Postural Effects on Brain Blood Flow and Cognition in Heart Failure

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any final revisions, as accepted by my examiners.

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

Abstract

With the aging population on the rise, the prevalence of heart failure is expected to increase in the coming years. Heart failure is independently correlated with cognitive decline and has a negative impact on quality of life, morbidity and mortality. Reduced cardiac output (Q) and cerebral blood flow (CBF) are proposed mechanistic links between heart failure and cognitive decline; however, reports are limited to the supine position and the response to an everyday upright posture is unknown. The purpose of this thesis was to primarily investigate the CBF response to a common upright seated position encountered in daily life in heart failure patients compared to healthy age- and sex-matched controls. Furthermore, we sought to determine whether cognitive performance or cognitive-activated hemodynamics were posture-dependent in the heart failure group. The secondary objective of this thesis was to be inclusive to patients that represent those encountered in clinical practice—specifically to include patients with higher left ventricular ejection fractions (LVEF) and atrial fibrillation with co-existing heart failure. Our findings confirmed greater cognitive impairments and a low supine CBF and Q in heart failure compared to controls and importantly, for the first time, a greater reduction in CBF with an upright seated position compared to healthy age- and sex- matched controls. When a cognitive task was performed supine and seated, performance outcomes were independent of posture in heart failure patients. However, mean flow velocity through the middle cerebral artery (MFV_{MCA}) increased less in response to the cognitive task seated. With regard to our secondary objectives, the results suggest that those with higher LVEF are equally at risk for cognitive decline and cerebral hypoperfusion due to a low Q. Furthermore, high variability in Q and MFV_{MCA} were detected in association with the beat-to-beat variation inherent to atrial fibrillation and suggest that this may be an underappreciated pathway to cognitive impairments in this sub-

group. Together, these results suggest that upright cerebral hypoperfusion throughout the day may contribute to cognitive decline in heart failure and create a basis for further work to be done with larger sample sizes. Moreover, cerebral hypoperfusion with higher LVEF and the blood flow variation in atrial fibrillation represent important pathways contributing to cognitive decline in these under investigated sub-groups.

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List of Acronyms

ABP: arterial blood pressure

aCBF: anterior cerebral blood flow

BMI: body mass index

BSA: body surface area

CBF: cerebral blood flow

CBF$_{RICA}$: cerebral blood flow through the right internal carotid artery

CCA: common carotid artery

CFS: chronic fatigue syndrome

CVD: cardiovascular disease

CVRi: cerebrovascular resistance index

DFV: diastolic flow velocity

DHF: diastolic heart failure

ETCO$_2$: end tidal carbon dioxide

GDS: geriatric depression scale

HFpEF: heart failure preserved ejection fraction

HFrEF: heart failure reduced ejection fraction

HR: heart rate

ICA: internal carotid artery

ICD: implanted cardiac defibrillator

ICP: intracranial pressure

IMT: intima-media thickness

LVEF: left ventricular ejection fraction

MBF: mean blood flow

MCA: middle cerebral artery

MCI: mild cognitive impairment

MFV: mean flow velocity

MFV$_{MCA}$: mean flow velocity through the middle cerebral artery

MFV$_{RICA}$: mean flow velocity through the right internal carotid artery

MMSE: mini mental state examination

MoCA: Montreal Cognitive Assessment

NYHA: New York Heart Association

OH: orthostatic hypotension

PaCO$_2$: partial pressure of carbon dioxide

PI: pulsatility index

PP$_{brach}$: brachial pulse pressure

PP$_{car}$: carotid pulse pressure

Q: cardiac output

Qi: cardiac index (cardiac output corrected for body size)

Q_Fin: cardiac output from the Finometer

Q_Inn: cardiac output from the Innocor

RAAS: renin-angiotensin-aldosterone system

RI: resistance index

SFV: systolic flow velocity

SHF: systolic heart failure

SV: stroke volume

SVi: stroke index (stroke volume corrected for body size)

