbon dioxide ($P_{ET}CO_2$), portable transcranial Doppler ultrasound measured cerebral blood flow velocity (CBFV), and near infrared spectroscopy (NIRS) measured cerebral oxygenation. Participants with HF had lower cardiac index (Q_i), compared to control participants during seated and supine rest ($P < 0.001$), quiet standing ($P < 0.001$), and normal and slow pace walking ($P = 0.006$). Participants with HF had an attenuated Q_i response during walking compared to control participants (group x speed interaction: $P = 0.008$), suggesting a poor cardiac response to low intensity activity. Cerebral oxygenation was lower in participants with HF during seated and supine rest ($P = 0.020$), quiet standing ($P = 0.034$), and normal and slow pace walking ($P = 0.004$), compared to control participants. Repeated-measures correlation analysis was used to examine the relationship between Q_i and cerebral oxygenation across exercise challenges (quiet standing, as well as slow and normal pace walking). Interestingly, there was a significant negative relationship between Q_i and cerebral oxygenation ($r_{rm} = -0.53$, P

< 0.001) in the participants with HF, whereas there was a significant positive relationship ($r_{rm} = 0.35, P = 0.003$) in the control participants. This was likely the consequence of ineffective blood flow redistribution, which has been previously documented during exercise in individuals with HF; however, this finding in the present study is particularly problematic as the experimental conditions (quiet standing and walking) are extremely common during daily living. Sustained cerebral desaturation experienced repeatedly during daily function may manifest as ischemic damage in cerebral tissue with adverse clinical outcomes. In particular, cerebral desaturation during standing and low intensity activity may partially explain poor exercise tolerance and cognitive impairment previously reported in individuals with HF.

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List of Acronyms

ADL: activity of daily living
ATP: adenosine triphosphate
BP: blood pressure
cfPWV: carotid-femoral pulse wave velocity
CBF: cerebral blood flow
CBFV: cerebral blood flow velocity
CCA: common carotid artery
FinAP: finger arterial pressure
Q: cardiac output
Qi: cardiac index
HF: heart failure
HFmEF: heart failure mid ejection fraction
HFpEF: heart failure preserved ejection fraction
HFrfEF: heart failure reduced ejection fraction
HR: heart rate
Ht: height correction
IMT: intima media thickness
LVEF: left ventricular ejection fraction
MAP: mean arterial pressure
MCA: middle cerebral artery
MoCA: Montreal cognitive assessment
MRI: magnetic resonance imaging
NYHA: New York Heart Association
NIRS: near infrared spectroscopy
PNS: parasympathetic nervous system
PCO₂: partial pressure of carbon dioxide
P_{ET}CO₂: partial pressure of end-tidal carbon dioxide
SNS: sympathetic nervous system
SPECT: single-photon emission computed tomography
SV: stroke volume
SVi: stroke volume index
TCD: transcranial Doppler ultrasound
TPR: total peripheral resistance
TSI: tissue saturation index

1.0 Literature Review

Heart failure (HF) is a complex, systemic, and multifactorial disease that can be challenging to manage from a clinical perspective. Presented below are sections of text extracted from the review paper, “The influence of ejection fraction on cerebral perfusion in the setting of heart failure: a scoping literature review” currently submitted to JACC HF by KR Murray, JAM Poirier, RL Hughson, RS McKelvie, and GA Heckman that outlines of the current literature of the epidemiology and pathophysiology of HF. The pathophysiology discussed will have a specific focus on the structural and functional changes of the central cardiac and peripheral systems that might precipitate cerebral hypoperfusion during rest, orthostasis, and physical activity. Importance should be placed on understanding these mechanisms as ischemic damage from cerebral hypoperfusion may clinically manifest as cognitive impairment in individuals with HF, further complicating disease management. As well, these mechanisms may present novel treatment targets to prevent adverse health outcomes in this patient group.

1.1 Epidemiology of Heart Failure

The global burden of HF is substantial, with over 26 million people affected world-wide (Ponikowski et al., 2014). HF is associated with increased costs of healthcare due to direct (e.g., hospitalization) and indirect (e.g., rehabilitation and management) costs, which are expected to increase in the coming decades due to increased prevalence from improved HF management and aging populations (Dickstein et al., 2008; Ambrosy et al., 2014; Blecker et al., 2013; Farré et al., 2016).

HF is a condition characterized by low cardiac output (Q), along with underlying structural and functional changes to cardiac tissues such as fibrosis, changes in left ventricular morphology, and changes in contractility (Savarese & Lund, 2017). This results in a mismatch

between oxygen requirement and delivery in peripheral tissues. These anatomical and physiological changes lead to HF being originally classified as either systolic or diastolic, but since both systolic and diastolic dysfunction can coexist in individuals with HF it has become more clinically relevant to classify HF based on left ventricular ejection fraction (LVEF). Recent Canadian Cardiovascular Society management guidelines proposed three subtypes of HF: preserved ejection fraction (HFpEF), > 50% LVEF; mid range ejection fraction (HFmEF), 40-49% LVEF; and reduced ejection fraction (HFrEF), < 40% LVEF (Ezekowitz et al., 2017). Recent data have shown a global shift in the prevalence of each HF subtype, with HFpEF becoming more prevalent than HFrEF (Ambrosy et al., 2014). This has been attributed to increased life expectancy and aging populations, increased prevalence of both cardiovascular and non-cardiovascular comorbidities, and increased recognition of HFpEF by clinicians (Oktay et al., 2013) It is also relevant and common clinical practice to characterize HF patients by functional symptomology. Dyspnea, either at rest or during exercise, is often experienced by individuals with HF and is the basis for the New York Heart Association (NYHA) classification system, which is summarized in Table 1.1 (Criteria Committee of the New York Heart Association, 1974; Raphael et al., 2007; Apostolo et al., 2012).

Table 1.1 NYHA functional classification system (modified from Raphael et al., 2007)

Class	NYHA functional classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome

	may be present even at rest. If any physical activity is undertaken, discomfort is increased.
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Despite advances in disease management, HF is associated with high rates of mortality and hospitalization (Dunlay et al., 2009). Clinical trials often focus on measuring these outcomes, but of equal importance are the changes in physiology of end-organs caused by hypoperfusion and ischemic damage, as well as the clinical impacts of these changes. The brain is particularly susceptible to hypoperfusion injury, as it requires 60% of blood glucose, 15-20% of Q at rest, and is considered a high-flow, low-resistance organ (Williams & Leggett, 1989; Berg et al., 2002). The clinical manifestation of cerebral end-organ damage in the setting of cardiac disease was originally termed “cardiogenic dementia”, but recent literature classifies this as a form of vascular cognitive impairment (Lancet Editorial, 1997; Rizzi et al., 2014). In light of the projected two-fold increase in dementia cases globally (estimated at an overwhelming 81 million), it is increasingly apparent that understanding the link between cardiovascular and neurological disease is vital (Ferri et al., 2005). A recent review from Brassard and Gustafsson (2016) detailed the effects of HF, its comorbidities, and its treatments on cerebral blood flow (CBF) and oxygenation, with a focus on exercise intolerance in this patient group. This review conclusively presents the need for an integrative understanding of cerebrovascular physiology in the setting of HF to improve the quality of life and health outcomes.

1.2 Pathophysiology of Heart Failure

Some differences exist in the pathological progression of HF subtypes, but in general HF can be thought of as a vicious cycle in which sustained activation of early compensatory mechanisms leads to progressive ventricular dysfunction and terminal HF. Central to the mechanism of HF is low Q, which in the absence of compensatory mechanisms, lowers mean arterial pressure (MAP). Initially, MAP is rescued by the Frank-Starling mechanism: increased

end diastolic volume elevates end diastolic pressure, leading to increased myocardial stretch and Q (Westerhof & O’rourke, 1995; Kemp & Conte, 2012). Inability of the Frank-Starling mechanism to fully rescue MAP leads to recruitment of the sympathetic nervous system (SNS), which while initially adaptive, leads to maladaptive secondary symptomology with chronic adaptation (Kemp & Conte, 2012). By elevating heart rate (HR) and contractility, as well as promoting systemic vasoconstriction, increased activation of the SNS increases stroke volume (SV) and total peripheral resistance (TPR), thereby increasing MAP (Lee & Tkacs, 2008; Chagger et al., 2009; Kemp & Conte, 2012). However, sustained sympathetic activity is detrimental to the myocardium and peripheral vasculature. Sympathetic toxicity compromises contractility of the heart, decreasing ejection fraction, and promoting arrhythmias (Chagger et al., 2009). Sympathetic activation also results in upregulation of the global and vascular renin-angiotensin-aldosterone system (RAAS), which augments MAP by promoting sodium retention, thirst, and vasoconstriction. Similar to SNS activity, sustained activation of RAAS is detrimental, promoting peripheral artery stiffness and progressive changes in cardiac tissue (Chagger et al., 2009).

With sustained hemodynamic stress, the heart undergoes morphological changes in mass, shape, and ventricular function, a process termed cardiac remodelling (Kitzman et al., 2002). While these changes initially increase SV and Q, progressive remodelling hastens disease progression through cardiac fibrosis and myocardial apoptosis (Curry et al., 2000; Kemp & Conte, 2012). Interestingly, there are stark differences in ventricular remodelling between HFpEF and HFrEF, while HFmEF exists on a spectrum between the two extremes. HFrEF classically manifests with a normal SV, but significant dilation of left ventricular chamber dimensions (Kitzman et al., 2002; Fukuta & Little, 2007), whereas HFpEF often presents with

normal chamber size, but increased wall thickness and myocardial fibrosis (Kitzman et al., 2002; Borlaug et al., 2010).

As cardiac function worsens, and insufficiency develops, the inability of the heart to adequately handle venous return results in peripheral and pulmonary edema (Kemp & Conte, 2011). Congestive HF is a term used to describe HF patients with pulmonary edema and these patients often experience shortness of breath, particularly in supine posture, and fatigability as edema of the lungs and hypoperfusion of working muscles drastically impact respiratory dynamics and oxygen delivery, respectively.

1.3 Cerebral Hypoperfusion at Rest in Heart Failure

Cerebral hypoperfusion has been observed in patients with HFrEF and HFmEF. In 17 stable HF patients (73.7 ± 5.4 years, LVEF $< 50\%$), single-photon emission computed tomography (SPECT) revealed significantly reduced cerebral perfusion in several regions of the brain, compared to healthy age-matched controls. Interestingly, cerebral hypoperfusion was correlated to impaired visual memory, a symptom commonly experienced by older adults with dementia (Alves et al., 2005). Choi and colleagues (2006) measured global cerebral perfusion using radionuclide angiography in a younger adult cohort of 52 patients with advanced congestive HF secondary to idiopathic dilated cardiomyopathy (aged 41 ± 11 years, and LVEF $\leq 35\%$). This study revealed areas of significant hypoperfusion in HF patients, compared to healthy age-matched controls (Choi et al., 2006). Arterial spin labelling investigations, using magnetic resonance imaging (MRI), have also shown similar hypoperfusion in HF patients. This recent study showed lower CBF in 19 HF patients (aged 55.5 ± 9.1 years, LVEF $30.5 \pm 11.5\%$), compared to healthy age-matched controls. Reduced CBF was noted in numerous regions of the

brain, concomitant with impairments in multiple autonomic, mood, and cognitive regulatory sites (Roy et al., 2017).

While hypoperfusion and reduced LVEF are certainly related, limited evidence suggests that CBF is correlated to LVEF in patients with HFrEF. Outside of conventional neuroimaging techniques, CBF can be quantified using Doppler ultrasound of the extracranial arteries that supply the brain (bilateral internal carotid and vertebral arteries). Loncar and colleagues (2011) used this method to investigate CBF in 71 men (aged 68 ± 7 years LVEF $29 \pm 8\%$), and found that extracranial CBF was lower compared to healthy age-matched controls, as well as positively correlated with LVEF ($r = 0.271$, $p = 0.022$). While a sexually homogenous cohort limits the external validity of a study, HFrEF shows a slight sex bias (62% of patients are male), and thus these findings may be relevant to most HFrEF patients (Borlaug & Redfield, 2011).

Cerebral autoregulation is the physiological mechanism that maintains consistent CBF across a range of blood pressure (BP). However, even for BP within the autoregulatory range, both acute (Levine et al., 1994; van Lieshout et al., 2001; Ogawa et al., 2007) and chronic (Rajagopalan et al., 1984; Paulson et al., 1984; van Bommel et al., 2010; Loncar et al., 2011) reductions in Q have been shown to lower CBF. While acute suppression of Q appears to have no effect on cerebral autoregulation (Deegan et al., 2010), cerebral ischemia from chronically low Q in the setting of HF may be exaggerated by impaired cerebral autoregulation. A study of 52 ischemic HF patients (aged 64.3 ± 9 years, LVEF 20-45%), demonstrated that HF patients were more likely to show impaired dynamic cerebral autoregulation during supine rest, compared to age-, sex-, and BP-matched controls (Caldas et al., 2016). More recent work in a group of 40 HF patients (aged 62.9 ± 8.7 years, LVEF 30-40%) determined that dynamic cerebral autoregulation was more likely to be impaired during sub-maximal handgrip exercise,

compared to healthy age-matched controls (Caldas et al., 2018). However, the possibility of an impaired cerebral autoregulatory response may only affect CBF in patients with severe HF. A group of 15 patients with mild HF (median age = 48 years, interquartile range = 37-56 years, and median LVEF = 32%, interquartile range = 26-43%) were more likely to show differences in cerebral autoregulation and vasomotor reactivity, without showing changes in CBF (Erkelens et al., 2016).

Hyperventilation and Cheyne-Stoke breathing are common symptoms of HF that lead to chronic hypocapnia (Fanfulla et al., 1998; Oldenburg et al., 2015). As carbon dioxide is a potent stimulus of vasodilation, hypocapnia causes elevated cerebral vascular resistance, and may exacerbate reduced CBF in HF patients. The complex pathophysiological mechanisms that result in reduced CBF in the setting of HF, as described above, are summarized in Figure 1.1.

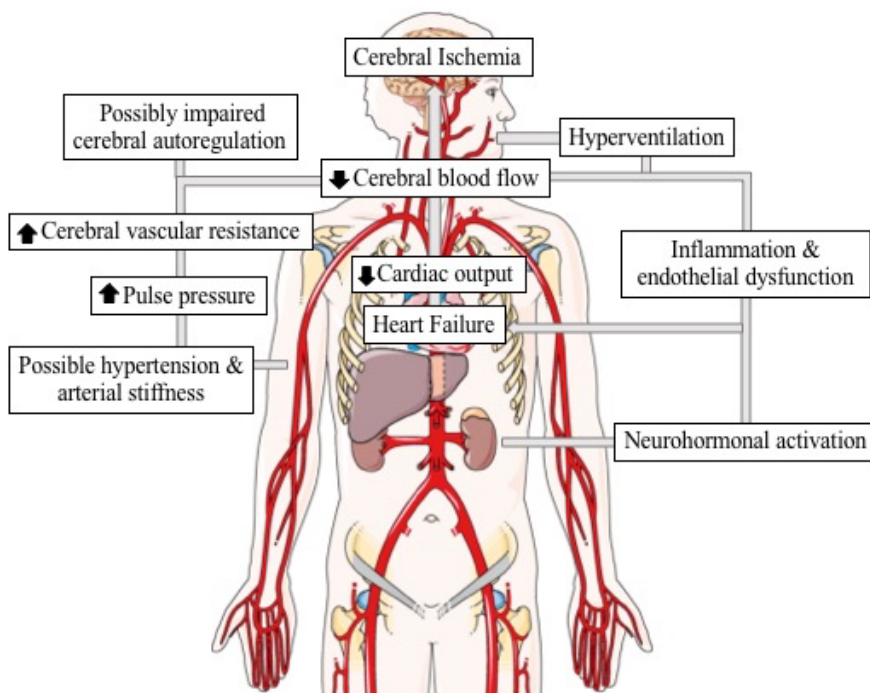


Figure 1.1 Systemic interactions promote reduced CBF in the setting of HF

HF and reduced Q directly lower CBF. Comorbid hypertension and arterial stiffness may also be present, and are commonly seen in HFpEF. These increase pulse pressure, which causes vascular damage, increasing cerebral vascular resistance. The potential of an impaired cerebral autoregulatory response, may lead to further reductions in CBF. Neurohormonal activation,

systemic inflammation, and endothelial dysfunction have also been hypothesized to indirectly affect CBF, further promote cerebral ischemia in HF patients.

In addition to the mechanisms previously described, ischemic damage to cerebral tissue can also develop as a result of an embolic stroke. HF increases the risk of stroke by two- to three-fold, and is the second leading cardiac cause of stroke. Estimates suggest for every 5% decrease in LVEF, stroke risk increases by 18% (Sila, 2007). Clinically, HF is considered a hypercoagulable state. Progressive left ventricular dysfunction and chamber dilation promote intra-cardiac stasis and thrombus formation (Gibbs et al., 2001; Sila, 2007). Concomitantly, systemic endothelial dysfunction and rheological abnormalities (e.g., hypersensitivity of the coagulation cascade) satisfy Virchow's triad and place HF patients at risk of complication from thromboembolism formation (Gibbs et al., 2001; Chin et al., 2003; Lip & Gibbs, 1999).

Atrial fibrillation, another common comorbidity of HF due to shared risk-factors, also promotes intra-cardiac stasis and increases ischemic stroke risk (Wang et al., 2003; Wolf et al., 1991). In atrial fibrillation, the sinoatrial node fails to trigger atrial contraction, leading to uncoordinated depolarizations. As a result, the rate of atrial contraction is greater than ventricular contraction, which causes ineffective ventricular filling and low Q (Daoud et al., 1996). Improper ventricular filling also contributes to intra-cardiac stasis as stagnant blood remains in the left atrium, further elevating the risk for thromboembolism formation and peripheral ischemia secondary to a thromboembolic event.

1.4 Cerebral Blood Flow During Orthostasis in Heart Failure

The cardio- and cerebrovascular system of HF patients is often unable to adequately maintain CBF during supine rest; however, impairment of additional mechanisms responsible for maintaining BP and CBF during orthostasis challenges worsens CBF regulation during such challenges. During transition from supine-to-standing posture, the body experiences a

redistribution of blood volume such that blood pools predominantly in the abdomen and lower limbs, which decreases venous return to the heart (Swenne, 2013). Resultant decreases in ventricular filling lower Q, and subsequently decrease BP. During non-pathological conditions, this response is detected by a group of stretch-sensitive mechanoreceptors, termed baroreceptors, which are located in the aortic arch and carotid sinus (Swenne, 2013). Decreased BP results in decreased stretch of the baroreceptors, which is relayed to the cardiovascular control centre in the medulla oblongata, resulting in modulation of the parasympathetic nervous system (PNS) and SNS. Initially, vagal withdrawal increases HR, but secondary activation of the SNS further increases HR, SV, and promotes vasoconstriction (Swenne, 2013). Together, these responses increase Q and TPR to restore BP.

Studies have reported abnormalities in the baroreflex of patients with HF. Using a neck chamber device to perform a step-wise modulation of the apparent pressure detected by the carotid baroreceptors (i.e., loading or unloading the baroreceptors by decreasing or increasing the pressure in the neck chamber, respectively), a study of 14 mostly HFrEF patients (aged 38-68 years, LVEF 11-62%) showed impaired baroreflex sensitivity in this group (Sopher et al., 1990). Caution should be taken in drawing conclusions from this finding, as increased arterial stiffness, an expected pathology in both healthy older adults and those with cardiovascular disease, has been shown to be an independent predictor of impaired baroreflex sensitivity in older populations (Mattace-Raso et al., 2007). Abnormalities in the baroreflex of these patients could be explained in part by the attenuation of the HR response during upright posture seen in HF patients (Levine et al., 1983). Some HFrEF patients undergo a paradoxical vasodilation, opposed to expected vasoconstriction, in peripheral vascular bed during orthostasis (Goldsmith et al., 1983a; Wroblewski, 1994). Both of these factors would greatly impact the baroreflex response,

but HF patients also exhibit elevated levels of neurohormonal factors at rest, indicating some degree of autonomic dysfunction. These molecules (e.g., arginine vasopressin) are potent vasoconstrictors, and elevated resting levels attenuate their release in response to orthostasis, further limiting the efficacy of the baroreflex response in these patients (Goldsmith et al., 1983b).

Several studies have been conducted to investigate if these abnormal physiological responses to orthostasis predispose HF patients to reductions in CBF during upright posture. A group of forty HF_rEF patients (aged 53 ± 7.5 years, LVEF = $26.8 \pm 8.3\%$) showed lower middle cerebral artery (MCA) blood flow velocity, and abnormal vasomotor reactivity during several autonomic challenges, including a 5% carbon dioxide and hyperventilation tests, Valsalva, and orthostatic tilt (Serber et al., 2014). A more recent cross-sectional study examined extracranial CBF in 22 HF patients (aged 69 ± 9 years, LVEF = $33 \pm 11\%$, 4 participants had LVEF $\geq 45\%$). Compared to healthy age-matched controls, HF patients had lower resting CBF in supine posture, and a greater decrease in CBF in response to upright posture (Fraser et al., 2015). These two studies suggest that impairment of the protective physiological mechanism responsible for maintaining CBF may predispose HF_rEF and HF_mEF patients to both acute and chronic cerebral ischemia during transient autonomic challenges (e.g., orthostasis) and sustained upright posture as is common during activities of daily living (ADL), both of which are risk factors for falls in older adults (Tinetti & Williams, 1997; Finucane & Kenny, 2017).

1.5 Cerebral Blood Flow During Acute Physical Activity in Heart Failure

CBF was assumed to remain unchanged in healthy adults when transitioning from rest to exercise (Scheinberg et al., 1954; Zobl et al., 1965), but recent evidence from both transcranial Doppler ultrasound and MRI studies have shown that global CBF increases with exercise

intensity up to approximately 70% $\text{VO}_{2\text{ max}}$ (Madsen et al., 1993; Subudhi et al., 2008; Smith et al., 2012). This has been attributed to multiple factors, including, elevations in Q (Querido and Sheel, 2007; Meng et al., 2015), cerebral metabolic and neuronal activity which overcome SNS induced cerebral vasoconstriction (Secher et al., 2008; Brassard et al., 2010), central command (Sato et al., 2009), and mechanoreflex (Jørgensen 1992a,b, 1993) .

In the setting of HF, several cardiac and non-cardiac pathologies may limit the expected increase in CBF during exercise, thereby contributing to exercise intolerance in this patient population. In a summary of the report by Hellstrom et al. (1997), it was noted that when healthy individuals perform single-leg exercise, mean cerebral blood flow velocity (CBFV) increased by approximately 20% and was maintained during double-leg exercise; however, individuals with HF did not increase mean CBFV during single-leg exercise, and double-leg exercise decreased mean CBFV. In HFrEF, reduced maximal HR, lower HR reserve, and an attenuated exercise-induced increase in SV all contribute to reduced maximal Q during exercise (Sullivan et al., 1989; Cooke et al., 1998; Florea et al., 1999). In the case of HFpEF both HR and SV are also inadequately modulated in response to exercise, but elevated afterload, likely a consequence of vascular endothelial dysfunction, is an important component in reduced Q and elevated ventricular filling pressure (associated with dyspnea) during exercise (Bourlag et al., 2006; Bourlag et al., 2010; Andersen et al., 2012; Maeder et al., 2012). Non-cardiac factors affecting exercise tolerance are similar between HF subtypes. Impaired lung function and excessive dead space ventilation (observed as a high ventilation rate to expired carbon dioxide ratio (V_E / V_{CO_2})) during exercise are considered hallmarks of HF (Wasserman et al., 1997; Clark et al., 2000). In addition, increased peripheral and central chemoreflex and ergoreflex responses contribute to increased ventilation during exercise in individuals with HF. The peripheral chemoreceptors are

located in the carotid bodies, and respond primarily to hypoxaemia, but potassium and hydrogen ions, and carbon dioxide also influence peripheral chemoreceptor activation. The central chemoreceptors are found in the region of the brainstem, and activate in response to hypercapnia. Regardless of the location, activated chemoreceptors initiate a physiological cascade that results in hyperventilation and sympathetic activation (Kara et al., 2003). Hypersensitivity of the chemoreflex has also been associated with attenuated baroreflex sensitivity and poor prognosis in ambulatory individuals with HF (Ponikowski et al., 2001a). The ergoreflex is initiated in response to muscle contraction and metabolite accumulation, such that activation of muscle ergoreceptors stimulate sympathetic drive, ventilation, and peripheral vasoconstriction (Schmidt et al., 2005). In individuals with HF hypersensitivity of the ergoreflex has been associated with exercise intolerance and hyperventilation, worse symptomology, and increased central chemosensitivity (Ponikowski et al., 2001b). Overall, the chemo- and ergoreflex are important homeostatic feedback mechanisms for BP and respiratory regulation, and their disruption explains the common occurrence of oscillatory breathing, hyperventilation, and dyspnea in HF patients during exercise (Schmidt et al., 2005; Dhakal and Lewis, 2016). In particular, oscillatory breathing during exercise has been shown to be present in both HFrEF and HFpEF, and individuals with HF and oscillatory ventilation during exercise have lower peak VO_2 , and peak and resting P_{ETCO_2} (Cornelis et al., 2015). This reflects lower exercise capacity in this population, which may also be limited by the stronger sensation of dyspnea experienced by individuals with HF and oscillatory ventilation during exercise (Matsuki et al., 2013). Together, this may help explain results from a meta-analysis that showed that individuals with HF and oscillatory breathing during exercise are fourfold more likely to experience adverse health outcomes compared to individuals with HF but no oscillatory breathing during exercise (Cornelis

et al., 2015). The spiral phenomenon which is observed on the plot of VCO_2 and VO_2 for some individuals with HF and oscillatory breathing during cardiopulmonary exercise testing is attributed to phase and amplitude differences between VCO_2 and VO_2 (Nagayama et al., 2015). These individuals exhibit greater cardiopulmonary dysfunction (lower peak VO_2 and $P_{ET}CO_2$, and steeper VE- VCO_2 slope) compared to individuals with HF that do not exhibit the spiral phenomenon (Nagayama et al., 2015). These respiratory disturbances contribute to lower CBF and oxygenation seen in HF patients as they reduce arterial carbon dioxide, in turn promoting cerebral vasoconstriction.