TCD: transcranial Doppler

TIA: transient ischemic attack

TPR: total peripheral resistance

VA: vertebral artery

WHR: waist-hip ratio

WMH: white matter hyperintensities

1.0 Literature Review

1.1 Definition and Epidemiology of Heart Failure

Heart failure is characterized by a progressive loss of functional cardiomyocytes that disrupt the heart's ability to generate force and thus compromises the delivery of adequate blood to the rest of the body (Klabunde, 2005). The loss of cardiomyocytes is initiated by an 'index event' such as a myocardial infarction, hemodynamic pressure-volume overload or a variety of genetic or viral cardiomyopathies. Regardless of the initial etiology, the final clinical outcome is a decline in the output of blood from the heart to the rest of the body (Libby *et al.*, 2008). The decline in heart output that characterizes heart failure is initially compensated by the suppression of parasympathetic tone and elevation of the sympathetic nervous system which increases heart rate (HR) and peripheral resistance. This compensatory mechanism becomes pathological over time as long-term activation causes structural remodelling at the heart, sometimes fatal arrhythmias, fluid retention and increased work demand on the failing heart (Floras, 1993). Heart failure is associated with cognitive decline that has been attributed to reduced blood flow to the brain as a consequence of reduced heart output (Q-cardiac output). To date, Q and brain blood flow in patients with heart failure have been examined only in the supine posture. Therefore, it is the purpose of this thesis to examine these variables in the upright seated posture that is relevant to the challenges of daily life.

Heart failure is the most common reason for older adult hospitalizations in North America (Liao *et al.*, 2008). A diagnosis of heart failure places a significant burden on the patient as it is associated with reduced quality of life and substantial morbidity and mortality (Johansen *et al.*,

2003; Lesman-Leegte *et al.*, 2009). A financial burden is also placed on the health care system as it is one of the most costly chronic conditions in North America (Liao *et al.*, 2008). Heart failure is predominantly an aging disorder, increasing exponentially with older age (Roger *et al.*, 2012; Ho *et al.*, 1993). Projections to 2030 indicate that there will be a 25% increase in prevalence (Roger *et al.*, 2012) coinciding with a doubling of the Canadian population that is over 65 years of age (Statistics Canada, 2010). Additionally, improved treatment of acute cardiovascular disease (CVD) such as hypertension and myocardial infarction has resulted in patients living longer and becoming prone to secondary cardiovascular complications, such as heart failure (Coats, 1998).

Heart failure has historically been defined as either systolic or diastolic based on impairment of the pumping or relaxation capacity, respectively. Diastolic heart failure (DHF) is characterized by two main pathological conditions, diastolic dysfunction that includes abnormal left ventricular relaxation and filling, and combined ventricular/arterial stiffening leading to eventual concentric left ventricular hypertrophy (Kindermann *et al.*, 2008). Additional diagnostic features include heart failure signs and symptoms and absent or mild abnormalities in pump function which is typically assessed clinically by left ventricular ejection fraction (LVEF) (Alagiakrishnan *et al.*, 2012). LVEF is the proportion of blood ejected from the left ventricle with each heart beat relative to total ventricular volume and has been used as a global measure of systolic function (Klabunde, 2005). In contrast to DHF, systolic heart failure (SHF) is predominantly associated with reduced pump functioning and the development of eccentric left ventricular hypertrophy (Maeder & Kaye, 2009). The use of the terminology SHF and DHF has recently come into question with the finding that patients previously diagnosed with DHF have reduced systolic function compared to age-matched controls (Yip *et al.*, 2002) and have pathophysiological

aspects other than diastolic abnormalities (Borlaug & Paulus, 2011). To better reflect the two forms of heart failure, the terminology heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) is more appropriate and has been increasingly used in the literature. Epidemiological studies have suggested that the prototypical patient with HFpEF is elderly, female, and obese and has hypertension and atrial fibrillation (Philbin *et al.*, 2000; Masoudi *et al.*, 2003; Lenzen *et al.*, 2004). Patients with HFpEF constitute a sizable 50% of the heart failure population (Owan *et al.*, 2006; Ho *et al.*, 2012). Despite its importance, most clinical investigations exclude this group and focus on HFrEF resulting in large gaps in knowledge about the pathophysiology and management of HFpEF. An additional goal of this thesis is to include this subset of the population.

1.2 Cognitive Decline and Heart Failure

The term 'cardiogenic dementia' was first used in 1977 to describe the association between cognitive impairment and heart failure (Lancet Editorial, 1977). Since that time there has been a large amount of research in this area and although the term cardiogenic dementia is no longer common, the relationship between heart failure and abnormal brain changes is now well accepted. In fact, heart failure has emerged as an independent correlate of cognitive decline (Trojano *et al.*, 2003). After adjusting for confounding variables, the presence of cognitive impairments was 1.96 times greater in heart failure patients than controls (Cacciatore *et al.*, 1998). In a recent review of the literature from 2002 to 2007, cognitive deficits have been reported to be present in 25 to 50% of those with heart failure (Pressler, 2008); these values are likely higher when considering the amount of mild deficits that go undetected. Mild cognitive impairment (MCI) is a transitional period between normal age-related cognitive decline and a