While exercise intolerance has long been identified as a consequence of HF, only recently has reduced CBF, resulting from the pathologies discussed above, been identified as a key to understanding this intolerance. Thus, there are a limited number of studies that have measured CBF and oxygenation during exercise in the setting of HF. Fu and colleagues used near-infrared spectroscopy to monitor cerebral oxygenation of the frontal lobe in NYHA Class II ($n = 53$ aged, 66.5 ± 1.2 , LVEF 38.6 ± 1.1) and NYHA Class III ($n = 48$, aged 67.5 ± 1.5 , LVEF 38.5 ± 1.5) HF patients, as well as matched controls. The Class III HF group showed a significant reduction in frontal lobe oxygenation which was associated with ventilatory abnormalities (Fu et al., 2011). Similarly, a group of 34 mostly male HF patients (aged 56 ± 13 years, LVEF $32 \pm 14\%$) showed lower resting cerebral oxygenation and peak oxygenation during an incremental cardiopulmonary exercise test, compared to healthy controls (Chen et al., 2018).

1.6 Cognitive Impairment in Heart Failure

Decreased CBF impairs the delivery of glucose and oxygen to the brain, reduces adenosine triphosphate (ATP) production, and contributes to injury and death of cerebral tissue. Sustained cerebral injury clinically manifests as cognitive impairment, which is diagnosed in 25-

75% of HF patients, and may progress to dementia if the primary cause of the cognitive impairment is left untreated (Ampadu & Morley, 2015).

The high prevalence with which structural brain abnormalities are present in HF patients was uncovered with advancements in neuroimaging (Ampadu & Morley, 2015). This increased prevalence has been attributed to hypoxia and ischemic damage due to reduced LVEF and Q commonly seen in HF (Alosco et al., 2013). As previously discussed, a variety of physiological mechanisms are responsible for low CBF and subsequent cerebral ischemia. In response to ischemic damage, cerebral tissue releases local vasodilators (e.g., endothelial nitric oxide), and vasoconstrictors (e.g., endothelin-1) in an effort to regulate CBF (de la Torre, 2012). Unfortunately, these vasoactive molecules have been linked to impaired clearance of beta-amyloid and phosphorylated tau proteins, and thus may contribute to the progression of Alzheimer's dementia (Ampadu & Morley, 2015).

Cross-sectional studies have implicated a link between reduced LVEF and cognitive impairment in the setting of HF. A group of 57 patients (aged 77 ± 1 years) showed a positive nonlinear association between LVEF and cognitive function ($\beta = 0.58$, $p = 0.001$), such that patients with $LVEF < 30\%$ had significantly greater cognitive impairment than patients with $LVEF \geq 30\%$ (Zuccalà et al., 1997). It is noteworthy that this study utilized the Mini-Mental State Examination to quantify cognitive impairment, which, while commonly used by clinicians, has been shown to be less effective in assessing clinically relevant cognitive deficits compared to other screening techniques (Cameron et al., 2013). A cohort of 55 mostly male patients (aged 55 ± 7.8 years, $LVEF 22.4 \pm 12.8\%$) showed similar results, demonstrating a correlation between LVEF and subjective cognitive impairment, assessed with the Cerebral Insufficiency Self Report Inventory (Steinberg et al., 2011). Harkness and colleagues (2014) extended the knowledge of

cognitive impairment in HF by assessing cognitive function and self-care management in 100 HF patients (aged 72.4 ± 9.8 years, LVEF $\leq 45\%$). Of the patients in this study population, 71% were diagnosed with mild cognitive impairment, and only 21% had adequate self-care management. A backwards regression model, controlling for age and sex, revealed a significant interaction ($p = 0.001$) between cognitive function and self-care management, highlighting the difficulty with which some HF patients have with maintaining adequate self-care, particularly in the setting of cognitive dysfunction (Harkness et al., 2014).

LVEF may also be predictive of cognitive aging outside of the setting of HF. Brain and cardiac MRI of 1114 healthy Framingham Heart Study Offspring Cohort participants free from clinical stroke or dementia (aged 67 ± 9 years, LVEF $67.3 \pm 6.7\%$) revealed a nonlinear, positive relationship between LVEF and mean cognitive performance (Jefferson et al., 2011). While these cross-sectional studies cannot establish causality, they do suggest a link between cognitive function and LVEF, in both healthy older adults and patients with chronic HF_rEF. However, no studies have examined the relationship between cognition and LVEF in and HF_pEF, even though potential differences in cognition between HF_rEF and HF_pEF have been noted (Witt et al., 2016), and subclinical cerebral infarcts (which have been related to cognitive dysfunction) are highly prevalent in patients with HF_pEF (Chen et al., 2014; Cogswell et al., 2017).

In HF_rEF, several studies have shown that improvements in LVEF and Q are associated with improved cognitive function. Thirty-six HF patients (aged 66 ± 8 years, LVEF $32 \pm 12\%$) showed improvement in Q following enhanced external counterpulsation therapy, which artificially improves venous return back to the heart. Compared to a standard medical treatment control group, the experimental treatment group also exhibited significantly greater improvement

in several cognitive domains, including spontaneous naming, attention, and executive function (Kozdağ et al., 2013). Cardiac resynchronization therapy in 27 HF patients (aged 68 ± 9 years, baseline LVEF 31.4%) resulted in improvements in LVEF, which had a significant effect on improving several cognitive domains over a 3-month treatment period (Hoth et al., 2010). The use of both pulsatile ($n = 18$, aged 50 ± 10 years, LVEF = $20 \pm 5\%$) and continuous ($n = 11$, aged 56 ± 15 years, LVEF = $20 \pm 6\%$) ventricular assist devices in patients with terminal HF improved cognitive function (Zimpfer et al., 2006). Independent studies of patients with severe HFrEF have shown that cardiac transplantation improves both CBF (Gruhn et al., 2001) and several domains of cognitive function (Grimm et al., 1996; Deshields et al., 1996).

Although the pathophysiology and disease progression of HF are still not fully understood by clinicians and researchers, a clear but complex interaction exists between HF, reduced CBF, and cognitive impairment. Efforts to further characterise the mechanism of this interaction should reveal therapeutic targets and intervention strategies to ameliorate adverse health outcomes in HF patients.

2.0 Study Rationale

Compared to healthy controls, individuals with HF have lower CBF during supine rest, and an exaggerated reduction in CBF in upright posture (Fraser et al, 2015). Cerebral oxygenation is also lower in individuals with HF during upright posture, compared to healthy controls (Chen et al., 2018). While previous investigations in individuals with HF have only assessed CBF and oxygenation in the confines of strictly imposed laboratory conditions, advances in ambulatory monitoring technologies allow for the assessment of cerebral hemodynamics and oxygenation in both healthy and clinical populations during dynamic real-life scenarios. Impaired blood pressure regulation and orthostatic hypotension, commonly observed in older adults, may lead to cerebral hypoperfusion, presyncope or syncope, and increased falls risk (Tinetti & Williams, 1997; Finucane & Kenny, 2017). For individuals with HF, the prevalence of orthostatic hypotension has been reported to range from 8% in community-dwelling individuals to 83% in elderly hospitalized patients (Potocka-Plazak and Plazak 2001; Mehagnoul-Schipper et al., 2002; Gorelik et al., 2016). An inability to effectively regulate cerebral perfusion may predispose individuals with HF to cerebral ischemia, as well as further exacerbate the risk of falls; however, it is unknown how CBF and oxygenation respond to dynamic ADLs in individuals with HF. The purpose of this study was to investigate the effects of posture transitions and walking on CBF and oxygenation in individuals with HF. Chronic cerebral ischemia as a result of reduced CBF and cerebral oxygenation during ADLs may result in chronic cerebral ischemia, which has been linked to cognitive impairment in individuals with HF (Loncar et al., 2011; Zucalla et al., 1997). Cognitive impairment has become increasingly apparent in individuals with HF, elevating their risk for hospitalization and adverse health outcomes. This research will generate critical information to assess dynamic cardio- and

cerebrovascular adaptations and their impact on cerebral oxygenation under conditions reflecting real-life scenarios in individuals with HF.

3.0 Study Objectives and Hypotheses

Primary Objective 1:

To investigate the central cardiac response to walking in individuals with HF and healthy-matched controls.

Hypothesis 1:

Compared to healthy-matched controls, participants with HF will have an attenuated rise in cardiac index ($Q_i = Q/\text{body surface area}$) in response to walking.

Primary Objective 2:

To investigate the acute and sustained cerebrovascular responses during supine-to-stand and sit-to-walk transitions in participants with HF and age-matched controls without HF.

Hypothesis 2a:

Compared to healthy-matched controls, participants with HF will have a lower absolute cerebral tissue saturation index (TSI) and mean CBFV nadir after transitioning from supine rest to upright standing, as well as from upright seated posture to walking.

Hypothesis 2b:

Participants with HF will have lower absolute mean CBFV and cerebral TSI during quiet standing and walking, compared to healthy-matched controls.

Secondary Objective 1:

To determine if LVEF, arterial stiffness, and cognition are associated with cerebral perfusion during supine rest.

Hypothesis 3a:

Across the range of physiological characteristics anticipated with the HF and control participants, the absolute mean CBFV and cerebral TSI measured during supine rest will be

positively correlated with carotid distensibility and LVEF, and negatively correlated with carotid-femoral pulse wave velocity.

Hypothesis 3b:

In both HF and control participants the absolute mean CBFV and cerebral TSI measured during supine rest will be positively correlated with Montreal Cognitive Assessment (MoCA) score.

4.0 Methods

4.1 Ethics

The experimental procedures for this study were approved by the Office of Research Ethics at the University of Waterloo (ORE #21025).

4.2 Recruitment

Participants for each study group (individuals with HF and age-matched controls who considered themselves to be relatively healthy, “healthy controls”) were recruited from both the community and primary care centers. Both sexes were recruited. For the HF cohort, patients with HFrEF, HFmEF, and HFpEF were recruited using inclusion/exclusion criteria shown in Table 4.1. The control group consisted of age-matched healthy individuals, free from cardio- and cerebrovascular disease.

Table 4.1 Inclusion/exclusion criteria (also provided in Poirier, see Declaration (pg. ii))

Inclusion criteria	Exclusion Criteria
<ul style="list-style-type: none">• Age greater or equal to 65 years old• Assistive devices for walking were permitted.	<ul style="list-style-type: none">• Taking alpha adrenergic blocking agents• Transplant recipients• NYHA functional class IV• Major hospitalization for cardiovascular events or procedures within the last 4 weeks• Hospital admission that required an overnight stay within the past 3 months (risk of delirium)• Psychiatric illness or use of psychoactive drugs• History of myocardial infarction in the past 3 months• History of drug/alcohol abuse• Carotid stenosis > 50% (ICA systolic peak velocity > 125cm/s)• Atrial fibrillation requiring Warfarin or Coumadin• Uncontrolled hypertension (greater or equal to 140/90) and/or resting HR >110• Severe arthritis or arthralgia limiting mobility• Prior diagnosis of dementia• Prior diagnosis of sleep apnea• Medicine regimen changed in the past 6 weeks.

4.3 Data Collection

4.3.1 Study Overview

To investigate the two primary objectives of this project, the proposed sample size was calculated for $\alpha = 0.05$, power = 0.8 using GPower 3.1.9.4 (Faul et al., 2007). Estimated mean and standard deviation values were taken from Fraser 2014. Using seated Qi data (Primary Objective 1) sample size was estimated at 5 participants per group, and using seated CBF data (Primary Objective 2) sample size was estimated at 15 participants per group (sample size calculation also presented in Poirier, see Declaration (pg. ii)). Overall we were able to recruit 10 individuals with HF and 13 relatively healthy age-matched controls. During each testing session, resting vascular and cardiac investigations were conducted to assess cardiovascular health. Following resting investigations, participants were outfitted with ambulatory monitoring devices to assess their cardio- and cerebrovascular responses during ADLs. For this study, ADLs were operationalized as three transitions: supine to quiet standing, sitting to walking at a self-selected normal pace, and sitting to walking at a self-selected slow pace. Transitions were block randomized such that the two walking trials were always completed one after the other, but the order of the walking transitions was random, and the supine-to-stand transition randomly preceded or followed the walking transitions.

4.3.2 Cognitive Testing

Global cognition was assessed with the MoCA. This short duration, minimal burden examination assesses domains of attention and concentration, executive function, memory, language, visual/constructional skills, conceptual thinking, calculations, and orientations (Harkness et al., 2011). The MoCA is sensitive to cognitive deficits seen in older HF patients, with a sensitivity of 90% and a specificity of 78% for mild cognitive impairment (Harkness et

al., 2011). It is currently recommended by the Canadian Stroke Network and used in large population-based studies, including the Irish Longitudinal Study on Aging (Nolan et al., 2017).

4.3.3 8-Meter Walk Test

An 8-meter walk test was used to determine gait speed as a measure of frailty in both participant groups (Castell et al., 2013). Participants were allowed to use walking devices if they were required. Following a countdown, participants began walking at their normal pace. The time required to walk 8-meters was recorded but participants were instructed to walk past the 8-meter mark so that deceleration did not influence their gait speed measurement.

4.3.4 Ultrasound (methodology also reported in Poirier, see Declaration (pg. ii))

Both vascular and cardiac ultrasound were conducted using a standard clinical ultrasound system (iE33 xMatrix, Koninklijke Philips Electronics, NV USA). The right common carotid artery (CCA) was imaged with a 10-17 MHz linear array transducer (L9-3, Koninklijke Philips Electronics, NV USA) to assess arterial wall thickness and CCA stiffness. Applying American Society for Echocardiography guidelines, a cardiac probe (X5-1, Koninklijke Philips Electronics, NV USA) was used to assess LVEF and diastolic function (e.g., E/A, E/e') (Lang et al., 2005; Nagueh et al., 2016).

4.3.5 Applanation Tonometry (methodology also reported in Poirier, see Declaration (pg. ii))

Tonometry (SPT-301, Millar Instruments, Houston TX USA) was used to determine pulse pressure of both the CCA and femoral artery. To determine carotid distensibility, the tonometer was held to the left CCA for 10-15 cardiac cycles while ultrasonography of the right CCA was being conducted (see 4.4.3). The tonometer was then held against the right CCA for 30-40 cardiac cycles, while a second tonometer was held against the right femoral artery for the same 30-40 cardiac cycles. Calipers were used to measure the distance between the carotid and

femoral measurement sites, and 80% of this distance was used to calculate carotid-femoral pulse wave velocity (cfPWV; see Eq1), the criterion standard measure of central arterial stiffness (Townsend et al., 2015).

$$\text{cfPWV (cm/s)} = \frac{0.8 \times \text{cf distance (cm)}}{\text{cf pulse wave transit time (s)}} \quad [\text{Eq1}]$$

4.3.6 Ambulatory Monitoring (similar methodology reported in Poirier, see Declaration (pg. ii))

Hemodynamics: Both HF and control participants were outfitted with ambulatory devices to monitor cardio- and cerebrovascular parameters during transitions and walking. The Portapres (Portapres Model-2, Finapres Medical Systems, Amsterdam The Netherlands) was used to measure continuous arterial BP through finger cuff photoplethysmography. While this device is portable, it is too cumbersome for older adults to carry, and therefore, was placed on a walker which moved with the participant. The continuous finger BP waveform yields beat-by-beat estimate of brachial BP, Q, and SV by using the Modelflow algorithm. Estimated Q and SV were normalized to echocardiography derived values of Q and SV (see 4.4.4 *Echocardiography Measurements*)

MCA Blood Velocity: A portable transcranial Doppler (TCD) device (TCD-X, Atys Medical, Soucieu-en-Jarrest France) was used to measure MCA blood velocity during posture transitions and walking. This device is equipped with a robotic probe, which maintains signal quality during movement and is ideal for ambulatory monitoring. While TCD only measures blood flow velocity, it is often used as a surrogate marker of CBF under the assumption that the MCA diameter remains constant. Studies have shown that the diameter of the MCA remains unchanged during perturbations in blood gases and orthostatic stimulus (Serrador et al., 2000; Verbree et al., 2014), while others has shown changes in MCA diameter during hyper- and hypocapnia (Coverdale et al., 2014; Coverdale et al., 2015). In an older HF population, there

may be considerable variation in MCA diameter due to genetics, sex, and risk of atherosclerosis. Differences in blood gases at rest, during transitions, and walking may also affect MCA diameter. Thus, TCD was only be used as a measure of MCA blood flow velocity, not CBF. This was considered in conjunction with measures of tissue oxygenation to characterise cerebral hemodynamics during posture transitions and walking.

Cerebral Oxygenation: A near infrared spectroscopy (NIRS) system (PortaLite, Artinis Medical Systems, Zetten The Netherlands) was placed on the right side of the forehead of participants, such that oxygenation data were collected from the pre-frontal cortex. This device uses near infrared light to determined changes in oxygenated (Oxy Hb), deoxygenated (HHb), and total hemoglobin (tHb) concentration and derives a tissue saturation index (TSI) in real-time.

Expired CO₂: Participants were outfitted with a nasal cannula, connected to a portable gas analyser (Capnostream 35, Metronic, United States) in order to determine breath-by-breath P_{ET}CO₂.

Walking Speed: During both the slow and normal walking conditions participants traversed back and forth along a straight hallway. Pylons were place a know distance apart at either end of the hallway and gait speed was calculated as the time required to completed each hallway length. The participants' overall gait speed for each condition was then calculated as the average of the gait speeds for each hallway length completed.

4.4 Data Analysis

4.4.1 Anthropometric Calculations

Body mass index (BMI), based on height and weight, was calculated as a measure of body size (calculation also presented in Poirier, see Declaration (pg. ii)).

$$\text{BMI (kg/m}^2\text{)} = \text{mass (kg)} / (\text{weight (m)})^2 \quad [\text{Eq2}]$$

The Dubois formula was used in this study to estimate human body surface area (Du Bois & Du Bois, 1989). Measures of SV and Q were normalized to body surface area for each participant to account for differences in body size.

$$\text{BSA (m}^2\text{)} = 0.007184 \times \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \quad [\text{Eq3}]$$

4.4.2 Cognitive Testing

Total MoCA scores were calculated as the sum of the individual cognitive domain scores. The six domains tested are: short-term memory, visuospatial function, executive function, attention, concentration and working memory, language and orientation scores. An additional point was added for participants with less than 12 years of formal education (Nasreddine et al., 2005).

4.4.3 Vascular Measurements

Carotid intima-media thickness (IMT) was calculated from B-mode images of the right CCA using the ultrasound systems built-in software (QLAB, Koninklijke Philips Electronics). IMT is known to change across the cardiac cycle; therefore, measurements were assessed at end diastole and averaged over ten separate cardiac cycles (Polak et al., 2012).

Distensibility of the CCA was calculated as an indication of the relative change in arterial diameter for a given pressure and is inversely proportional to arterial stiffness.

$$\text{Distensibility (mmHg}^{-1}\text{)} = \frac{\Delta \text{ Cross Sectional Area}}{(\text{Pulse Pressure}) (\text{Minimum Cross Sectional Area})} \quad [\text{Eq4}]$$

4.4.4 Echocardiography Measurements (methodology also reported in Poirier, see Declaration (pg. ii))

Apical four-chamber and two-chamber echocardiography images were used in the “gold standard” Simpson’s biplane method to quantify LVEF (Schiller et al., 1989; Otterstad, 2002). Doppler ultrasound of mitral valve inflow in the apical four-chamber view was used to quantify

early (E) and late (A) diastolic filling velocities. Tissue Doppler Imaging of the left ventricular septal and lateral walls were used to determine myocardial relaxation (e'). From these values, diastolic function was characterized using E/A and E/ e' ratios (Nishimura et al., 2014). As well, parasternal long axis and apical five-chamber echocardiography images were used to measure the cross-sectional area of the aorta during peak systole, and the velocity time integral of the Doppler spectrum of the left ventricular outflow tract, respectively. From these values, SV was calculated as described in Eq5 and Q was calculated as the product of SV and HR during echocardiography assessment. These values were then used to adjust Modelflow estimates of SV and Q in a single point calibration method described in Eq6, where $Q_{\text{Modelflow}}$ is the beat-by-beat estimate of Q, Q_{Echo} is the echocardiography derive value of Q, and Q_{Baseline} is the 90-second average Modelflow Q from the baseline time point during supine rest. Figure 4.1 shows echocardiography derived Q_i plotted against baseline Q_i predicted from Modelflow.

$$SV \text{ (mL)} = (\text{Velocity Time Integral})(\text{Cross Sectional Area}) \quad [\text{Eq5}]$$

$$\text{Adjusted Q} = Q_{\text{Modelflow}} \times \left(\frac{Q_{\text{Echo}}}{Q_{\text{Baseline}}} \right) \quad [\text{Eq6}]$$

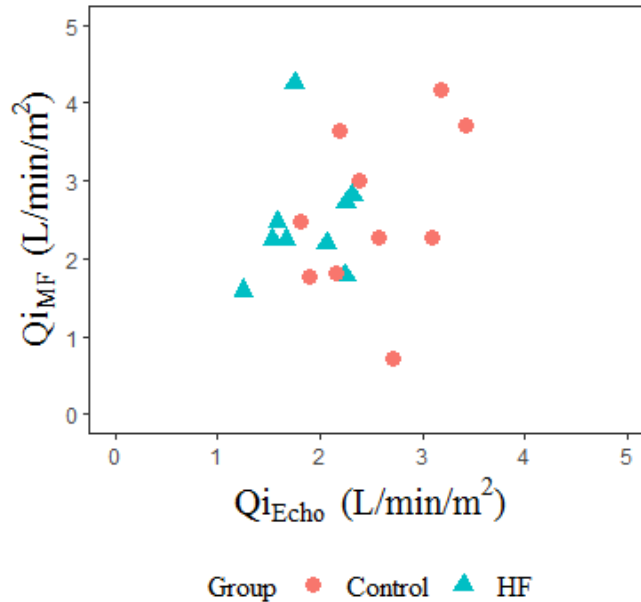


Figure 4.1 Modelflow vs. echocardiography derived estimates of Q_i

Salmon circles represent control participants and blue triangles represent participants with HF. $Q_{i_{MF}}$ – Modelflow estimate of cardiac output estimate during 90-seconds of supine rest; $Q_{i_{Echo}}$ – echocardiography estimate of cardiac output.

4.4.5 Continuous Variables During Transitions and Walking

Continuous central hemodynamics, CBFV, cerebral oxygenation, and respiratory data were time-aligned post-collection. This was accomplished using time-sync markers that were added to the data from each collection device at the beginning and end of each data collection. The alignment of beat-by-beat data (central hemodynamics and CBFV) was further refined by RR interval matching using Matlab 9.4 (The MathWorks, Natick, Massachusetts, United States). Finally, central hemodynamic, CBFV, and cerebral oxygenation data were visually inspected at each transition for the characteristic transient reduction in mean BP, mean CBFV, and oxygenation, as well as in RR interval for central hemodynamics and CBFV. An example time aligned dataset can be seen in Figure 4.3. Baseline was defined as a 90 second average of stable signal during supine/seated rest, prior to orthostatic transition. Nadir values were calculated as the lowest single value after transition to upright posture and mean values were calculated for

each variable at 30 to 60 seconds (early transition), 90 to 120 seconds (middle transition), and 150 to 180 seconds (late transition) after each transition and compared between groups. CBFV data were susceptible to data dropout and thus, was cleaned using a spline interpolation function in R 3.6.0 (R Core Team, Vienna, Austria; see Appendix C). Beat-by-beat variables were interpolated to second-by-second data using SigmaPlot 12.5 (Systat Software, Inc., Chicago, Illinois, United States). Data alignment process also described in Poirier, see Declaration (pg. ii). For some variables, data could not be collected on all participant due to poor signal quality. In figures, the number of participants collected is indicated by the number of individual data points, and in tables the number of participants collected is indicated in the associated text for variables that do not have a full complement of data.

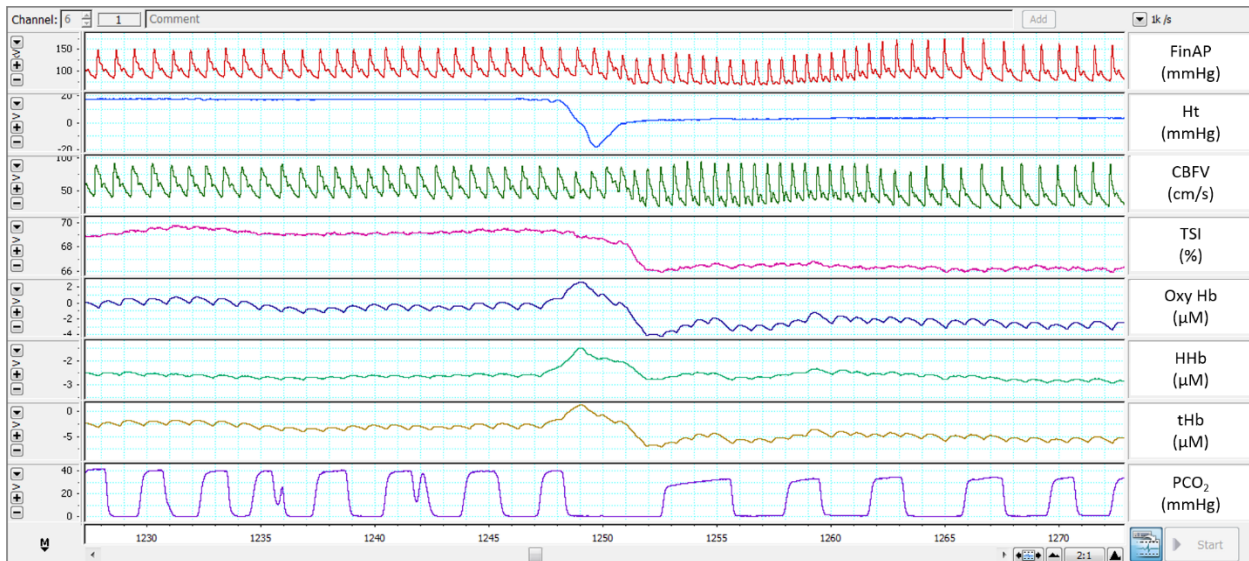


Figure 4.2 Representative time-aligned data set

Representative data from a participant during a supine-to-stand transition prior to beat-by-beat and breath-by-breath data extraction. FinAP – finger arterial pressure; Ht – height correction, CBFV – cerebral blood flow velocity; TSI – tissue saturation index; Oxy Hb – oxygenated hemoglobin; HHb – deoxygenated hemoglobin; tHb – total hemoglobin; PCO₂ – partial pressure of carbon dioxide.

4.5 Statistical Analysis

All variables were assessed for normality using the Shapiro-Wilk’s test and visual

examination of frequency distributions. Group gait speed, MoCA score, and resting vascular measurements were summarized as mean \pm standard deviation values. Comparisons between HF and control participants were made using independent Student's t-tests for normally distributed data and Mann-Whitney U Rank Sums tests for non-normally distributed continuous variables. Comparisons between HF and control participants were made using Fisher's exact test for categorical variables. Seated and supine baseline, nadir, early middle, and late values were compared by linear mixed model analysis with Tukey's honestly significant difference used for post-hoc testing. Pearson's r correlations were used to assess relationships between LVEF, MoCA score, cfPWV, and carotid distensibility with mean CBFV and TSI during supine rest. Due to the inherent grouping of LVEF values correlation analysis was conducted on both the group as a whole and independently on the HF and control groups. Repeated measures correlation analysis was used to assess relationships between cardio- and cerebrovascular variables during the early, middle, and late phases of the supine-to-stand transition and both sit-to-walk transitions. Analysis was conducted on the participant group as a whole, as well as on the HF and control groups separately. Statistical significance was set *a priori* at $\alpha = 0.05$ and trends were reported at $\alpha = 0.1$. All statistical analysis was completed using R 3.6.0 (R Core Team, Vienna, Austria).

5.0 Results

5.1 Participant Characteristics (also reported in Poirier, see Declaration (pg. ii))

Characteristics of the 10 HF and 13 age-matched healthy control participants are summarized in Table 5.1, and medication characteristics are summarized in Table 5.2. The ratio of male/female participants in the HF group (7/3) and control group (4/9), and while not significantly different ($P = 0.10$) these ratios probably influenced some of the physiological characteristics. Participants with HF were significantly taller ($P = 0.04$), weighed more ($P = 0.004$), and had a greater BMI ($P = 0.012$), compared to control participants. A history of smoking was more prevalent in participants with HF ($P < 0.001$), and they also had a slower gait speed ($P = 0.02$) compared to control participants.

Brachial SBP and DBP, measured during supine rest, were not significantly different between groups. Similarly, carotid IMT, distensibility, β Stiffness, and cfPWV were not significantly different between groups. The HF group included individuals with HF_rEF, HF_mEF, and HF_pEF, thus participants with HF had a large range of LVEF (20-61%), as well as a significantly lower LVEF, compared to control participants ($P < 0.001$). There were no significant differences in measures of diastolic function (E/A and E/e') between groups.

The control group included both non-hypertensive and treated hypertensive individuals, therefore, some control participants were on similar medication regimens to the participants with HF. However, more participants with HF were on β -blockers ($P < 0.001$), angiotensin converting enzyme (ACE) inhibitors ($P = 0.02$), diuretics ($P = 0.006$), and anticoagulants ($P = 0.007$) compared to control participants. There were no significant differences in the number of angiotensin receptor blockers (ARB), calcium channel blockers, angiotensin receptor-neprilysin inhibitors (ARNi), statins, or nitroglycerin sprays used by each group.

5.2 Changes in Cardiac Index in Response to Walking

Figure 5.1 compares the Q_i response to slow and normal pace walking in both participants with HF and control participants. The significant group x speed interaction effect was due to a greater increase in Q_i at the normal pace walking speed in control participants compared to the participants with HF ($P = 0.008$).

5.3 Cardiorespiratory and Cerebrovascular Response to Posture Transition and Walking

5.3.1 *Supine and Seated Rest*

The cardiorespiratory and cerebrovascular response during supine and seated rest are presented in Figure 5.2 and 5.3. An average of the baseline values from both sit-to-walk transitions was used as the seated baseline for each variable. Both MAP and SBP trended lower in the participants with HF during both supine and seated rest (main effect of group: $P = 0.08$ and 0.06 , respectively). Control participants had a lower resting HR in supine compared to seated posture (group x condition interaction: $P < 0.001$), but there were no differences between the participants with HF and control participants. In both seated and supine posture, SV_i and Q_i were lower in participants with HF compared to control participants (main effect of group: $P < 0.001$ for both). While there were no differences in peak CBFV, both min and mean CBFV were higher in supine compared to seated posture (main effect of condition: $P = 0.018$ and 0.047 , respectively). There was also a trend for participants with HF to have lower min CBFV compared to control participants (main effect of group: $P = 0.089$). TSI was also lower in HF participants compared to control participants in both supine and seated posture (main effect of group: $P = 0.020$). Lastly, there was a trend for P_{ETCO_2} (partial pressure of end-tidal carbon dioxide) to be lower in participants with HF compared to control participants in both supine and seated posture (main effect of group: $P = 0.094$).

5.3.2 *Supine-to-Stand and Sit-to-Walk Nadirs*

Nadir values for both central and cerebral hemodynamics during the supine-stand transition are shown in Figure 5.4 and Appendix I. There was a trend for lower MAP nadir in the control participants compared to participants with HF ($P = 0.067$). Both SV_i ($P = 0.028$), and Qi ($P = 0.021$) nadirs were significantly lower in participants with HF compared to control participants. There were no between group differences in HR, min, peak, mean CBFV, or TSI or relative Oxy Hb, HHb, or tHb nadir.

Figure 5.5 and Appendix J show nadir values for both slow and normal pace sit-to-walk transitions. Compared to the slow pace condition, SBP was higher at nadir in the normal pace walking condition (main effect of condition: $P = 0.036$). There were no significant differences in MAP, DBP or HR. Both SV_i and Qi nadir were lower in participants with HF compared to control participants in both walking conditions (main effect of group: $P = 0.007$ and $P < 0.001$, respectively). There was no difference in peak, min, mean CBFV nadir. TSI nadir was lower in participants with HF compared to control participants during both walking conditions (main effect of group: $P = 0.009$), but there were no differences in relative Oxy Hb, HHb, or tHb nadir.

5.3.3 *Quiet Standing after Supine-to-Stand Transition*

The early, middle, and late phases of the quiet standing period after the supine-to-stand transition are shown in Figure 5.6 and 5.7, and Appendix K. Both SBP and MAP were significantly lower across all time points in the participants with HF, compared to the control participants (main effect of group: $P = 0.041$ and 0.028 , respectively). As well, MAP and SBP increased in both groups from early to middle ($P = 0.012$ and 0.025 , respectively), and early to late ($P = 0.033$ and 0.020 , respectively). Similarly, DBP increased significantly in both groups from early to middle stand ($P = 0.013$), and trended toward an increase from early to late stand

($P = 0.063$). There were no significant differences in HR during quiet standing, but SV_i and Q_i were both lower in participants with HF compared to control participants (main effect of group: $P = 0.005$ and 0.006 , respectively). There was no significant difference in peak, min, or mean CBFV. TSI was significantly lower in participants with HF compared to control participants across all time points (main effect of group: $P = 0.034$). While TSI did not change across time points, both relative HHb ($P < 0.001$) and tHb ($P < 0.001$) increased from early to middle stand, and relative Oxy Hb ($P = 0.025$), HHb ($P = 0.010$), and tHb ($P = 0.002$) increased from early to late stand. There were no significant differences in P_{ET}CO₂.

5.3.4 Slow and Normal Pace Walking after Sit-to-Stand Transition

Figure 5.8 shows the blood pressure response between normal and slow pace walking, as well as across time points. MAP was significantly lower in participants with HF compared to control participants (main effect of group: $P = 0.043$) and trended to be higher in the normal compared to slow pace walking conditions (main effect of condition: $P = 0.062$). Similarly, SBP was lower in participants with HF compared to control participants (main effect of group: $P = 0.006$) and was higher in the normal compared to slow pace walking conditions (main effect of condition: $P = 0.008$). There were no significant differences in DBP.

Figure 5.9 shows the central cardiac response across walking conditions and time points. HR was significantly higher in the normal compared to the slow pace walking condition (main effect of condition: $P < 0.001$) and increased from early to late walking ($P = 0.007$). SV_i was lower in participants with HF compared to control participants (main effect of group: $P = 0.001$) and in the slow pace compared to the normal pace walking condition (main effect of condition: $P = 0.013$). Similar to HR, Q_i increased from early to late walking ($P = 0.013$). There was also a significant group x condition interaction effect due a greater Q_i in the control participants

compared to participants with HF in both the normal ($P < 0.001$) and slow ($P = 0.001$) pace walking conditions, as well as in the normal compared to the slow pace walking condition in both the control participants ($P < 0.001$) and the participants with HF ($P = 0.017$).

Depicted in Figure 5.10 and Appendix L is the CBFV and oxygenation, and respiratory response between normal and slow pace walking, as well as across time points. Mean CBFV had a trend to increase from early to middle walking ($P = 0.056$) and increased significantly from early to late walking ($P = 0.011$). Mean CBFV also had a significant group x condition interaction effect due to lower mean CBFV in participants with HF compared to control participants in the slow pace walking condition ($P = 0.019$), as well as lower mean CBFV in the slow compared to the normal pace walking condition within the HF group ($P = 0.002$). Participants with HF also had a trend for lower mean CBFV compared to control individuals in the normal pace condition ($P = 0.078$). Peak CBFV had a significant group x condition interaction effect due to the participants with HF having a lower peak CBFV in the slow compared to the normal pace walking condition ($P = 0.048$). Similarly, min CBFV had a significant group x condition interaction effect due to lower min CBFV in in the slow compared to the normal pace walking condition within the HF group ($P = 0.008$), as well as a trend for participants with HF to have lower min CBFV compared to control participants in the slow pace walking condition ($P = 0.54$).

TSI was significantly lower in participants with HF compared to control participants (main effect of group: $P = 0.004$) and decreased from early to late walking ($P = 0.027$). There were no significant differences in Oxy Hb. HHb trended to increase from early to middle walking ($P = 0.052$), and significantly increased from early to late walking ($P = 0.012$). HHb also had a significant group x condition interaction effect from participants with HF having

lower HHb in the normal compared to the slow pace condition ($P = 0.012$). There was also a trend for participants with HF to have lower HHb, compared to control participants in the normal pace condition ($P = 0.090$). Similarly, tHb had a significant group x condition interaction effect due to participants with HF having lower tHb than control participants in the normal pace condition ($P = 0.024$) and tHb was lower in the normal compared to the slow pace condition ($P = 0.016$) within the HF group. P_{ETCO_2} was significantly higher in the slow compared to the normal pace condition (main effect of condition: $P = 0.035$).

Appendix P shows a relatively consistent cerebral hemodynamic response within the individuals with HF between sustained slow and normal pace walking.

5.4 Reparatory Dysfunction

As noted in the above literature review, a variety of abnormal respiration patterns are common in individuals with HF. While technological limitations prevented a formal and robust assessment of abnormal respiratory patterns in this participant group (see Future Directions), visual inspection of capnography data did suggest that one participant with HF presented with periodic breathing, which was not noted on the health screening questionnaire. Unfortunately, we were unable to collect CBFV data on this participant, but cerebral oxygenation seemed well preserved in this individual as TSI never dropped below 68% and the early, middle, and late averages never deviated by more than 2% from the supine or seated baseline average.

5.5 Cognitive Function

MoCA scores are summarized in Table 5.3. Neither total MoCA score, nor the number of individuals with an abnormal score ($MoCA < 26$) were significantly different between groups. There were also no significant between group differences in the scores for the individual

cognitive domains assessed by the MoCA (visuospatial, executive function, attention and concentration, short term memory, language, and orientation).

5.6 Resting and Repeated-Measures Correlation Analysis

5.6.1 Mean CBFV and TSI During Supine Rest

Figure 5.11 shows scatterplots with correlations of LVEF, MoCA Score, cfPWV, and carotid distensibility with mean CBFV during supine rest. There was no significant relationship between LVEF or carotid distensibility and mean CBFV. MoCA score had a significant positive relationship ($r = 0.58, P = 0.018$), while cfPWV had a significant negative relationship ($r = -0.67, P = 0.005$) with mean CBFV.

Figure 5.12 shows scatterplots with correlations of LVEF, MoCA Score, cfPWV, and carotid distensibility with TSI during supine rest. There was a significant positive relationship between LVEF and TSI for the full group ($r = 0.46, P = 0.040$), but no significant relationship was detected when analysis was conducted on the groups independently. There were no significant relationships between supine TSI and MoCA Score, cfPWV, or carotid distensibility.

5.6.2 Repeated-Measures Correlation Analysis

As Q is known to impact CBF (reviewed by Meng et al., 2015), relationships between Qi and cerebral perfusion were investigated during the early, middle, and late time points from the supine-to-stand, sit-to-walk normal pace, and sit-to-walk slow pace condition for each participant using repeated-measures correlation analysis.

Figure 5.13 shows the repeated-measures correlation analysis for mean CBFV and Qi. There was a significant positive correlation between mean CBFV and Qi in the full group ($r_{rm} = 0.36, P < 0.001$), control participants ($r_{rm} = 0.37, P = 0.004$), and in the participants with HF ($r_{rm} = 0.29, P = 0.036$).

Figure 5.14 shows repeated-measures correlations for TSI and Qi. There was no significant relationship between TSI and Qi when analysis was conducted on the full group, but there was a significant positive relationship ($r_{rm} = 0.35, P = 0.003$) in the control participants, whereas there was a significant negative correlation ($r_{rm} = -0.53, P < 0.001$) in the participants with HF.

Table 5.1 Participant characteristics

	Control	HF	P-value
Age (years)	78.8±7.8	78.4 ±8.4	n.s.
Sex (Male/Female)	4/9	7/3	n.s.
Height (cm)	163±11.6	173.3±10.9	0.040
Weight (kg)	64.8±15.3	87.3±18.1	0.004
BMI (kg/m ²)	24.2±4.2	28.8±3.6	0.012
Smoking history	1 (8%)	8 (80%)	< 0.001
Gait speed (m/s)	1.2±0.3	1.0±0.2	0.02
Brachial SBP (mmHg)	136.6±13.7	132.8±10.7	n.s.
Brachial DBP (mmHg)	70.8±6.8	68.5±12.6	n.s.
HR (bpm)	59.5±11.0	65.0±7.8	n.s.
Vascular Measures			
Carotid IMT (mm)	0.7±0.1	0.8±0.1	n.s.
Carotid distensibility (mmHg ⁻¹)	0.0019±0.0008	0.0022±0.0007	n.s.
β Stiffness (AU)	13.1±5.5	11.5±2.5	n.s.
cfPWV (m/s)	10.6±2.8	9.4±2.0	n.s.
Systolic Cardiac Function			
LVEF (%)	61.4±5.5	45.2±11.6	< 0.001
SVi	42.8±8.2	31.2±5.7	0.002
Qi	2.5±0.6	1.9±0.4	0.004
Diastolic Cardiac Function			
E/A (unitless)	1.2±0.4	1.2±0.4	n.s.
E/e' (unitless)	6.7±1.8	7.2±1.2	n.s.

All values are mean±standard deviation, except sex (n) and smoking history (n (%)). BMI – body mass index; MoCA – Montreal cognitive assessment; SBP – systolic blood pressure; DBP – diastolic blood pressure; IMT – intima-media thickness; cfPWV – carotid-femoral pulse wave velocity; LVEF – left ventricular ejection fraction; SVi – stroke volume index; Qi – cardiac index; E – early diastolic peak mitral inflow velocity; A – late diastolic peak mitral inflow velocity; e' – early diastolic peak mitral annular velocity. Carotid distensibility/ β Stiffness: HF n = 9, control n = 11; SVi/Qi: HF n = 10, controls n = 10; E/A: HF n = 6, control n = 12. All blood pressure, vascular, and cardiac measurements were taken during supine posture. Table also reported in Poirier, see Declaration (pg. ii).

Table 5.2 Participant medications

	Control	HF	P-value
β-blocker	0 (0)	8 (80)	< 0.001
ACE-inhibitor	1 (8)	6 (60)	0.020
ARB	1 (8)	1 (10)	n.s.
ARNi	0 (0)	1 (10)	n.s.
Calcium channel blocker	1 (8)	3 (30)	n.s.
Diuretics	1 (8)	7 (70)	0.006
Thiazide	1 (8)	0 (0)	n.s.
Loop	0 (0)	6 (60)	0.002
Potassium-sparing	0 (0)	2 (20)	n.s.
Anticoagulants	0 (0)	5 (50)	0.007
Statins	3 (23)	6 (60)	n.s.
Nitroglycerin spray	0 (0)	3 (30)	n.s.

All values are n (%). ACE – angiotensin converting enzyme; ARB – angiotensin II receptor blocker; ARNi – angiotensin receptor-neprilysin inhibitor. Table also reported in Poirier, see Declaration (pg. ii).

Table 5.3 MoCA score

	MoCA Item	Total possible score	Control	HF	P-value
Overall score		30	25.2±3.9	24.1±3.9	n.s.
Visuospatial function	Cube, clock	4	3.5±0.7	2.9±0.9	n.s.
Executive function	Trails, fluency, abstraction	4	3.4±0.8	2.8±0.9	n.s.
Attention, concentration, working memory	Digit, serial 7, letter	6	4.7±1.8	5.2±1.0	n.s.
Short-term memory	Delayed recall	5	3±1.6	2.5±1.6	n.s.
Language	Naming, sentence repetition, fluency	6	5.3±0.9	4.8±1.0	n.s.
Orientation	Orientation	6	5.7±0.9	5.9±0.3	n.s.
Abnormal score (<26)	-	-	5 (38)	6 (60)	n.s.

All values are mean±standard deviation, except abnormal score (n (%)).

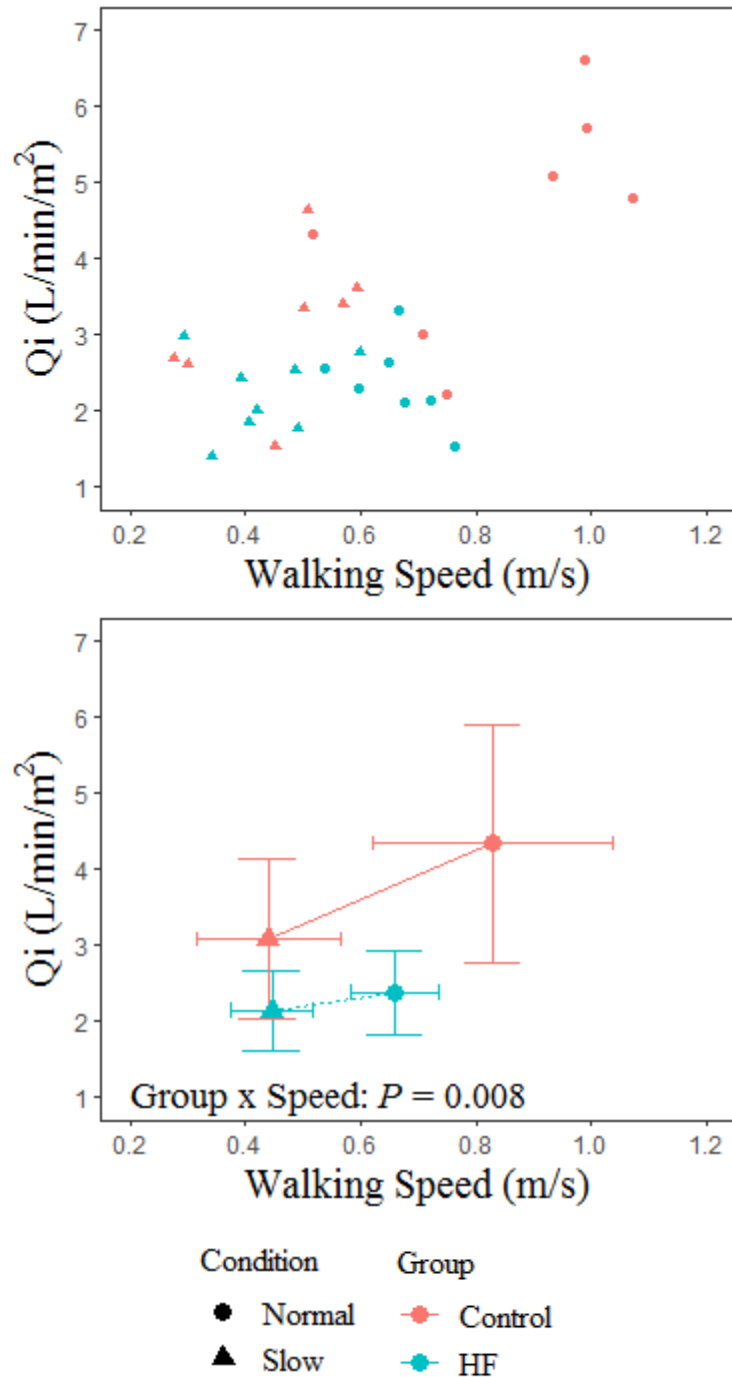


Figure 5.1 Cardiac index response to different walking speeds during slow and normal paced walking

Salmon colouration and solid line represents the control group and blue colouration and dashed line represent the HF group. Circles represent the normal pace condition and triangles represent the slow pace condition. Error bars indicate the standard deviation of both walking speed and cardiac index. Qi – cardiac index. Group x speed interaction effect is shown in the lower left corner of the graph.

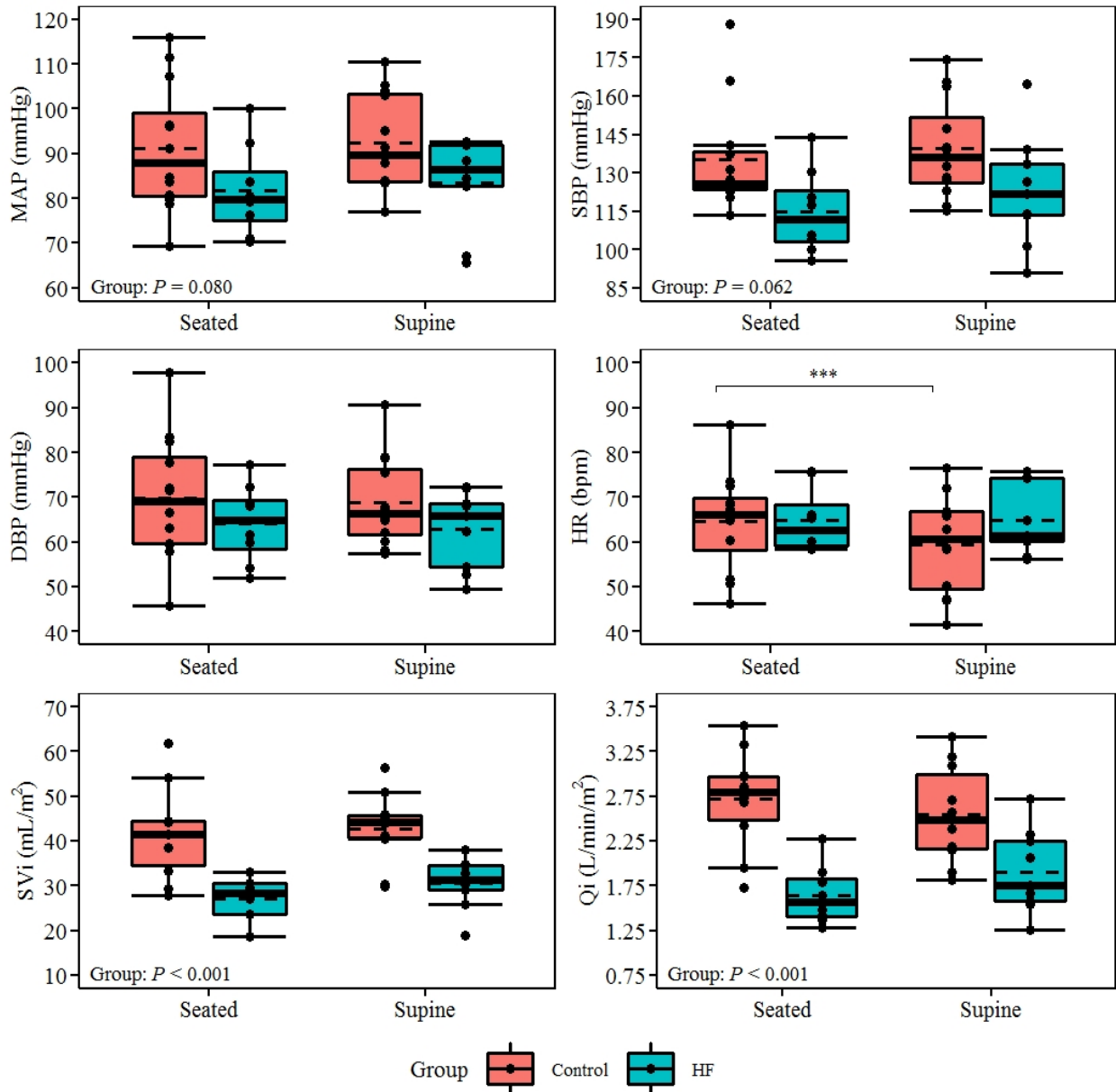


Figure 5.2 Supine and seated resting central hemodynamics

Salmon coloured bars represent the control group and blue coloured bars represent the HF group. The lower and upper boundary of the box indicate the 25th and 75th percentile, respectively. The solid line within the box indicates the median and the dashed line within the box indicates the mean. Error bars indicate the minimum and maximum, while data outside of the error bars are considered outliers. Individual data are displayed as single points. MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; SVi – stroke volume index; Qi – cardiac index. *** indicates significant difference $P < 0.001$. Significance lines centered above a single bar indicate an interaction effect, while significance lines centered between two bars indicate a main effect of condition. Group main effects are shown in the lower left corner of each graph.

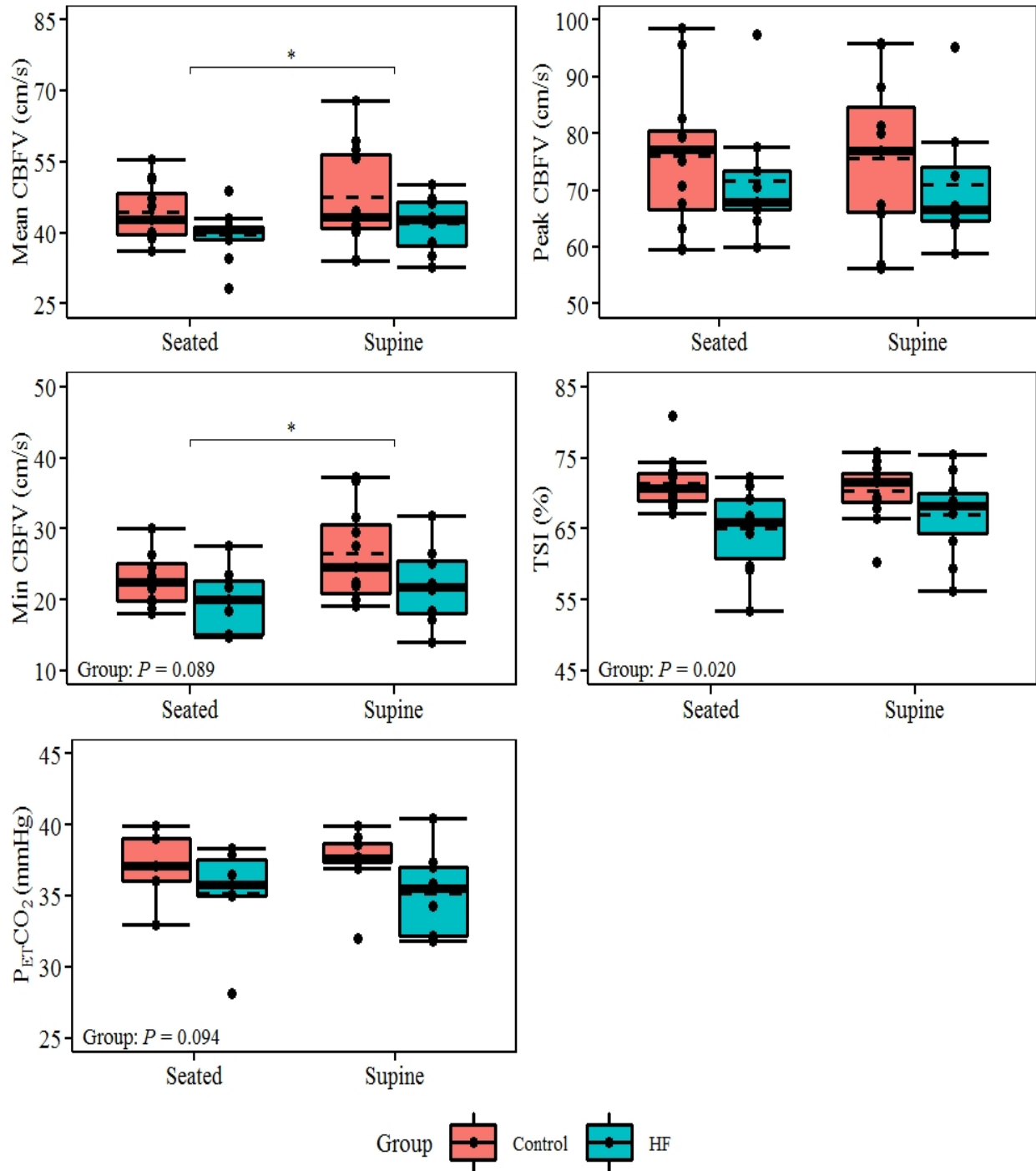


Figure 5.3 Supine and seated resting cerebral hemodynamics and respiration

Graph format is the same as described in Figure 5.2. CBFV – cerebral blood flow velocity; TSI – tissue saturation index; $P_{ET}CO_2$ – partial pressure of end-tidal carbon dioxide. * indicates significant difference $P < 0.05$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition. Group main effects are shown in the lower left corner of each graph.

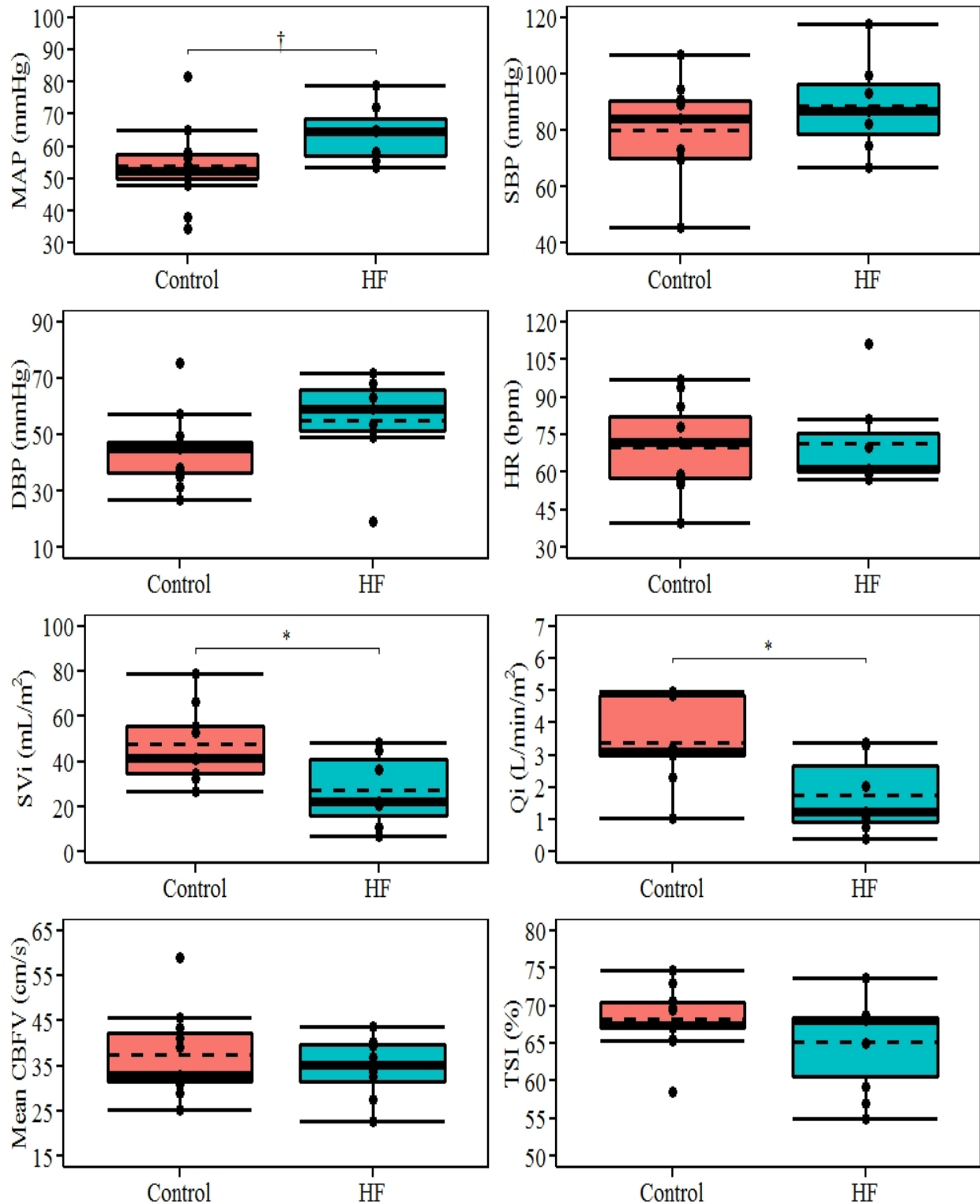


Figure 5.4 Central and cerebral hemodynamic nadirs during supine-to-stand transition
 Graph format is the same as described in Figure 5.2. MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; SVi – stroke volume index; Qi – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index. * indicates significant difference $P < 0.05$; † indicates a trend to be different $P < 0.1$.

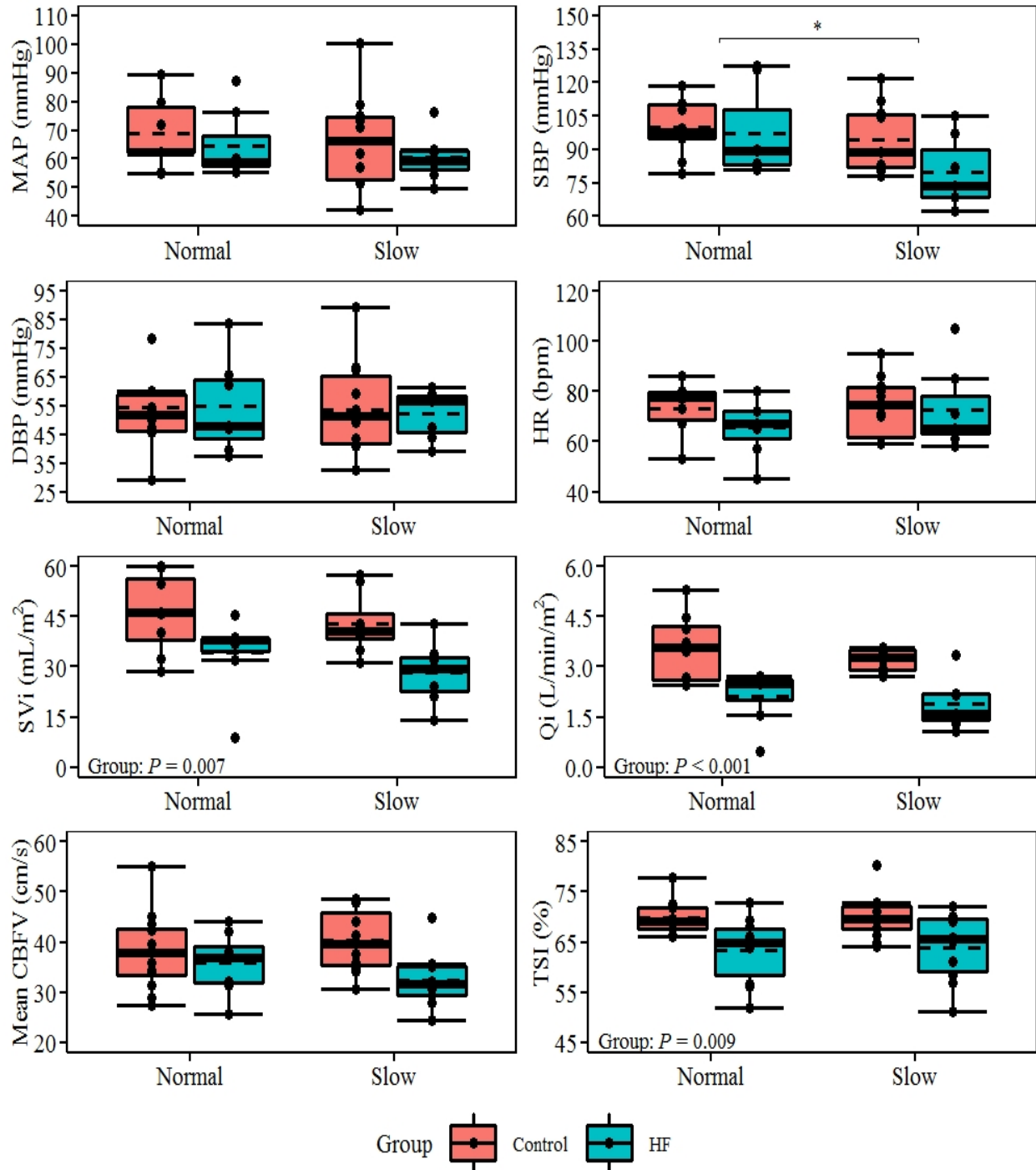


Figure 5.5 Central and cerebral hemodynamic nadirs during sit-to-walk (slow) and sit-to-walk (normal) transition
 Graph format is the same as described in Figure 5.2. MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; SVi – stroke volume index; Qi – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index. * indicates significant difference $P < 0.05$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition. Group main effects are shown in the lower left corner of each graph.

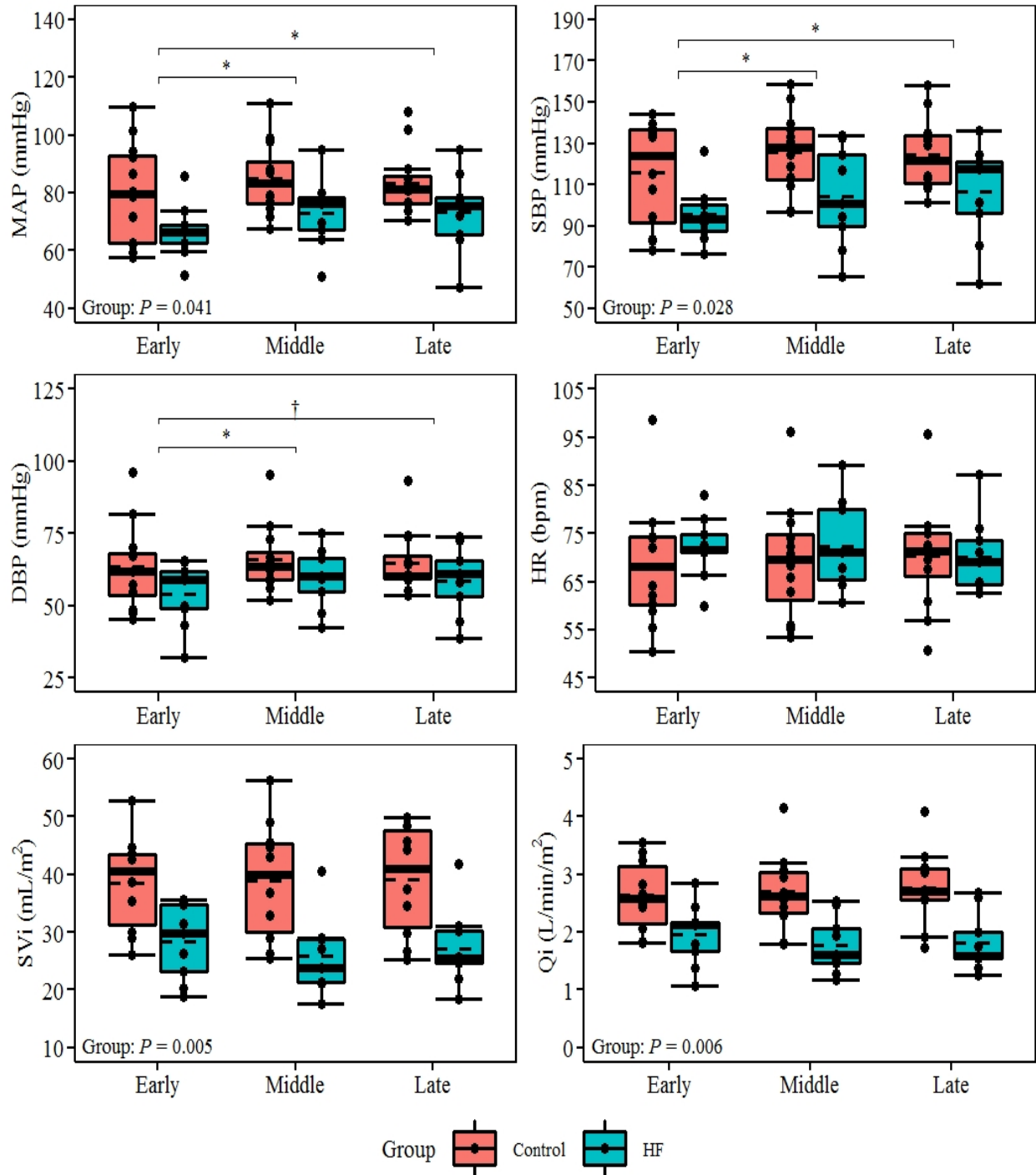


Figure 5.6 Central hemodynamics during early, middle, and late phase standing after supine-to-stand transition

Graph format is the same as described in Figure 5.2. MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; SVi – stroke volume index; Qi – cardiac index. * indicates significant difference $P < 0.05$; † indicates a trend to be different $P < 0.1$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition. Group main effects are shown in the lower left corner of each graph.

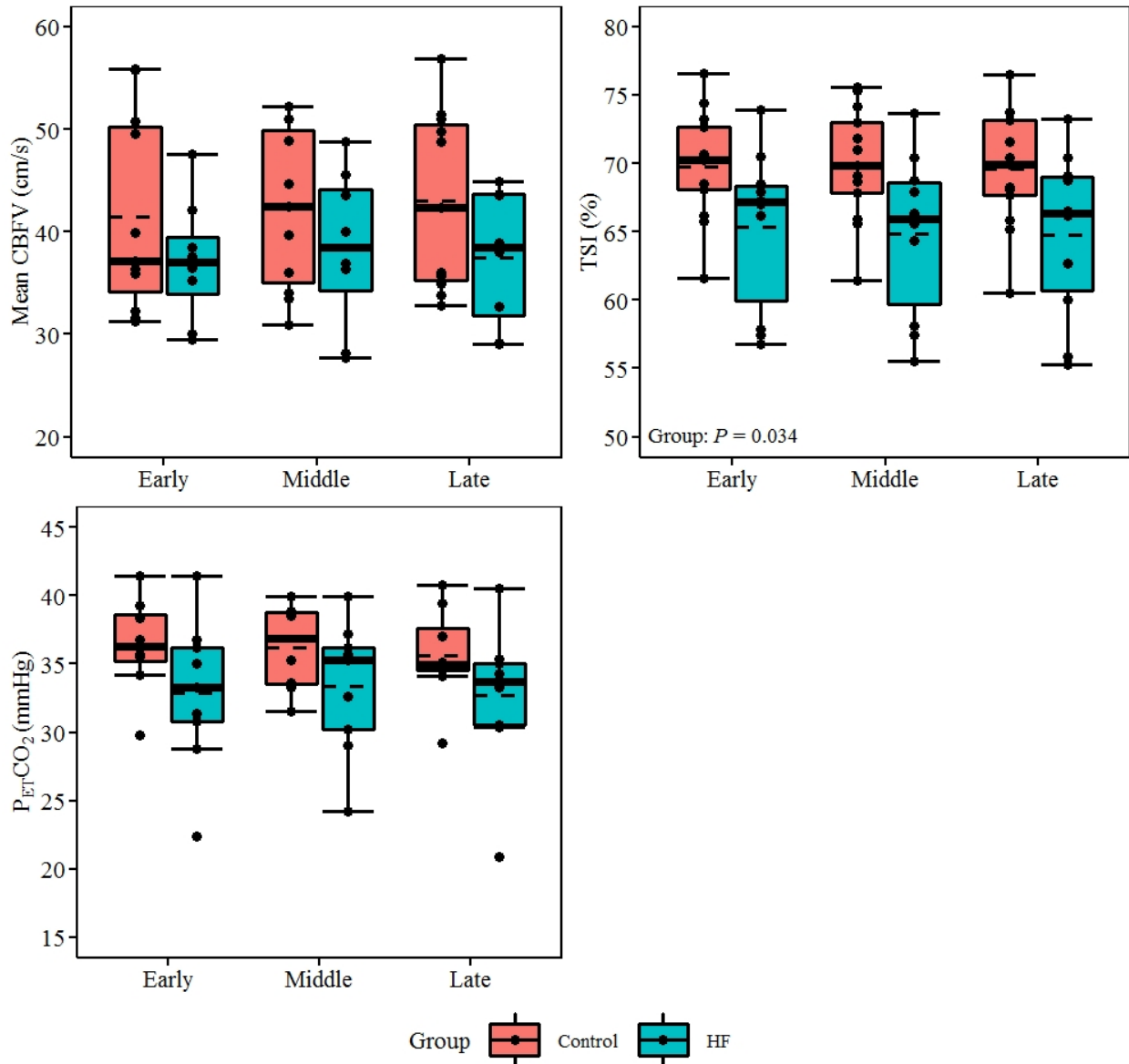


Figure 5.7 Cerebral hemodynamics and respiration during early, middle, and late phase standing after supine-to-stand transition

Graph format is the same as described in Figure 5.2. CBFV – cerebral blood flow velocity; TSI – tissue saturation index; P_{ET}CO₂ – partial pressure of end-tidal carbon dioxide. Group main effects are shown in the lower left corner of each graph.

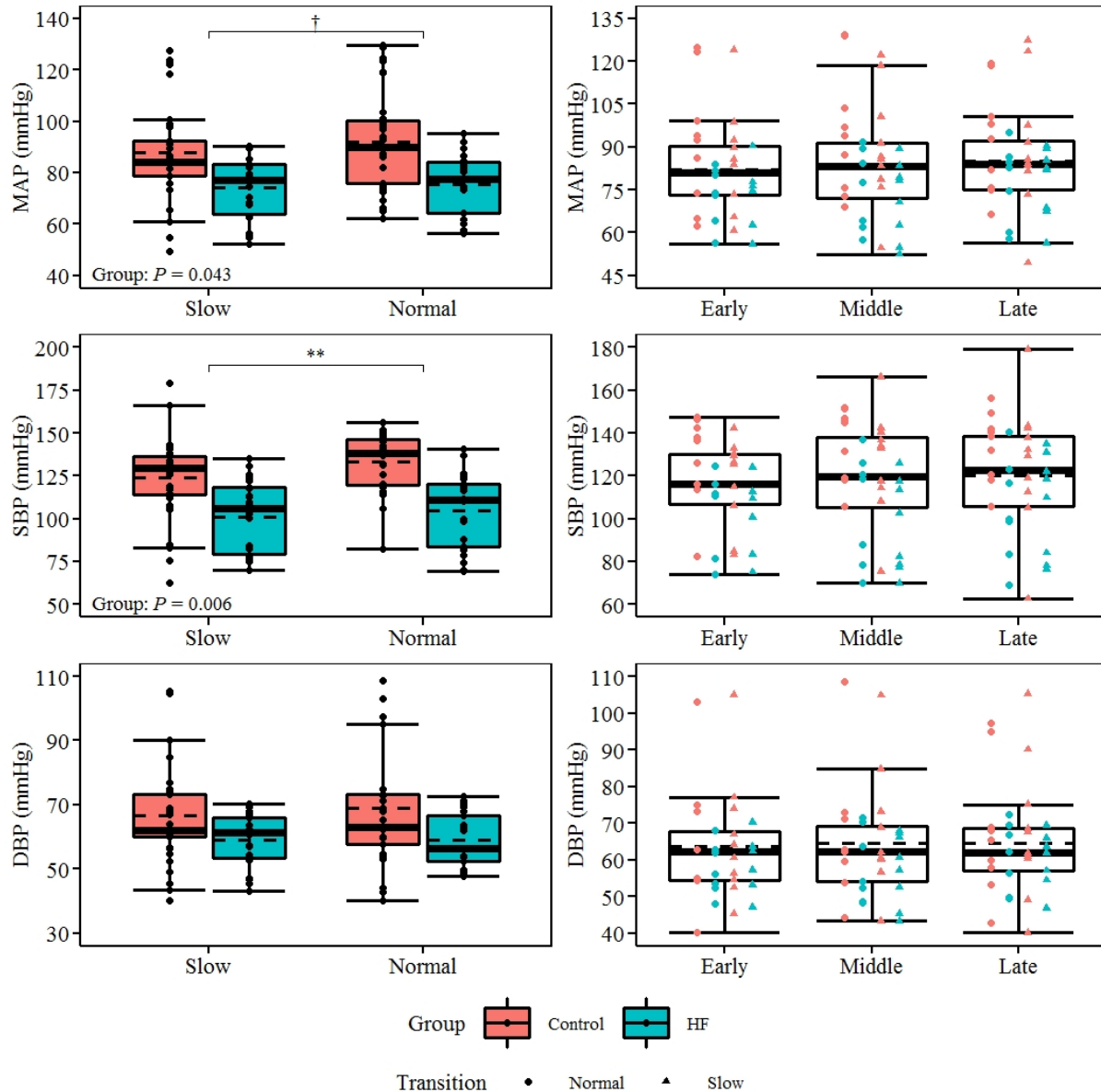


Figure 5.8 Blood pressure response during early, middle, and late phase slow and normal pace walking after sit-to-walk transition

Left: Graph format is the same as described in Figure 5.2. Right: Salmon coloured points represent the control group and blue coloured points represent the HF group. Circles indicate normal pace walking and triangles indicate slow pace walking. The lower and upper boundary of the box indicate the 25th and 75th percentile, respectively. The solid line within the box indicates the median and the dashed line within the box indicates the mean. Error bars indicate the minimum and maximum, while data outside of the error bars are considered outliers. Individual data are displayed as single points. MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure. ** indicates significant difference $P < 0.01$; † indicates a trend to be different $P < 0.1$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition (left) or a main effect of time (right). Group main effects are shown in the lower left corner of each graph.

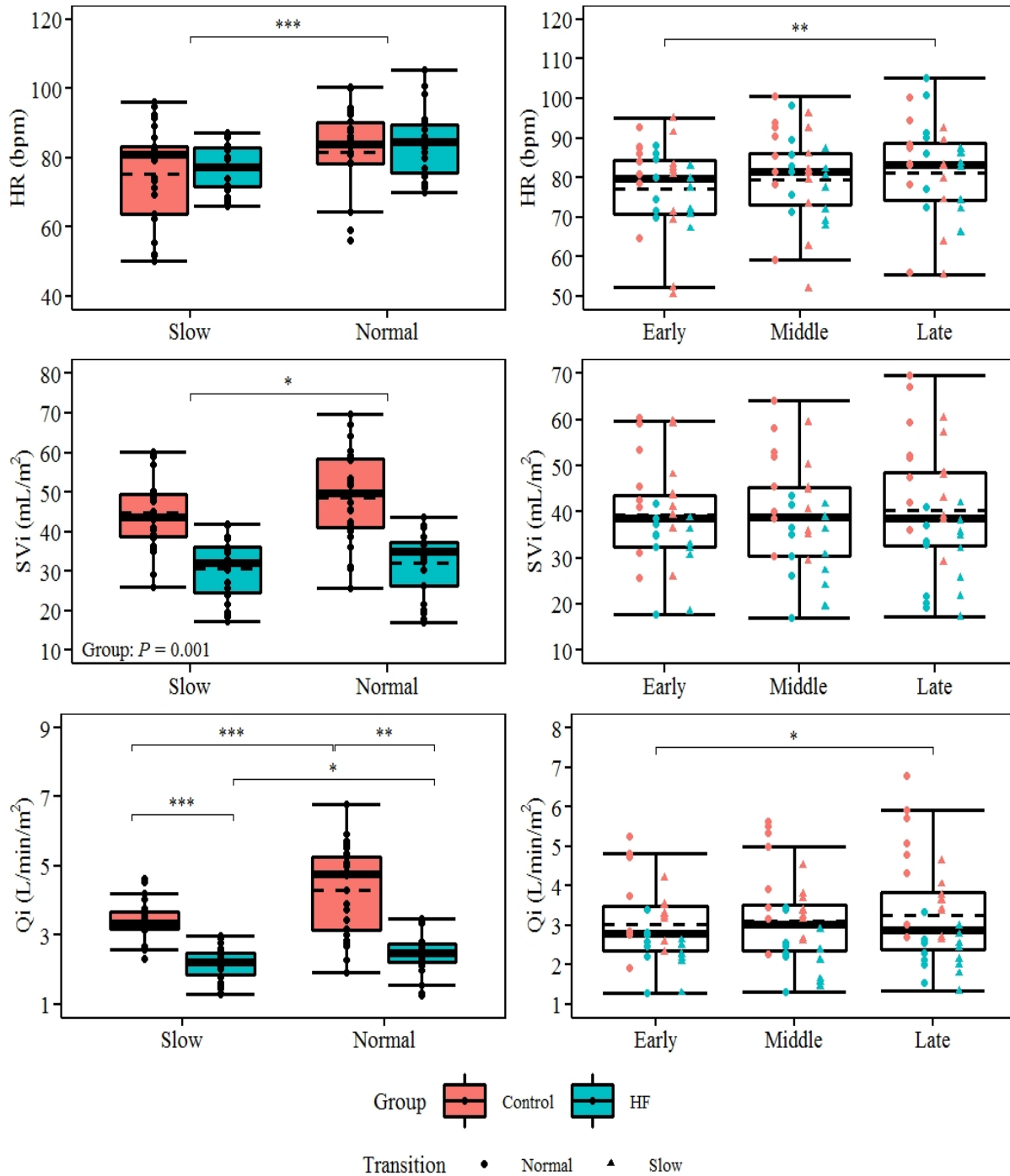


Figure 5.9 Cardiac response during early, middle, and late phase slow and normal pace walking after sit-to-walk transition

Graph format is the same as described in Figure 5.8. HR – heart rate; SVi – stroke volume index; Qi – cardiac index. * indicates significant difference $P < 0.05$; ** indicates significant difference $P < 0.01$; *** indicates significant difference $P < 0.001$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition (left) or a main effect of time (right). Group main effects are shown in the lower left corner of each graph.

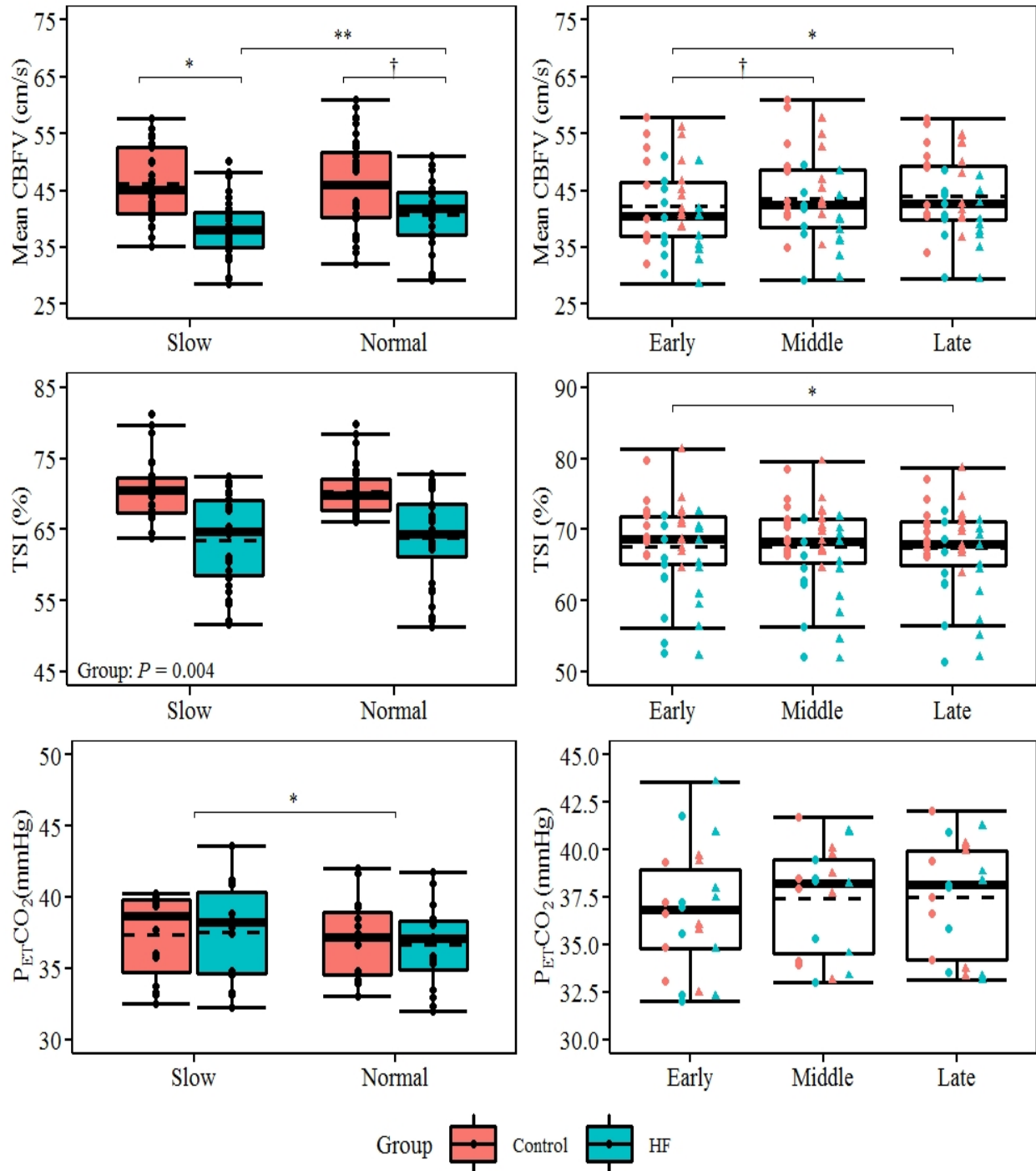


Figure 5.10 Cerebral hemodynamic and respiratory response during early, middle, and late phase slow and normal pace walking after sit-to-walk transition

Graph format is the same as described in Figure 5.8. CBFV – cerebral blood flow velocity; TSI – tissue saturation index; P_{ET}CO₂ – partial pressure of end-tidal carbon dioxide. * indicates significant difference $P < 0.05$; ** indicates significant difference $P < 0.01$; † indicates a trend to be different $P < 0.1$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition (left) or a main effect of time (right).

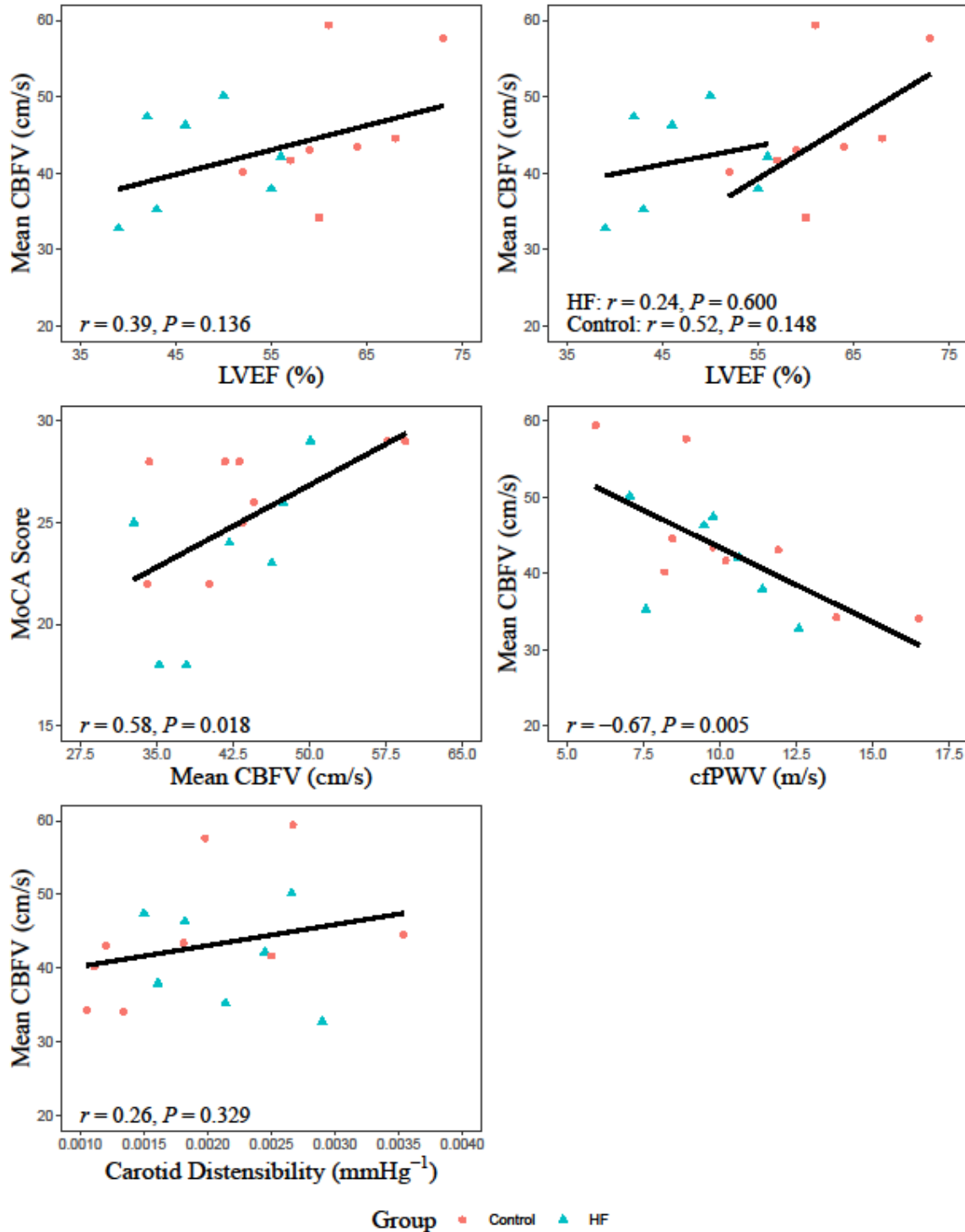


Figure 5.11 Relationship between mean CBFV and LVEF, MoCA Score, cfPWV, and carotid distensibility during supine rest

Salmon coloured circles represent the control group and blue coloured diamonds represent the HF group. Solid black line indicates the linear regression and r and P values are listed in the lower left hand corner of each graph. LVEF – left ventricular ejection fraction; CBFV – cerebral blood flow velocity; cfPWV – carotid-femoral pulse wave velocity.

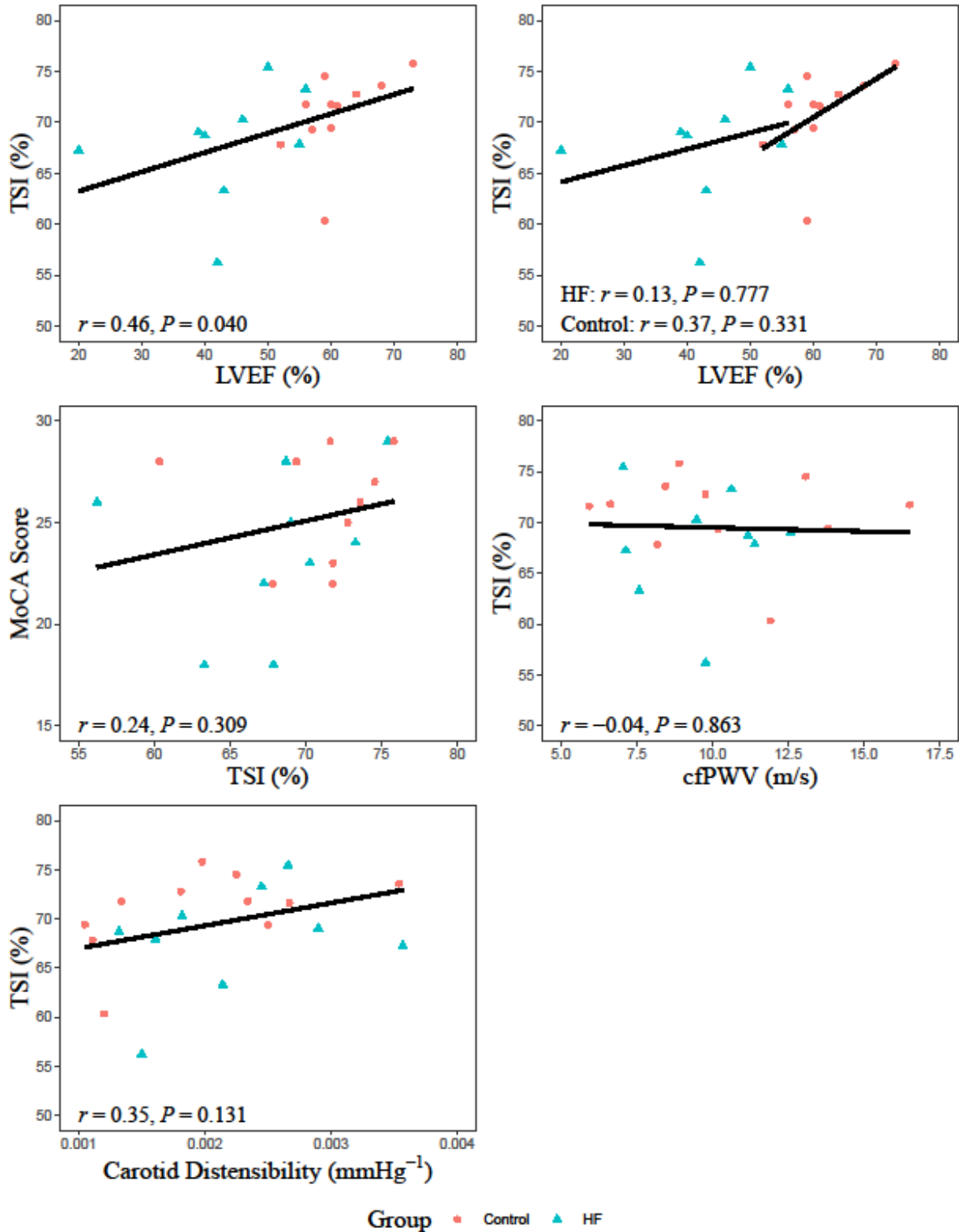


Figure 5.12 Relationship between TSI and LVEF, MoCA Score, cfPWV, and carotid distensibility during supine rest

Graph format is the same as described in Figure 5.11. LVEF – left ventricular ejection fraction; TSI – tissue saturation index; cfPWV – carotid-femoral pulse wave velocity.

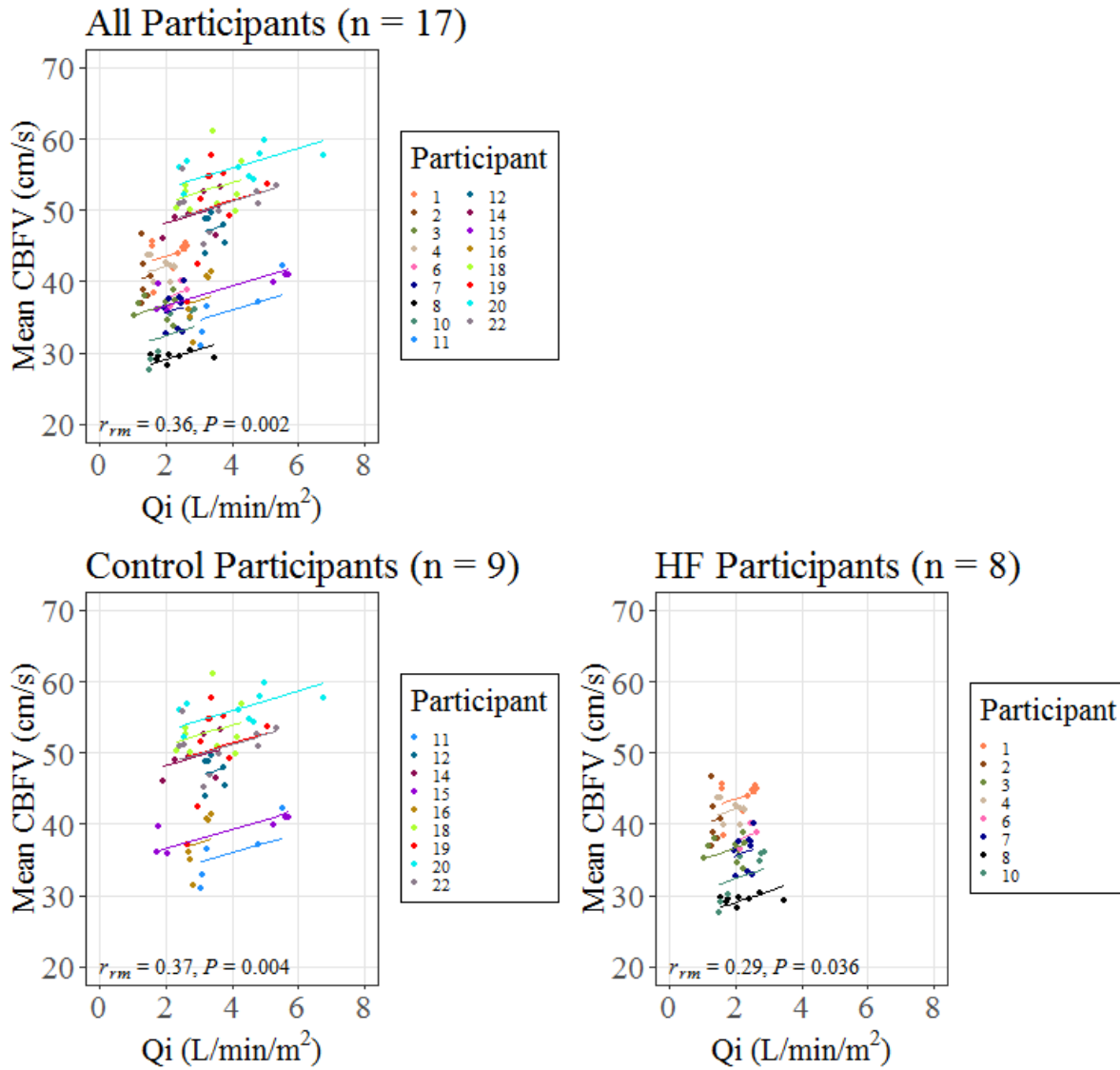


Figure 5.13 Repeated measures correlations between mean CBFV and Qi

Individual data from the early, middle, and late phase of quiet standing, and normal and slow pace walking are represented by circles with unique colours for each participant. Solid lines represent repeated measures correlations for each participant with colours matching the individual data points. For each graph r_{rm} and P values are shown in the bottom left corner. CBFV – cerebral blood flow velocity; Qi – cardiac index.

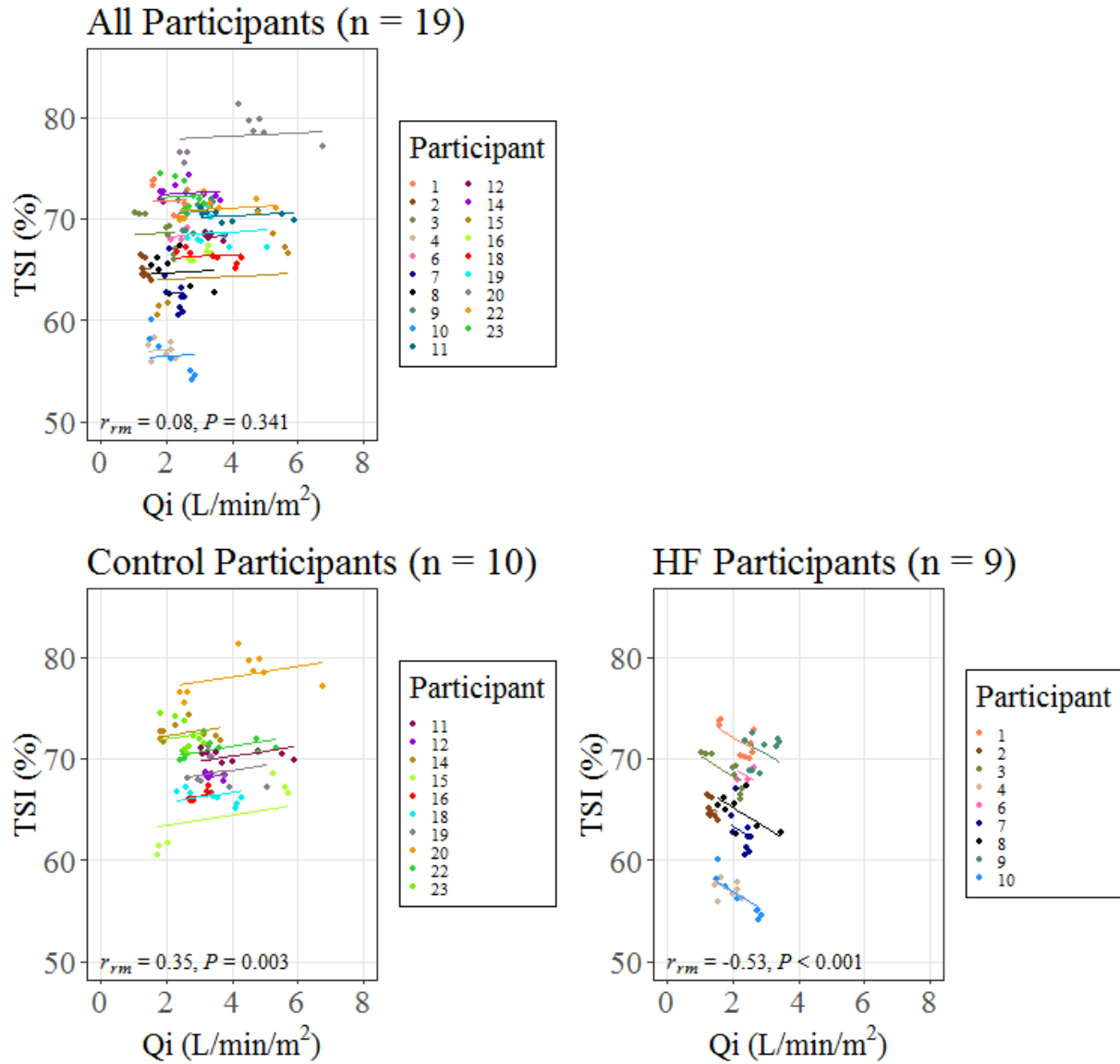


Figure 5.14 Repeated measures correlations between TSI and Qi

Graph format is the same as described in Figure 5.13. Individual data are from the early, middle, and late phase of quiet standing, and normal and slow pace walking for each participant. TSI – tissue saturation index; Qi – cardiac index.

6.0 Discussion

In the present study, participants with HF had characteristically low Q_i during supine and seated rest, as well as quiet standing and walking. In addition, the participants with HF had an attenuated rise in Q_i in response to walking at slow and normal paces, compared to control participants. This poor central cardiac response is likely the main factor responsible for lower cerebral oxygenation in the participants with HF compared to the control participants during supine and seated rest, standing, and walking. Participants with HF also had lower CBFV during walking compared to control participants, which again was likely driven by lower Q_i . Overall, participants with HF were ineffective at maintaining cerebral hemodynamics during posture transitions and walking, which was likely attributable to diminished cardiac function.

The primary objectives of this thesis were: 1) to determine the central cardiac response to walking in participants with HF, compared to control participants; and 2) to investigate the acute and sustained response of cerebral hemodynamics to posture transitions and walking. We hypothesized that participants with HF would have an attenuated rise in Q_i in response to walking, compared to control participants (Hypothesis 1), which was supported by the smaller increase in Q_i in response to walking in the participants with HF compared to control participants. With respect to changes in cerebral hemodynamics, we hypothesized that participants with HF would have a lower TSI and mean CBFV nadir after posture transition, compared to control participants (Hypothesis 2a), which was supported by the TSI response during the sit-to-walk conditions, but not evident in mean CBFV, or the supine-to-stand condition. We also hypothesized that participants with HF would have lower TSI and mean CBFV during quiet standing and walking, compared to control participants (Hypothesis 2b). This

hypothesis was supported by the TSI response to quiet standing and the TSI and mean CBFV response to the sit-to-walk conditions.

The secondary objective of this thesis was to assess relationships between cerebral perfusion and resting cardiac, cognitive, and vascular function in both participants with HF and control participants. We hypothesized that supine and seated TSI and mean CBFV would be positively correlated with carotid distensibility, and LVEF and negatively correlated with cfPWV (Hypothesis 3a). This hypothesis was supported by relationships between supine mean CBFV and cfPWV, seated TSI and LVEF, and supine TSI and LVEF, and cfPWV. We also hypothesized that supine and seated TSI and mean CBFV would be positively correlated with MoCA score (Hypothesis 3b), which was supported by relationships between MoCA score and supine mean CBFV as well as supine TSI.

The results of the present study are discussed below, with reference to the current understanding of cerebral perfusion in individuals with HF. It is important to note that the studies discussed below assessed cerebral hemodynamics in groups of mostly HFrEF, whereas the HF group in the present study was composed mostly of individuals with HFmEF and HFpEF.

6.1 The Effect of Walking Speed on Cardiac Index (Primary Objective 1)

To obtain continuous estimates of Q_i during walking activity, one of the few approaches available is calculation from the non-invasive measurement of finger arterial pressure with the Modelflow algorithm. This method tracks cardiac output well during exercise in young adults (Faisal et al., 2009); but, Modelflow derived estimates of Q are inaccurate in the setting of cardiovascular disease (Bogert et al., 2010). Thus, a single point calibration of Modelflow derived Q_i using an echocardiography estimate of Q_i , as shown in Eq6, was employed in the present study. The use of a single point calibration is generally less desirable than using a

multiple calibration technique, but a single point lithium dilution calibration of pulse contour analysis derived Q has shown similar efficacy to multiple calibrations during incremental exercise in healthy, young adults (Elliot et al., 2012). To assess the validity of the single point echocardiography calibration of Modflow derived Qi for ambulatory studies in healthy individuals and clinical populations, this technique should be validated using a portable rebreathing device, such as the Innocor (Innovision A/S, Odense, Denmark). This device has been shown to produce estimates of Q comparable to “gold standard” techniques, such as Fick and thermodilution (Dong et al., 2005; Sobanski et al., 2008). As such a validation was not possible in the present study, the potential inaccuracy of the single point calibration technique should be considered when interpreting reported values of Qi.

Determining the central cardiac response to exercise (e.g., cardiopulmonary exercise testing) has significant prognostic value for individuals with HF (Lee et al., 2012). In the present study, participants with HF had a poor central cardiac response to low intensity activity. Despite significantly lower SVi, in the participants with HF compared to control participants during late phase walking, there were no significant differences between groups in HR. This blunted HR response could potentially be attributed to β -blockade in participants with HF (Wilmore et al., 1983; Racine et al., 2003). Given that SVi was lower and there was no compensatory rise in HR, it follows that Qi was lower during late phase walking in the participants with HF compared to control participants. This finding is in agreement with others that have reported low Q during exercise in individuals with HF compared to healthy controls. (Fukuda et al., 2012; Abudiab et al., 2013).

The participants with HF also showed an attenuated rise in Qi in response to low intensity activity, which suggests a poor cardiac response to low intensity activity that is commonly

encountered during ADLs. These results are interesting considering that VO_2 increases linearly with Q (Burton et al., 2004), and since individuals with HF are less metabolically efficient (Kemp et al., 1996), it may be expected that they have a higher VO_2 , and thus Q for the same activity level compared to healthy individuals. Previous work has shown that individuals with HF have a lower change in Q relative to VO_2 during maximum exercise testing, and attributed reduced exercise capacity to an inadequate Q response to increased metabolic demand (Abudiab et al., 2013). Additionally, the potential impact low Q has on cerebral perfusion (review by Meng et al., 2015) may also help explain previously documented exercise intolerance (reviewed by Brassard & Gustafsson, 2016) even at low intensity activity, and functional deficits during ADLs (Dunlay et al., 2015) in individuals with HF.

Also noteworthy is that the participants with HF appeared to have a small range of walking speeds during the sit to walk transitions, as well as significantly slower gait speed during the 8-meter walk test. While slow gait speed during the walking trials may be a consequence of exercise intolerance in this patient group, slow gait speed is also an independent predictor of frailty in older adults (Castell et al., 2013). Frailty is associated with poor quality of life and health outcomes, and it is estimated that up to 79% of HF patients are frail (Vitale et al., 2018). While frailty is multifactorial, a poor cardiac response may contribute to decreased exercise tolerance and quality of life in the frail state, and measuring gait speed and the cardiac response to low intensity activity may be important for effective clinical management of HF.

6.2 Cerebrovascular Response to Posture Transition, Quiet Standing, and Walking

(Primary Objective 2)

6.2.1 Supine and Seated Rest

In both supine and seated rest, participants with HF had a trend for lower MAP and SBP,

compared to controls participants. This is likely the consequence of the participants with HF being on guideline recommended HF management therapy (Ezekowitz et al., 2017). In addition, both SVi and Qi were significantly lower in participants with HF compared to control participants in both supine and seated postures. Impairment of central hemodynamics has a direct effect on cerebral hemodynamics, and in the present study were likely responsible for between group differences in cerebral oxygenation.

During both supine and seated rest, cerebral oxygenation was lower in participants with HF compared to control participants. While no studies have reported lower cerebral oxygenation during supine rest in individuals with HF, Chen and colleagues (2018) showed lower cerebral oxygenation, measured by NIRS, in participants with HF compared to healthy control participants during upright seated posture. Seated cerebral oxygenation has also been shown to improve in response to decongestion treatment in individuals with acute HF (Madsen et al., 2000).

Surprisingly, despite lower cerebral oxygenation, there were no significant differences in mean CBFV during either supine or seated rest between the participants with HF and the control participants. This contradicts previous work, which reported lower mean CBFV in individuals with HF compared to control participants in both supine and seated posture (Vogels et al., 2008; Serber et al., 2014). Previous studies have also reported lower CBF in supine posture in participants with HF compared to healthy controls (Loncar et al., 2011; Fraser et al., 2015). In the present study the lack of difference between groups in mean CBFV is likely the consequence of response variability and small sample size.

Unlike in supine posture, the physiological mechanisms responsible for maintaining cerebral perfusion must overcome the hydrostatic gradient resulting from the force of gravity in

upright postures. This can result in lower cerebral perfusion while in upright compared to supine postures, as was observed in the present study and others (Alperin et al., 2005; Fraser et al., 2015; Garret et al., 2017). Fraser and colleagues (2015) reported a greater reduction in CBF when moving from supine to seated posture in individuals with HF compared to controls. This is in contrast to the present study, which found that there were no significant differences between groups in the reduction in mean CBFV when comparing seated and supine postures.

6.2.2 Acute Response to Posture Transition

No previous studies have reported the acute response of cerebral hemodynamics during supine-to-stand transition in individuals with HF. In the present study, there were no significant differences in mean CBFV or TSI nadir between participants with HF and control participants. The latter result is particularly interesting given that participants with HF started at a significantly lower TSI during supine rest compared to control participants; however, a trend for a higher MAP nadir in participants with HF may be indicative of better BP regulation in the acute phase of the supine-to-stand posture transition. Better BP regulation in the HF group could potentially be the consequence of the high male to female ratio (7/3) in the HF group, as men have been shown to have better orthostatic tolerance compared to women (Montgomery et al., 1977; Covertino 1998; Fu et al., 2004). While this has been attributed to the effect of sex hormones on peripheral vascular tone in young women (Shoemaker et al., 2001; Edgell et al., 2012), older postmenopausal women have shown decreased sensitivity of the cardiac arm of the baroreflex along with greater drops in BP in response to nitroprusside compared to young men and women (Barnes et al., 2012). Additionally, studies of older adults have shown that women have higher rates of orthostatic hypotension (Finucane et al., 2014), are more likely to fall (Finucane et al., 2017), and are more likely to present at an emergency department with syncope

(Groosman et al., 2005), compared to men. Better BP regulation could have helped attenuate the reduction in cerebral oxygenation, despite lower Q_i in participants with HF compared to the control participants. Additionally, the TSI nadir response in the participants with HF showed a high degree of variability, which could have affected the ability to detect differences between groups.

The TSI nadir was significantly lower in the participants with HF compared to the control participants in both the sit-to-walk normal and slow transitions. Unlike in the supine-to-stand transition, there were no significant differences in BP nadir between groups, which along with lower Q_i nadir, could contribute to the lower TSI nadir in participants with HF compared to control participants. It is important to note that estimates of SV_i , and consequently Q_i , during the acute phase of either posture transitions should be assessed with caution, as a recent report documented significant underestimation of SV by Modelflow during dynamic fluctuations in SV (Gibbons et al., 2018).

6.2.3 Sustained Response to Posture Transition

During the quiet standing period after the supine-to-stand transition, MAP, SBP, and Q_i were significantly lower in the participants with HF compared to the control participants. TSI was also significantly lower in the HF compared control group, but mean CBFV was not significantly different between groups. The latter result is in contrast to previous work which reported lower mean CBFV during quiet standing in individuals with HF compared to healthy controls (Serber et al., 2014). Previous reports have shown impaired baroreflex sensitivity in individuals with HF (Sopher et al., 1990; Rostagno et al., 1999) which could help explain lower BP during upright posture. Lower BP along with lower Q_i likely explain lower cerebral oxygenation in the HF group.

An interesting finding in the present study was that participants with HF had an effective BP response during the acute phase of the supine-to-stand transition (higher MAP compared to controls), but lower BP during the sustained phase of quiet standing after transition (lower MAP and SBP). A wide range of cardiovascular responses have been reported in individuals with HF, likely as a consequence of differing medication regimens between individuals (Bronzwaer et al., 2017). Both maintained (Abelmann & Fareeduddin, 1969), and significantly reduced (Kubo & Cody, 1983; Bronzwaer et al., 2017) BP immediately after transition to upright posture have been reported in individuals with HF, but a recent study also showed reduced BP and TPR during sustained quiet standing (Bronzwaer et al., 2017). Poor BP regulation during sustained quiet standing after posture transition has been attributed to increased venous pooling in some individuals with HF (Kubo & Cody, 1983), which could be the consequences of vasodilation of peripheral vasculature during upright posture (Goldsmith et al., 1983a; Wroblewski, 1994). In the present study, TPR was not significantly different between the participants with HF and the control participants at nadir (HF – 1.8 ± 1.6 mmHg/mL/s vs. Control – 1.2 ± 0.9 mmHg/mL/s $P = 0.435$) or in the sustained phase (early: HF – 1.2 ± 0.6 mmHg/mL/s vs. Control – 2.0 ± 1.6 mmHg/mL/s, middle: HF – 1.4 ± 0.6 mmHg/mL/s vs. Control – 2.1 ± 1.7 mmHg/mL/s, late: HF – 1.4 ± 0.5 mmHg/mL/s vs. Control – 2.1 ± 1.8 mmHg/mL/s, $P = 0.224$) of the supine-to-stand transition; however, a greater number of participants and additional measurement would likely be required to effectively assess the peripheral vascular response to orthostasis in this group.

In the present study, central hemodynamics (SBP, MAP, SV_i, and Qi) and cerebral oxygenation were lower in participants with HF compared to control participants during slow and normal pace walking. Previous work has shown BP (MAP and SBP) and cerebral oxygenation at peak exercise to be lower in participants with HF, compared to control

participants (Chen et al., 2018). Similar work has shown MAP, Q, and cerebral oxygenation to be lower from 20-80% peak exercise in individuals with HF and COPD, compared to individuals with COPD only (Oliveira et al., 2015). Together, these findings suggest that poor central cardiac function in individuals with HF may result in cerebral ischemia during acute high intensity activity, but also chronically during low intensity activities that are common of ADLs.

We also showed that the participants with HF had lower mean CBFV during slow pace walking and a trend for lower mean CBFV during normal pace walking compared to control participants. This is similar to the findings of Oliveira and colleagues (2015), which showed lower NIRS-based CBF index from 20-80% peak exercise in individuals with HF and COPD compared to individuals with COPD only. Low cerebral perfusion during walking and higher intensity exercise could be the result of a poor Q response to exercise or impaired cerebral autoregulation. As a result of reduced Q at rest, individuals with HF operate with lower CBF compared to healthy individuals (Fraser et al., 2015; reviewed by Meng et al., 2015). In addition, cerebral autoregulation has been previously documented to be more likely to be impaired in individuals with HF compared to controls during rest (Caldas et al., 2016) and sub-maximal handgrip exercise (Caldas et al., 2018). In the absence of effective autoregulation, individuals with HF may experience greater fluctuations in CBF during ADLs. Work completed in conjunction with this thesis attempted to characterize the cerebral autoregulation response in individuals with HF during posture transitions and walking, and showed potentially impaired static cerebral autoregulation in response to ambulation in this same group of HF participants (Poirier, see Declaration (pg. ii)).

6.3 Relationship between Cerebral Perfusion and LVEF, MoCA, and Arterial Stiffness (Secondary Objective 1)

6.3.1 Relationship between Cerebral Perfusion and LVEF

Previous work has shown a significant positive correlation ($r = 0.27$, $P = 0.022$) between supine CBF and LVEF in individuals with HF (Loncar et al., 2010). In the present study, LVEF was significantly lower in the HF group, and while there was no significant correlation between mean CBFV and LVEF it is possible that had supine mean CBFV data had been available for all participants in the study, and had we recruited more participants there would have been a significant relationship between LVEF and mean CBFV. We were able to collect supine TSI data on all of our participants, and this larger sample size likely helped reveal the significant positive relationship between LVEF and supine TSI ($r = 0.46$, $P = 0.040$).

6.3.2 Relationship between Cerebral Perfusion and MoCA

There were no significant between group difference in MoCA score, but there was a significant relationship between MoCA score and mean CBFV during supine rest ($r = 0.58$, $P = 0.018$). Previous studies have reported relationships between CBF and cognition in healthy adults (Leeuwis et al., 2018) and CBF and cognitive decline in individuals with hypertension (Kitagawa et al., 2009). Interestingly, despite a well described relationship between cerebral ischemia and cognitive impairment in the literature (Stradecki-Cohan et al., 2017) there was no relationship between MoCA score and supine TSI.

6.3.3 Relationship between Cerebral Perfusion and Arterial Stiffness

There were no significant between group differences in either carotid distensibility or cfPWV. This was particularly surprising given that hypertension, a common consequence of arterial stiffening, is the leading risk factor for HF (GDB 2016 Risk Factors Collaborators, 2017; Pinho-Gomes & Rahimi, 2019). There were no significant relationships between carotid artery distensibility and mean CBFV; however, there was a significant positive relationship between

cfPWV and supine mean CBFV. While no previous investigations have reported the relationship between mean CBFV and cfPWV in older adults with HF, studies of normo- and hypertensive older adults have shown a trend for a negative relationship between supine anterior cerebral blood flow and brachial-ankle PWV ($r_s = -0.36$, $P = 0.07$) as well as a significant positive relationship between supine cerebrovascular resistance and brachial-ankle PWV ($r_s = 0.59$, $P = 0.001$) (Robertson et al., 2009). There were no significant relationships between arterial stiffness and TSI. Evidence has linked elevated cfPWV to poor grey and white matter integrity in middle-aged adults, which presumably is the consequence of ischemic damage, but no similar investigations have been conducted in individuals with HF (Tsao et al., 2013; Maillard et al., 2016).

It was expected that mean CBFV and TSI would respond similarly to posture transitions and walking, as well as be similarly correlated to resting parameters. This is in contrast to what is shown in the above data and correlation analysis, and is further discussed in the limitations section.

6.3.4 Relationship between Cardiac Function and Cerebral Perfusion

Several studies have shown that HF results in compromised CBF at rest (Loncar et al., 2011; Fraser et al., 2015; Oliveira et al., 2015), and CBF and Q during exercise (Oliveira et al., 2015). Cerebral oxygenation has also been shown to be reduced as a consequence of HF at rest and during exercise (Oliveira et al., 2015; Chen et al., 2018). Here we showed an expected positive relationship between Qi and mean CBFV in both the participants with HF and control participants. Alternatively, there were differing relationships between TSI and Qi in the participants with HF and control participants, such that the relationship was positive in the control participants, and negative in the participants with HF. This suggests cerebral desaturation

in individuals with HF during quiet standing and low intensity activity, which was likely the consequence of both low Q, and elevated SNS activity promoting vasoconstriction in both cerebral and peripheral vascular beds, including a relative constriction in the working leg muscles that are almost certainly operating under reduced flow compared to healthy adults. Distribution of blood flow toward working muscles and away from the brain has been shown in previous work in healthy young adults (Ogoh et al., 2005), the relationship demonstrated in the present study is particularly problematic because the conditions evaluated (quiet standing, and slow and normal pace walking) are extremely common during ADLs. Consequently, there is the potential for individuals with HF to experience cerebral ischemia chronically, which may contribute to previously documented functional deficits during ADLs (Dunley et al., 2015), cognitive impairment (Heckman 2007; Harkness 2012; Ampadu & Morley, 2015), and exercise intolerance (reviewed by Brassard & Gustafsson, 2016) in individuals with HF. Further investigation into the mechanism responsible for cerebral desaturation in individuals with HF, and potential interventions, such as preventing hypoxia by increasing oxygen delivery by altering hemoglobin affinity for oxygen, a method shown to be effective in improving exercise tolerance in mice with chronic HF (Watanabe et al., 2008), is warranted.

7.0 Limitations

The main outcomes discussed, TSI and mean CBFV, were collected using NIRS and TCD ultrasound respectively, both of which have inherent limitations that should be considered. NIRS is susceptible to light attenuation from extracranial skin contamination, skin blood flow, and melanin, none of which are likely to be uniform between participants (Greenberg et al., 2017), impacting the absolute comparisons between groups. Also, while the NIRS signal was pulsatile, confirming that an arterial component was being measured, more than 70% of the hemoglobin in the brain is in venous beds; therefore, detected changes may predominately reflect changes in venous saturation (Wahr et al., 1996). Changes in cerebral hemoglobin saturation can result from either changes in oxygen delivery, due to changes in CBF or arterial saturation, or cerebral oxygenation utilization (Wahr et al., 1996) thus, changes in cerebral hemoglobin saturation measured by NIRS may not necessarily suggest changes in CBF. Finally, a wide range of cerebral oxygenation values have been reported in individuals with HF with no concrete clinical significance derived from the absolute value, thereby limiting the clinical implications of even a significant finding (Rifai et al., 2012).

The limitations of TCD ultrasound are also discussed in Poirier, see Declaration (pg. ii). TCD ultrasound is a non-imaging form of ultrasound, so it is not possible to determine the angle of incidence when calculating blood velocity from the Doppler spectrogram. As a result, an insonation angle of 0° is assumed, but may not always be accurate. Furthermore, due to the absence of an imaging component, TCD does not allow for estimation of vessel diameter; therefore, for CBFV to be an accurate estimate of CBF, vessel diameter is assumed to stay constant. Previous reports have shown MCA diameter to change in young healthy adults during hypo- and hypercapnia (Coverdale et al., 2014; Coverdale et al., 2015), but in the present study

there were no significant differences between groups in $P_{ET}CO_2$, suggesting relative normocapnia in the participants with HF. The effect of posture, and subsequently changes in BP at the level of the MCA may also result in changes in CBFV without corresponding changes in CBF. In the present study, control participants showed a reduction in mean CBFV in upright seated, compared to supine posture, whereas previous work showed that CBF was not significantly decreased in seated compared to supine posture in healthy controls (Fraser et al., 2015). The potential impact of age, genetics, and atherosclerotic risk in the present study population may impact MCA diameter. Additionally, changes in CO_2 affects cerebral vascular resistance and can alter CBF potentially without changing CBFV, and overall CBFV should not be directly interpreted as CBF.

Due to the difficulty in recruiting clinical populations, this study had a very small sample size ($n = 10$ for HF and $n = 13$ for controls) that was not effectively sex-matched (male/female: HF – 7/3; Control – 4/9). In addition, a cross-sectional design was employed, and participants only completed each transition in the experimental protocol once. There is large variability in the cardio- and cerebrovascular response to posture transition, and these responses may change within a person even over the course of the day. Also likely a consequence of the small sample size and subject variability was the lack of consistency between mean CBFV and TSI. Considering CBF is a major determinant in cerebral oxygenation, it was expected that TSI and mean CBFV would show similar responses; however, the above data and correlations, as well as Appendix N show inconsistency between these two variables. As noted, this is likely the consequence the small sample size, but may also be affected by changes in arterial oxygenation (see Appendix N; Munger et al., 1994).

Variability within the HF group was also likely impacted by the inclusion of individuals with HFrEF, HFmEF, and HFpEF. Each subtype of HF may differ in underlying pathophysiology, which in turn could affect the cardio- and cerebrovascular responses measured in this study; however, it is important that clinical research studies include individuals that are representative of a real-world clinical population, thus we included individuals from each HF subtype.

Some control participants were treated for hypertension and on similar BP regulating medications to the participants with HF. Still, the participants with HF were significantly more likely to be taking β -blockers ($P < 0.001$), ACE-inhibitors ($P = 0.020$), diuretics ($P = 0.006$), and anticoagulants ($P = 0.007$), and thus medication cannot be ruled out as a confounding factor. Additionally, the control group was comprised of community dwelling older adults who were presumed to be healthy. Some features of this group (e.g., arrhythmias and elevated cfPWV) may have affected comparisons between the HF and control groups. There is the potential that had the control group been “healthier”, then between group comparisons would have shown additional deficits in the HF group.

Finally, the inclusion of a sit-to-stand transition would have allowed for comparisons between quiet standing and walking. Unfortunately, due to time constraints, we were unable to include a sit-to-stand transition in the current study.

8.0 Future Directions

While this study was able to show lower cerebral oxygenation in individuals with HF compared to control participants, more robust conclusions could be drawn with continued data collection. Ideally, this study would include larger groups of participants with HFrEF, HFmEF, and HFpEF, as well as a healthy age- and sex-matched control group and a treated hypertensive age- and sex-matched control group. Each of these populations present unique characteristics that could allow for the further characterization of cerebral ischemia across the spectrum of HF.

A cross-sectional design allowed for only minimal interrogation of relationships between cerebral and central hemodynamics. Future work should attempt to further investigate how differences in pathophysiology between HFpEF and HFrEF (e.g., elevated rates of hypertension and potentially greater arterial stiffness in HFpEF) affect cerebral perfusion and oxygenation, both at rest and during ADLs. As noted, the acute and sustained BP response during the supine-to-stand transition also warrants further investigation in a larger study of individuals with HF, treated hypertensive, and healthy older adults as medication may significantly impact the responses observed in this study. Characterization of the peripheral vascular response to orthostasis in individuals with HF may reveal possible treatment avenues that help prevent adverse health outcomes as a result of falls in this older patient group. Similarly, we were unable to fully interrogate the effect of respiratory dysfunction, common in individuals with HF (e.g. exercise oscillatory ventilation), on CBF and oxygenation. There is the potential that respiratory abnormalities further reduce CBF adversely affect exercise tolerance and quality of life in individuals with HF. Further work should attempt to characterize cerebral hemodynamics during low and moderate intensity activity that is common of ADLs in individuals with HF and respiratory abnormalities.

Individuals with NYHA class IV HF were excluded from this study, as is common in the literature. This is perhaps due to limited mobility, and severe symptomology which frequently requires hospitalization. Efforts to characterize resting cerebral hemodynamics in these individuals may elucidate avenues for treatment that preserve quality of life.

In the present study we noted an interesting relationship between TSI and Q_i such that in individuals with HF cerebral oxygenation decreased in response to increased Q_i during low intensity activity. To determine if this relationship is the result of blood flow competition between working muscle and cerebral tissue, future work should attempt to measure TSI and Q_i during increases in Q that are not concomitant with blood flow competition, such as during a cold pressor test (Elias & Ajayi, 2019) or in response to acute dobutamide treatment (Dubin et al., 2017).

Finally, a longitudinal study that follows individuals with HF over the course of their disease progression could determine how cerebral perfusion is affected over the course of HF treatment. There is the potential that disease progression, or intervention through exercise and pharmacotherapy could drastically alter CBF and the cerebral hemodynamic response to functional challenges such as posture transitions and walking. Without longitudinal or randomized control trial data, the characterization of cerebral ischemia in individuals with HF will have minimal clinical impact, and not translate into improved quality of life in clinical populations.

9.0 Conclusion

We sought to investigate the cerebral hemodynamic response to posture transitions and walking in participants with HF. Overall, cerebral oxygenation was lower in participants with HF compared to control participants during rest, quiet standing, and walking. Reduced cerebral oxygenation is likely the consequence of the dysregulation of multiple physiological system, with BP and Q being the most suspect in the present study. Interestingly, participants with HF had a negative relationship between Q_i and TSI, whereas there was a positive relationship in the control participants. This suggests an ineffective blood flow redistribution during standing and walking in individuals with HF and may explain previously reported exercise intolerance and cognitive impairment in this population. These results clearly show the need for the further investigation of cerebral hemodynamics in individuals with HF, particularly those with HFpEF. These individuals often respond ineffectively to clinical treatment, and understanding the effect of changes in central cardiac function on cerebral integrity and cognitive function may precipitate treatment avenues that improve quality of life.

This study was the first to assess cardio- and cerebrovascular responses in real world conditions outside of the strict confines of a conventional laboratory setting. Experimental paradigms like in the present study, while challenging from a data collection perspective, allow for the characterization of hemodynamic responses that mimic the stress of daily function. Additional work should continue to characterize these responses by utilizing advanced ambulatory and optical monitoring technology, in an effort to interrogate clinically relevant questions that are also impactful to the challenges daily life and quality of life of older adults.

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Appendix

Appendix A: Health Status Questionnaire

Health Status Form

Study Title: Brain blood flow during activities of daily living in Heart Failure

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Participant ID: _____

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 ()

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
-------------------	---------------------------------	-------------------

Physical Activity

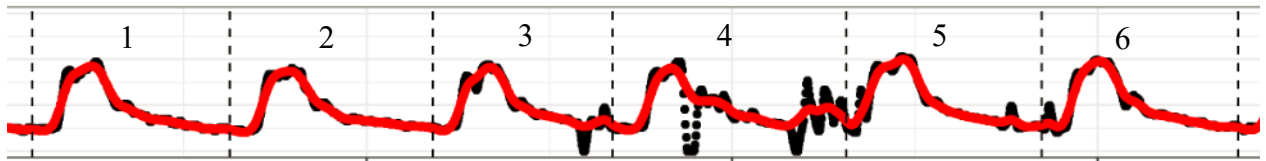
How many days per week do you participate in at least 30 minutes of continuous physical activity?
Circle one.

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.

Appendix B: Spline Interpolation of CBFV Trace



This sample figure shows the raw CBFV trace (black) and the clean CBFV trace generated from spline interpolation (red). Vertical dashed black lines indicate cardiac cycles. There is minimal difference between raw and clean data when the input signal is high quality (cardiac cycles 1 and 2), but spline interpolation prevented data loss when signal dropout occurred (cardiac cycles 3 and 4).

Appendix C: Cardiorespiratory and cerebrovascular variables during supine and seated rest

	Supine		Seated		P-value
	Control	HF	Control	HF	
HR (bpm)	59.5±11.0	65.0±7.8	64.6±11.1	64.9±7.3	int(b): < 0.001
MAP (mmHg)	92.5±10.9	83.5±10.4	91.3±14.5	81.7±10.3	gr: 0.062
SBP (mmHg)	139.4±19.6	122.8±21.8	135.0±21.5	114.8±16.5	gr: 0.079
DBP (mmHg)	68.9±10.1	62.9±8.6	69.8±14.1	64.2±8.8	n.s.
SV _i (mL/m ²)	42.8±8.2	30.5±5.6	41.7±10.6	27.1±4.8	gr: < 0.001
Q _i (L/min/m ²)	2.5±0.6	1.9±0.5	2.7±0.6	1.6±0.3	gr: < 0.001
Mean CBFV(cm/s)	47.5±11.0	41.9±6.1	44.3±6.0	39.6±5.7	con: 0.047
Peak CBFV (cm/s)	75.5±14.1	70.9±11.5	76.0±12.7	71.6±10.9	n.s.
Min CBFV (cm/s)	26.5±6.6	22.1±5.6	22.8±3.6	19.9±4.4	gr: 0.089; con: 0.018
TSI (%)	70.3±4.0	67.1±5.9	71.3±3.6	65.1±6.0	gr: 0.020
P _{ET} CO ₂ (mmHg)	37.4±2.4	35.2±2.9	37.0±2.7	35.1±3.7	gr: 0.094

All values are mean±SD. HR – heart rate; MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; SV_i – stroke volume index; Q_i – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index; P_{ET}CO₂ – partial pressure of end-tidal carbon dioxide. Statistical analysis: gr – group effect; con – condition effect; int(b) – control group: supine vs. seated.

Appendix D: Cardio- and cerebrovascular variables at nadir during supine-to-stand transition

	Control	HF	<i>P</i> -value
HR (bpm)	69.8±17.9	71.4±19.3	n.s.
MAP (mmHg)	53.8±12.6	64.0±9.2	0.066
SBP (mmHg)	80.2±16.7	88.7±16.8	n.s.
DBP (mmHg)	44.3±13.4	54.8±17.6	n.s.
SVi (mL/m ²)	47.9±17.0	27.2±16.3	0.028
Qi (L/min/m ²)	3.4±1.3	1.7±1.2	0.021
Mean CBFV (cm/s)	37.4±9.6	34.6±7.0	n.s.
Peak CBFV (cm/s)	69.1±17.6	66.4±11.1	n.s.
Min CBFV (cm/s)	17.5±5.1	16.3±3.7	n.s.
TSI (%)	68.2±4.0	65.1±6.0	n.s.
Relative Oxy Hb (μM)	-2.2±1.5	-2.2±1.7	n.s.
Relative HHb (μM)	-0.5±0.3	-0.5±0.6	n.s.
Relative tHb (μM)	-2.3±1.6	-2.5±2.2	n.s.

All values are mean±SD. HR – heart rate; MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; SVi – stroke volume index; Qi – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index; Oxy Hb – oxygenated hemoglobin; HHb – oxygenated hemoglobin; tHb – total hemoglobin.

Appendix E: Cardio- and cerebrovascular variables at nadir during sit-to-walk (normal) and sit-to-walk (slow) transitions

	Normal		Slow		P-value
	Control	HF	Control	HF	
HR (bpm)	73.2±12.0	65.4±11.5	73.9±12.5	72.9±16.7	n.s.
MAP (mmHg)	69.0±13.1	64.8±12.2	65.3±18.1	60.6±8.3	n.s.
SBP (mmHg)	99.8±12.4	97.1±20.4	94.4±15.3	79.7±16.0	con: 0.036
DBP (mmHg)	54.3±15.0	54.8±16.5	53.7±17.8	52.2±8.6	n.s.
SVi (mL/m ²)	46.0±11.9	34.1±11.8	42.9±9.2	28.2±9.4	gr: 0.007
Qi (L/min/m ²)	3.6±1.0	2.1±0.8	3.2±0.3	1.9±0.8	gr: < 0.001
Mean CBFV (cm/s)	38.1±7.8	36.0±6.0	40.3±6.2	32.5±5.8	n.s.
Peak CBFV (cm/s)	69.7±13.5	73.0±12.0	74.6±15.7	69.0±11.3	n.s.
Min CBFV (cm/s)	17.2±5.1	17.1±5.3	18.4±5.1	14.1±4.2	n.s.
TSI (%)	69.8±3.3	63.5±6.6	69.9±4.2	64.0±6.9	gr: 0.009
Relative Oxy Hb (μM)	-1.5±1.2	-1.5±0.9	-1.6±1.4	-1.5±1.0	n.s.
Relative HHb (μM)	-0.2±0.5	-0.4±0.3	-0.3±0.3	-0.3±0.2	n.s.
Relative tHb (μM)	-1.5±1.2	-1.9±1.0	-1.7±1.6	-1.6±1.1	n.s.

All values are mean±SD. HR – heart rate; MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; SVi – stroke volume index; Qi – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index; Oxy Hb – oxygenated hemoglobin; HHb – oxygenated hemoglobin; tHb – total hemoglobin. Statistical analysis: gr – group effect; con – condition effect.

Appendix F: Cardiorespiratory and cerebrovascular variables during early, middle, and late stand

	Early		Middle		Late		P-value
	Control	HF	Control	HF	Control	HF	
HR (bpm)	68.5±12.8	72.1±6.6	69.3±12.1	72.4±9.3	70.3±11.3	70.2±8.1	n.s.
MAP (mmHg)	79.7±17.5	66.5±9.5	85.0±12.7	73.1±12.2	83.5±11.3	73.5±13.8	gr: 0.041; ti(a): 0.016; ti(b): 0.033
SBP (mmHg)	115.6±25.2	95.3±14.1	124.4±19.6	104.2±24.4	124.4±17.7	106.3±23.6	gr: 0.028; ti(a): 0.025; ti(b): 0.020
DBP (mmHg)	63.4±14.8	54.0±11.3	65.9±11.7	59.5±10.2	64.8±11.0	58.8±11.8	ti(a): 0.016; ti(b): 0.033
SVi (mL/m ²)	38.6±8.4	28.4±6.5	38.9±10.4	25.9±6.7	39.1±9.5	27.2±6.7	gr: 0.005
Qi (L/min/m ²)	2.6±0.6	1.9±0.5	2.7±0.7	1.7±0.5	2.8±0.7	1.8±0.5	gr: 0.006
Mean CBFV(cm/s)	41.7±9.6	37.1±6.0	42.4±8.0	38.4±7.7	43.1±8.8	37.5±6.5	n.s.
Peak CBFV (cm/s)	72.1±15.4	69.7±12.2	72.5±14.8	70.1±11.4	73.4±15.2	68.7±8.6	n.s.
Min CBFV (cm/s)	22.1±4.7	19.1±4.9	22.8±3.5	20.3±6.3	23.1±4.5	19.0±5.5	n.s.
TSI (%)	69.7±4.0	65.3±5.9	69.9±4.2	64.8±6.0	69.6±4.3	64.8±6.1	gr: 0.034
Relative Oxy Hb (μM)	-1.6±1.1	-2.2±2.5	-1.4±1.2	-1.6±2.3	-1.4±1.2	-1.4±2.2	ti(b): 0.025
Relative HHb (μM)	0.4±0.8	0.4±0.8	0.6±0.7	0.7±0.9	0.7±0.8	0.8±1.1	ti(a): < 0.001; ti(b): 0.010
Relative tHb (μM)	-1.2±1.5	-1.8±2.9	-0.8±1.7	-0.9±2.5	-0.7±1.8	-0.6±2.3	ti(a): < 0.001; ti(b): 0.002
P _{ET} CO ₂ (mmHg)	36.4±3.5	33.4±5.4	36.2±3.2	33.9±4.8	35.4±3.5	32.9±5.3	n.s.

All values are mean±SD. HR – heart rate; MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; SVi – stroke volume index; Qi – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index; Oxy Hb – oxygenated hemoglobin; HHb – oxygenated hemoglobin; tHb – total hemoglobin; P_{ET}CO₂ – partial pressure of end-tidal carbon dioxide. Statistical analysis: gr – group effect; ti (a) – time effect: early vs. middle; ti(b) – time effect: early vs. late.

Appendix G: Cardiorespiratory and cerebrovascular variables during early, middle, and late slow walking

	Early		Middle		Late		P-value
	Control	HF	Control	HF	Control	HF	
HR (bpm)	73.6±15.9	74.9±6.0	76.2±14.9	76.6±6.8	76.5±12.9	79.7±7.9	ti(c): 0.007; cn: < 0.001
MAP (mmHg)	74.3±17.4	72.9±12.1	77.3±19.1	71.3±19.1	76.9±21.7	77.8±21.7	gr: 0.043; cn: 0.062
SBP (mmHg)	119.8±21.6	100.8±19.4	127.4±23.4	96.0±23.3	126.3±28.5	106.9±28.7	gr: 0.006; cn: 0.008
DBP (mmHg)	64.7±16.1	58.9±8.2	66.8±16.2	57.6±9.8	66.2±18.0	60.7±7.4	n.s.
SVi (mL/m ²)	44.0±10.7	31.4±7.0	44.4±10.5	29.7±8.6	45.7±9.7	30.8±8.5	gr: 0.001; cn: 0.013
Qi (L/min/m ²)	3.2±0.6	2.2±0.5	3.4±0.6	2.1±0.5	3.5±0.6	2.2±0.5	ti(c): 0.013; int(a): 0.001; int(c): 0.017; int(d): < 0.001
Mean CBFV(cm/s)	45.2±6.1	37.9±6.2	46.7±6.9	38.4±5.5	46.8±6.7	39.2±5.4	ti(a): 0.056 ti(c): 0.011; int(a): 0.019; int(c): 0.002;
Peak CBFV (cm/s)	81.7±10.1	76.2±10.6	83.3±10.6	76.8±9.6	83.3±11.0	77.0±10.2	int(c): 0.048
Min CBFV (cm/s)	21.4±5.3	16.7±5.2	21.3±5.6	16.5±5.3	20.9±5.1	16.7±5.4	int(a): 0.054; int(c): 0.008
TSI (%)	70.9±4.2	64.0±6.7	70.4±3.9	63.4±6.9	70.1±3.8	63.3±6.7	gr: 0.004; ti(c): 0.027
Relative Oxy Hb (μM)	-1.0±0.8	-1.3±1.0	-1.1±0.9	-1.6±0.9	-1.1±0.9	-1.5±0.9	n.s.
Relative HHb (μM)	0.2±0.3	0.3±0.4	0.4±0.3	0.4±0.4	0.5±0.4	0.5±0.4	ti(a): 0.052; ti(c): 0.011; int(c): 0.012
Relative tHb (μM)	-0.8±0.9	-1.1±1.0	-0.6±1.0	-1.1±1.0	-0.6±0.9	-1.0±1.0	int(c): 0.016
P _{ET} CO ₂ (mmHg)	36.6±5.4	37.8±4.1	37.9±4.8	37.7±3.3	37.5±5.3	37.2±2.9	cn: 0.035

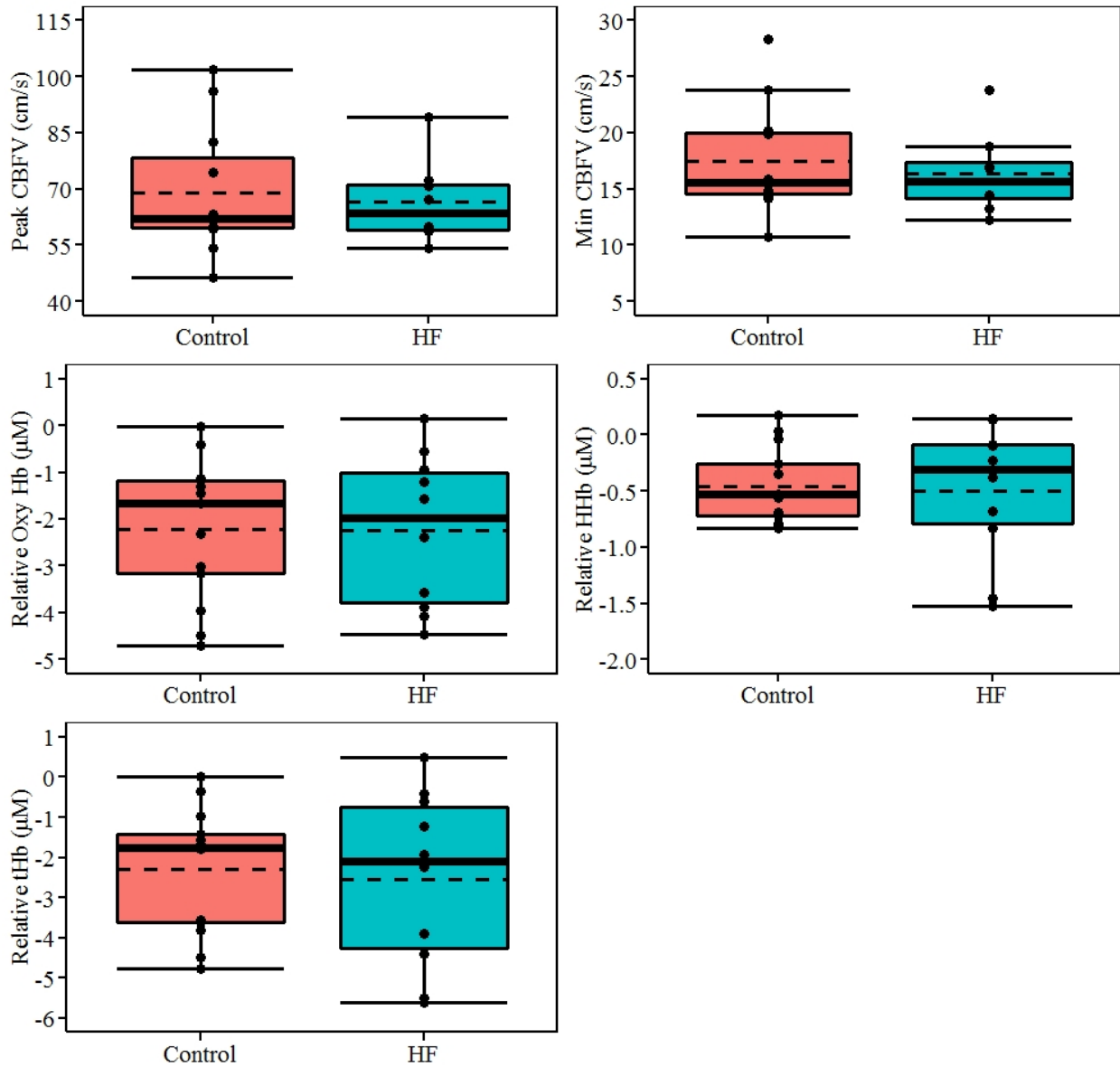
All values are mean±SD. HR – heart rate; MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; SVi – stroke volume index; Qi – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index; Oxy Hb – oxygenated hemoglobin; HHb – deoxygenated hemoglobin; tHb – total hemoglobin; P_{ET}CO₂ – partial pressure of end-tidal carbon dioxide. Statistical analysis: gr – group effect; cn – condition effect; ti (a) – time effect: early vs. middle; ti(b) – time effect: early vs. late; int(a) – slow pace walking: HF group vs. control group; int(c) – HF group: slow vs. normal pace; int(d) – control group: slow vs. normal pace.

Appendix H: Cardiorespiratory and cerebrovascular variables during early, middle, and late normal walking

	Early		Middle		Late		P-value
	Control	HF	Control	HF	Control	HF	
HR (bpm)	80.5±9.5	79.3±7.3	82.3±13.9	83.5±8.9	82.2±15.2	89.0±11.8	ti(c): 0.007; cn: < 0.001
MAP (mmHg)	90.8±21.4	73.4±10.0	94.5±21.3	75.3±14.1	91.1±18.2	77.4±14.0	gr: 0.043; cn: 0.062
SBP (mmHg)	128.7±20.0	104.3±18.8	136.1±16.4	105.6±26.1	134.2±15.3	104.5±24.3	gr: 0.006; cn: 0.008
DBP (mmHg)	69.3±20.4	57.6±7.0	70.7±21.6	58.4±9.9	66.6±17.3	61.0±9.2	n.s.
SVi (mL/m ²)	44.9±12.5	34.0±7.7	47.8±11.1	32.9±9.2	53.2±11.7	29.4±8.9	gr: 0.001; cn: 0.013
Qi (L/min/m ²)	3.9±1.2	2.5±0.7	4.3±1.3	2.5±0.7	4.8±1.4	2.4±0.6	ti(c): 0.013; int(b): < 0.001; int(c): 0.017; int(d): < 0.001
Mean CBFV(cm/s)	44.2±8.4	40.4±6.7	46.4±8.6	40.7±5.9	47.1±7.5	41.0±5.7	ti(a): 0.056 ti(c): 0.011; int(b): 0.078; int(c): 0.002;
Peak CBFV (cm/s)	79.7±12.7	78.7±10.5	81.2±12.9	77.6±10.9	83.0±12.3	77.7±11.6	int(c): 0.048
Min CBFV (cm/s)	19.8±5.3	18.4±7.1	21.0±4.3	18.8±6.2	20.3±4.9	18.6±5.3	int(a): 0.054; int(c): 0.008
TSI (%)	70.6±3.7	63.3±6.6	70.3±3.5	64.0±6.6	70.1±3.5	64.0±6.9	gr: 0.004; ti(c): 0.027
Relative Oxy Hb (μM)	-1.1±1.1	-1.6±1.1	-1.0±1.0	-1.5±1.0	-1.0±1.0	-1.4±1.1	n.s.
Relative HHb (μM)	0.2±0.4	0.0±0.5	0.5±0.7	0.1±0.5	0.5±0.9	0.1±0.6	ti(a): 0.052; ti(c): 0.011; int(b): 0.090; int(c): 0.012
Relative tHb (μM)	-1.0±1.1	-1.6±0.9	-0.5±1.0	-1.4±1.0	-0.5±0.9	-1.3±1.0	int(b): 0.024; int(c): 0.016
P _{ET} CO ₂ (mmHg)	36.2±2.4	36.0±3.6	37.2±3.3	36.9±2.7	38.0±2.9	37.3±2.8	cn: 0.035

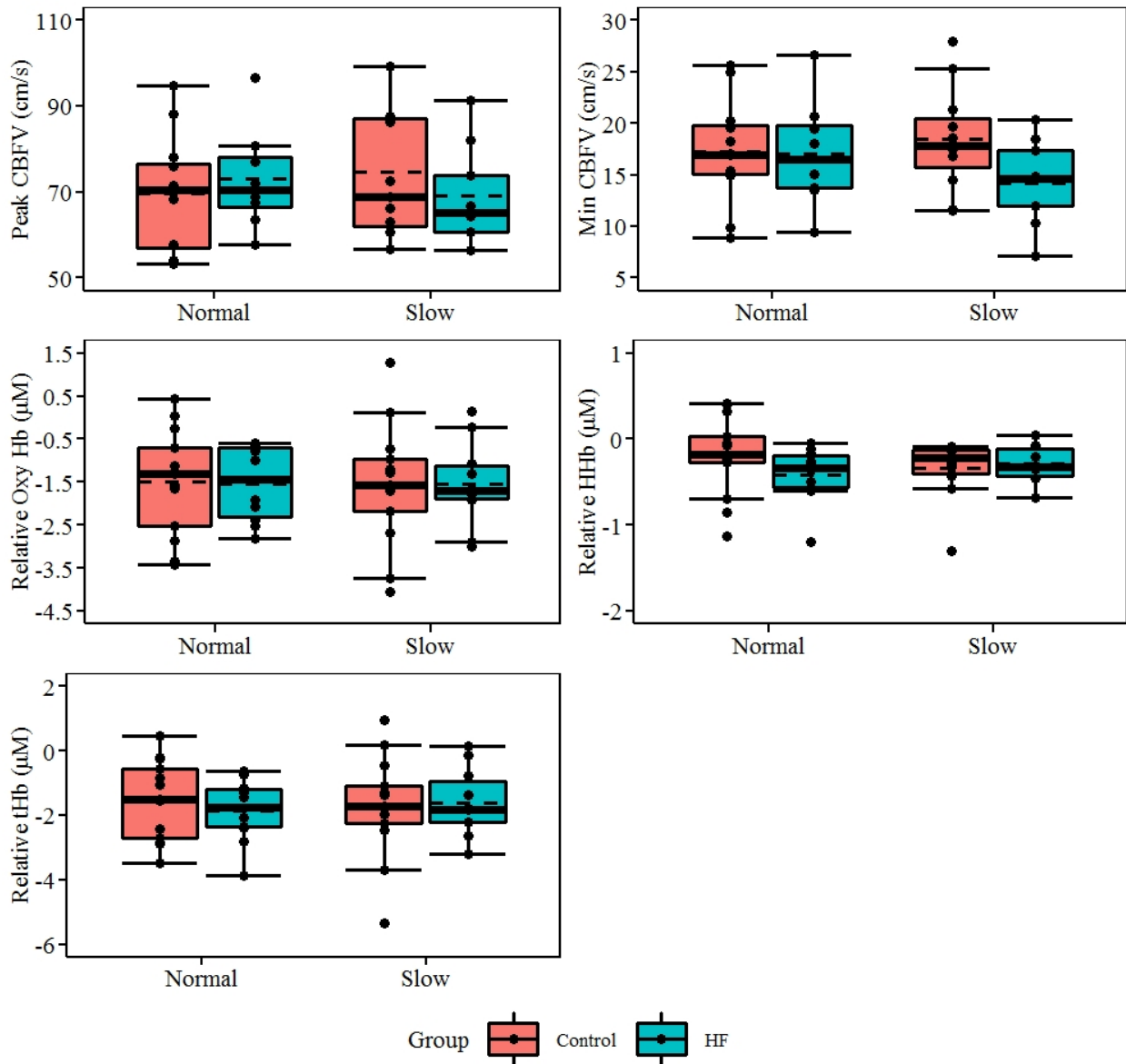
All values are mean±SD. HR – heart rate; MAP – mean arterial pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; SVi – stroke volume index; Qi – cardiac index; CBFV – cerebral blood flow velocity; TSI – tissue saturation index; Oxy Hb – oxygenated hemoglobin; HHb – deoxygenated hemoglobin; tHb – total hemoglobin; PETCO₂ – partial pressure of end-tidal carbon dioxide. Statistical analysis: gr – group effect; cn – condition effect; ti (a) – time effect: early vs. middle; ti(b) – time effect: early vs. late; int(b) – normal pace walking: HF group vs. control group; int(c) – HF group: slow vs. normal pace; int(d) – control group: slow vs. normal pace.

Appendix I: Cerebral hemodynamic and hemoglobin concentration nadirs during supine-to-stand transition



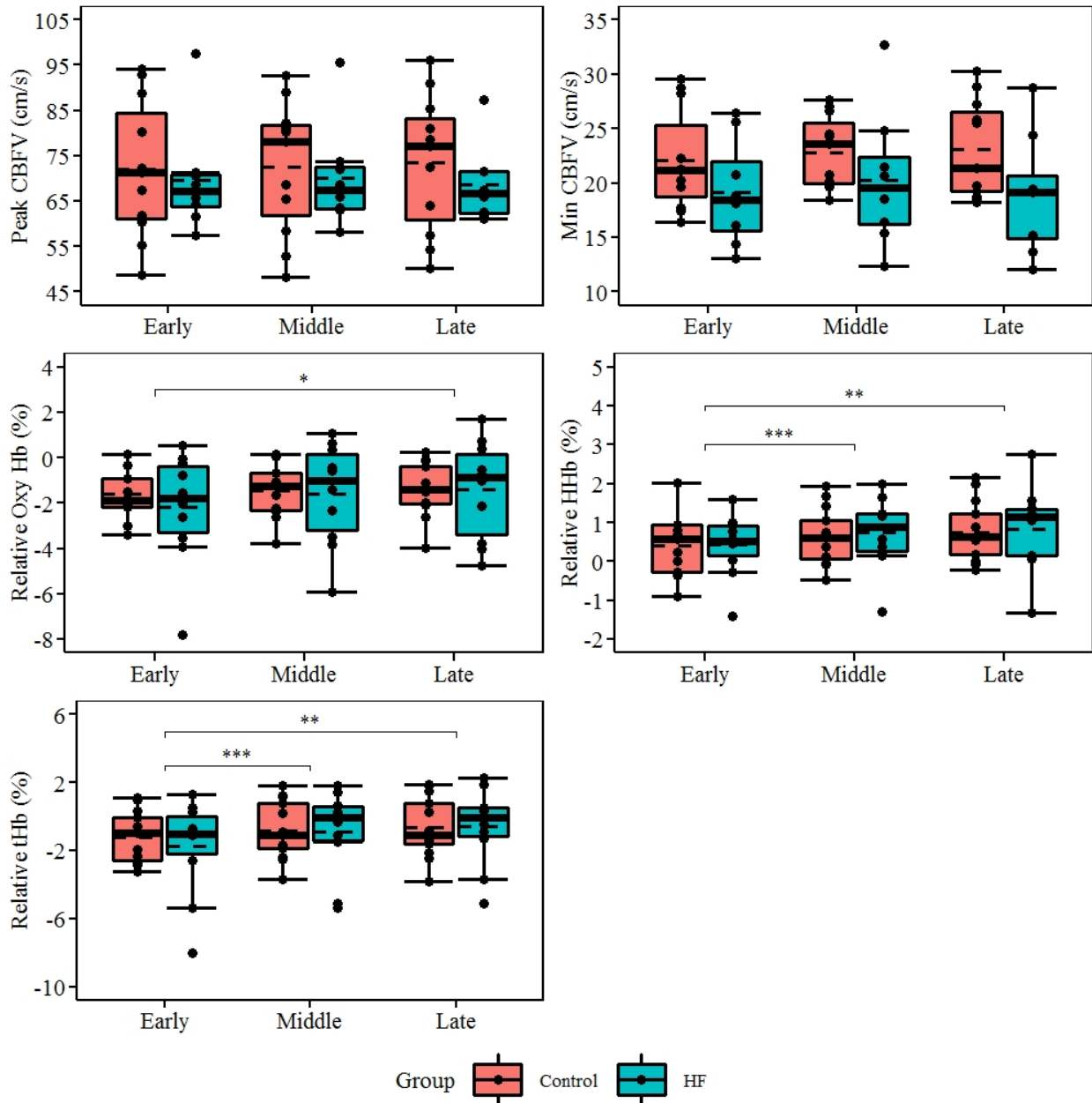
Graph format is the same as described in Figure 5.2. CBFV – cerebral blood flow velocity; Oxy Hb – oxygenated hemoglobin; HHb – deoxygenated hemoglobin; tHb – total hemoglobin. “Relative” indicates values are a change score from the baseline value.

Appendix J: Cerebral hemodynamic and hemoglobin concentration nadirs during sit-to-walk (slow) and sit-to-walk (normal) transition



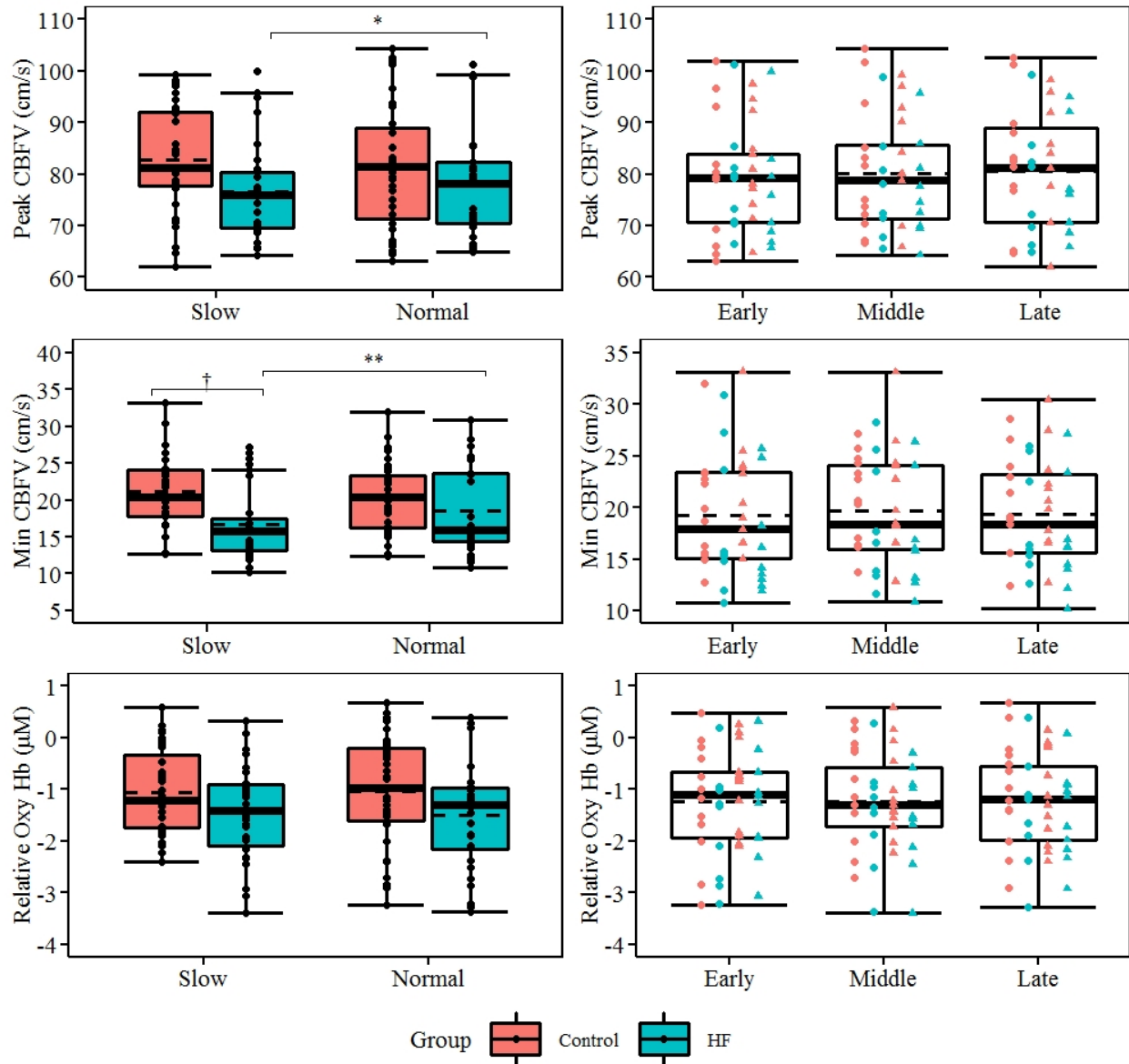
Graph format is the same as described in Figure 5.2. CBFV – cerebral blood flow velocity; Oxy Hb – oxygenated hemoglobin; HHb – deoxygenated hemoglobin; tHb – total hemoglobin. “Relative” indicates the values are a change score from the baseline value.

Appendix K: Cerebral hemodynamic and hemoglobin concentration response during early, middle, and late phase standing after supine-to-stand transition



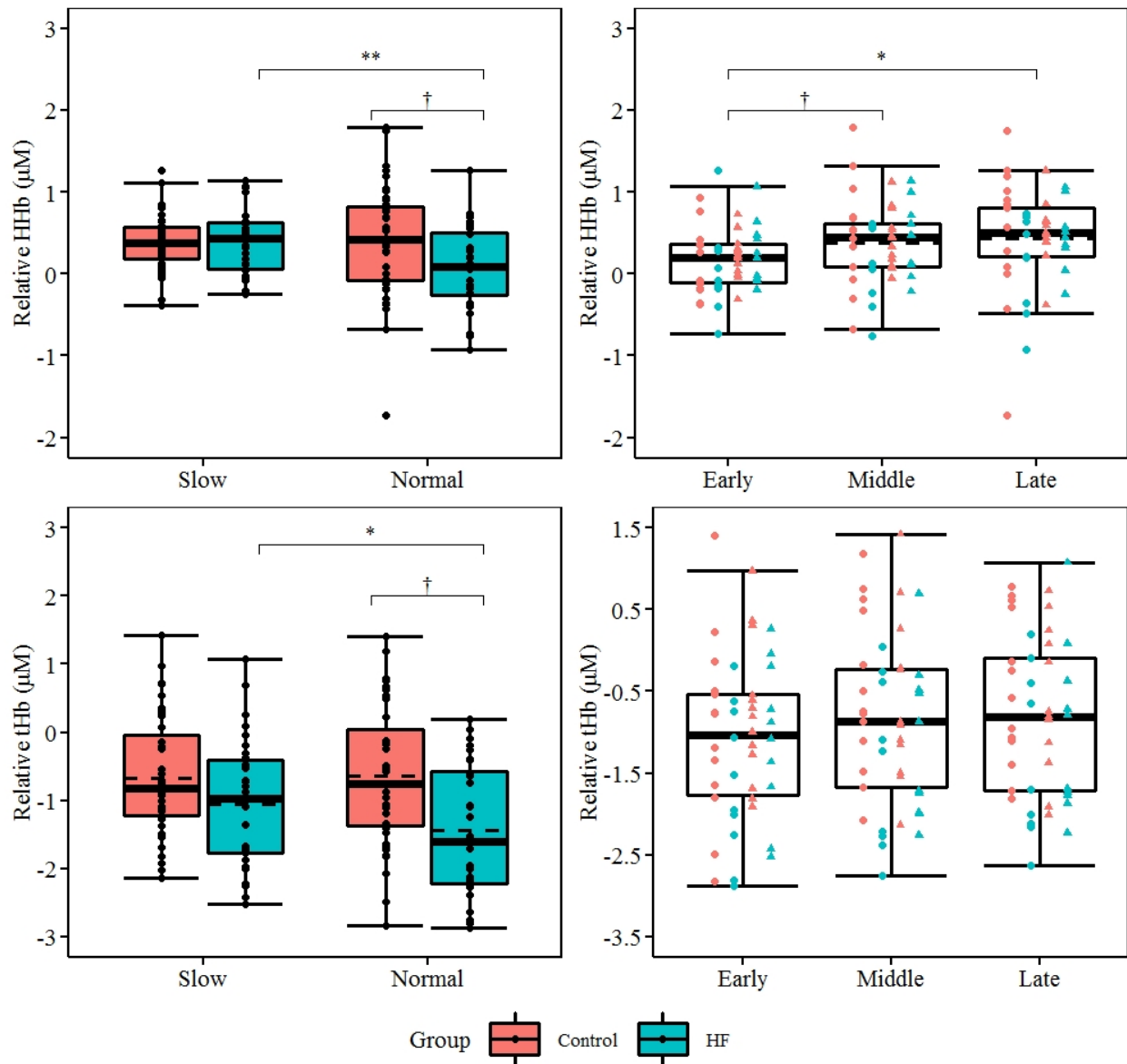
Graph format is the same as described in Figure 5.2. CBFV – cerebral blood flow velocity; Oxy Hb – oxygenated hemoglobin; HHb – deoxygenated hemoglobin; tHb – total hemoglobin. “Relative” indicates the values are a change score from the baseline value.

Appendix L: Cerebral hemodynamic and hemoglobin concentration response during early, middle, and late phase slow and normal pace walking after sit-to-walk transition



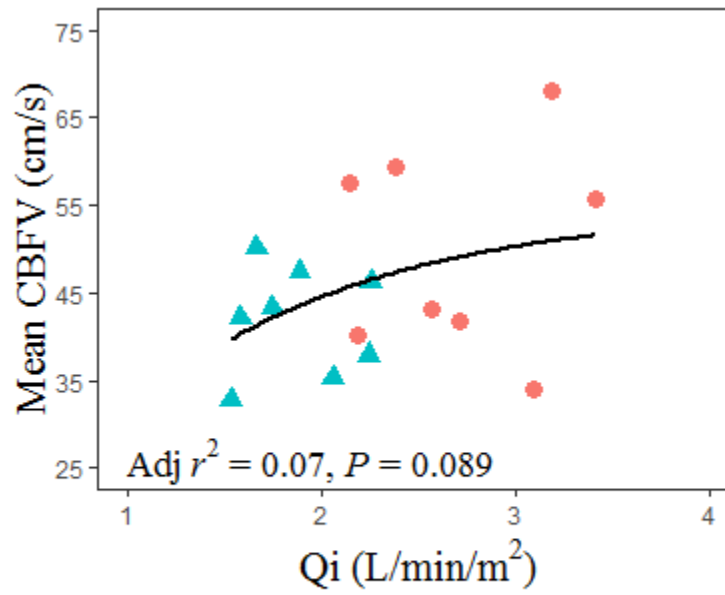
Graph format is the same as described in Figure 5.8. CBFV – cerebral blood flow velocity; Oxy Hb – oxygenated hemoglobin. * indicates significant difference $P < 0.05$; ** indicates significant difference $P < 0.01$; † indicates a trend to be different $P < 0.1$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition (left) or a main effect of time (right). Group main effects are shown in the lower left corner of each graph. “Relative” indicates the values are a change score from the baseline value.

Appendix M: Cerebral hemoglobin response during early, middle, and late phase slow and normal pace walking after sit-to-walk transition

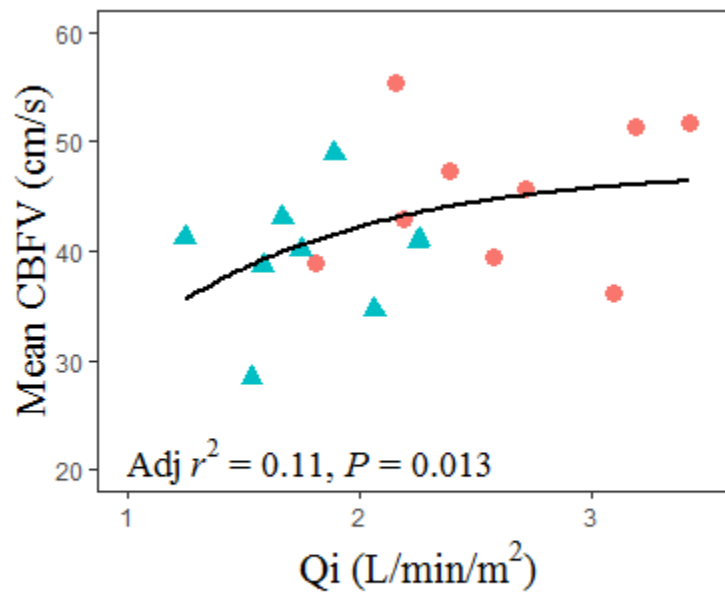


Graph format is the same as described in Figure 5.8. HHb – deoxygenated hemoglobin. * indicates significant difference $P < 0.05$; ** indicates significant difference $P < 0.01$; † indicates a trend to be different $P < 0.1$. Significance lines center above a single bar indicate an interaction effect, while significance lines centers between two bars indicate a main effect of condition (left) or a main effect of time (right). Group main effects are shown in the lower left corner of each graph. “Relative” indicates the values are a change score from the baseline value.

Appendix N: Relationship between mean CBFV and Qi at rest



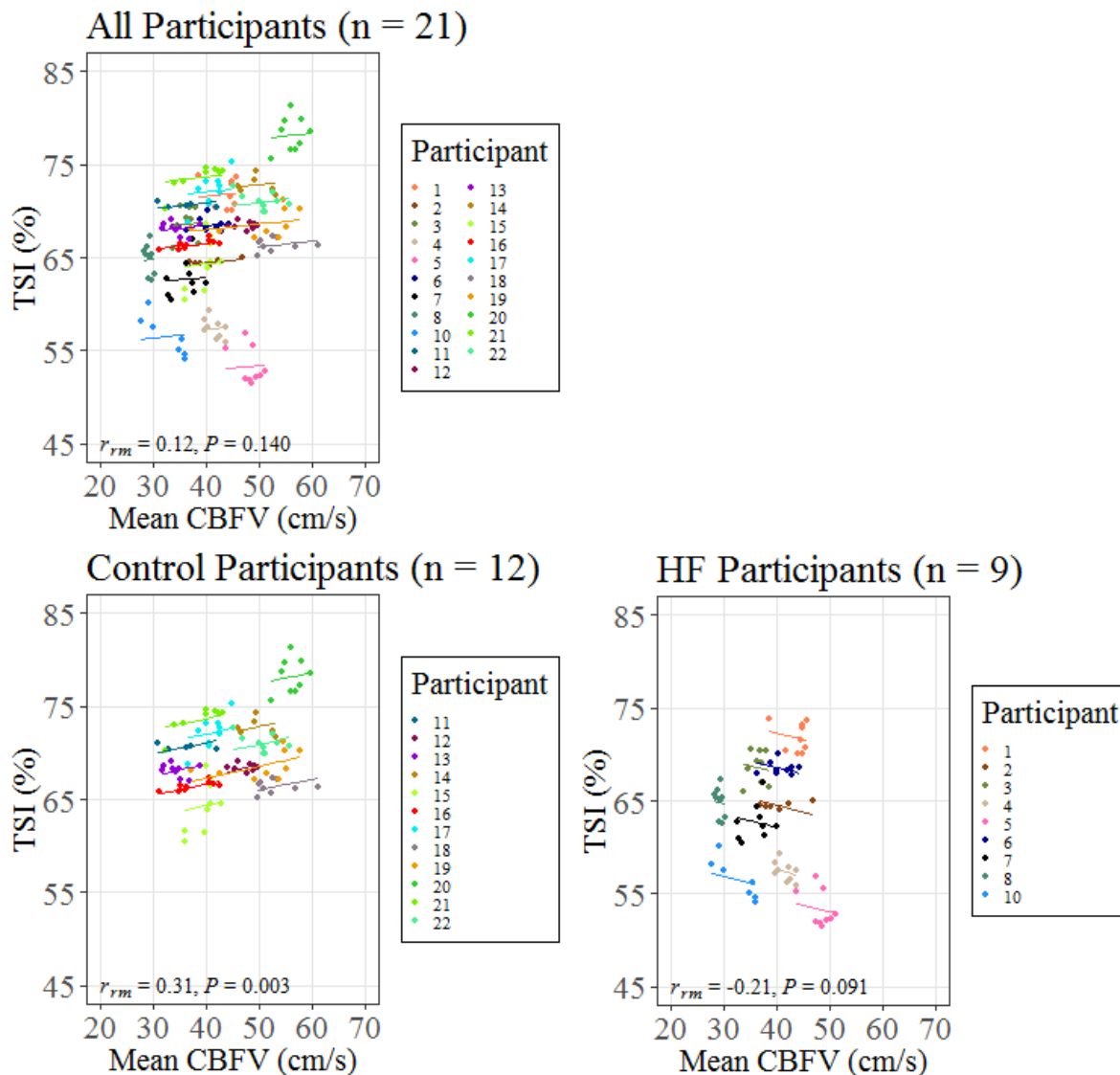
Group ● Control ▲ HF



Group ● Control ▲ HF

Salmon coloured circles represent the control group and blue coloured triangles represent the HF group. CBFV and Qi were measured in supine (top) and seated (bottom) posture. CBFV – cerebral blood flow velocity; Qi – cardiac index.

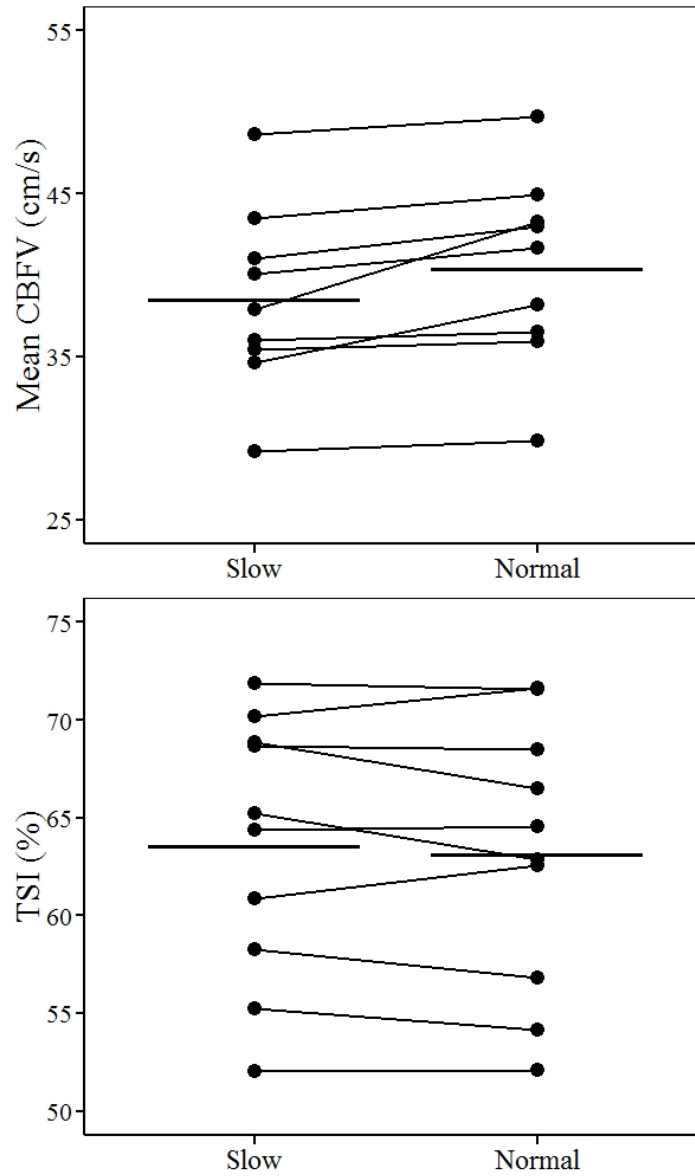
Appendix O: Repeated-measures correlations between TSI and mean CBFV



Graph format is the same as described in Figure 5.13. Individual data are from the early, middle, and late phase of quiet standing, and normal and slow pace walking for each participant. TSI – tissue saturation index; CBFV – cerebral blood flow velocity.

Shown here is a positive relationship between mean CBFV and TSI in the control participants, and a trend for a negative relationship in the participants with HF. It should be noted that the trend in the HF group was very weak ($r_{rm} = -0.21, P = 0.091$), and that this was unexpected as cerebral oxygenation should increase in response to increasing cerebral perfusion, outside the setting of arterial oxygen desaturation. In the present study we did not measure arterial oxygen saturation; however, it is possible that arterial desaturation could have occurred in the participants with HF as a previous ambulatory study showed that arterial saturation is not preserved during wakeful hours in individuals with HF (Munger et al., 1994).

Appendix P: Consistency of the mean CBFV and TSI response to walking in individuals with HF



Black circles connected by lines indicate individuals with HF during the slow and normal pace walking condition. CBFV – cerebral blood flow velocity; TSI – tissue saturation index.