dementia diagnosis that is common in heart failure. It is often characterized by subtle changes that are difficult to detect. While MCI is common, severe deficits also exist in this population making the degree of cognitive decline highly variable. Impairments in memory, attention and executive function have been commonly reported but it is not known whether a typical cognitive profile exists for this population (Jefferson *et al.*, 2007a; Trojano *et al.*, 2003; Pressler, 2008). The presence of cognitive impairments contributes to the deterioration of health-related quality of life in heart failure patients as it is an independent predictor of disability, morbidity and mortality and influences one's ability to perform instrumental activities of daily living (Alosco *et al.*, 2012; Zuccala *et al.*, 2001; Zuccala *et al.*, 2003). A five-fold increase in mortality risk was reported when cognitive impairments were present (Zuccala *et al.*, 2003). In addition to heart failure itself being age-dependent, cognitive impairments associated with heart failure become more prevalent with older age (Zuccala *et al.*, 1997; Almeida & Flicker, 2001). Therefore in the coming years, as the heart failure incidence rises with the growth of the elderly population, the amount of patients with cognitive impairments will also increase. It will become imperative to reduce the burden of cognitive dysfunction associated with heart failure to allow for gains in survival rates, improvements in quality of life and reductions in resource consumption. The key to improving prevention lies in a better understanding of the underlying mechanisms.

1.3 Cerebral Blood Flow in Heart Failure

The main mechanistic link for the relationship between cognitive impairments and heart failure is believed to be reduced brain perfusion to hypoxia sensitive structures in the brain (Roman, 2004). Experimental evidence from animal models supports the link between reduced brain blood flow and cognitive decline (Ohta *et al.*, 1997; De Jong *et al.*, 1999). Chronic

reductions in cerebral blood flow (CBF) were induced by ligation of either the common or internal carotid arteries. Over time, the animals developed impairments in learning and memory directly related to the degree of neuronal disorganization and also developed changes to the capillaries that supply the neurons in the hippocampal region (De Jong *et al.*, 1999; Ohta *et al.*, 1997). In humans, indirect evidence supplied by systemic perfusion studies and direct measurement of brain perfusion will be discussed in support of the hypoperfusion hypothesis.

1.3.1 Indirect Evidence

Cognitive decline in heart failure is believed to arise due to cardiac dysfunction altering systemic perfusion and consequently cerebral perfusion. Normally CBF is maintained by autoregulation, a process where despite changing cerebral perfusion pressure, blood flow to the brain is maintained via changes in vasomotor tone (Lassen, 1959). The integrity of cerebral autoregulation in heart failure has not been investigated but reports suggest that it is impaired with chronic systemic hypoperfusion (Tranmer *et al.*, 1992), a hallmark of heart failure. In addition, cerebrovascular reactivity, a measure of reserve dilatory capacity, has been reported to be compromised in heart failure (Georgiadis *et al.*, 2000). Therefore, the built in mechanisms responsible for maintaining blood flow to the brain in the face of impaired output from the heart may not be fully functional in heart failure. Furthermore, a low Q in heart failure may limit CBF (Saha *et al.*, 1993). Thus, indices of systemic perfusion are of interest when studying the relationship between heart failure and cognitive functioning. Several studies have attempted to draw associations between cognitive test scores and LVEF as an index of cardiac function and systemic perfusion. Zuccalà and colleagues investigated the relationship between LVEF and cognitive state assessed by the mini mental state examination (MMSE) in an elderly heart failure

sample. The authors reported that when entered into an age and sex adjusted regression model, LVEF was significantly associated with MMSE score (Zuccala *et al.*, 1997). Similarly, others have reported independent associations between cognitive functioning and LVEF (Hoth *et al.*, 2008; Festa *et al.*, 2011; Almeida & Tamai, 2001) supporting the role of reduced CBF secondary to diminished systemic perfusion as a main contributor to neuropsychological impairment in heart failure. However, conflicting reports have also been published where no relationship has been found between systemic hypoperfusion measured by LVEF and cognition (Jefferson *et al.*, 2007a; Wolfe *et al.*, 2006; Bornstein *et al.*, 1995).

The use of LVEF offers one explanation for these inconsistent findings. LVEF is a common clinical indicator of heart failure severity that is used to classify patients; however, it may not always provide accurate estimates (Jefferson *et al.*, 2007a). Therefore Q is proposed in this thesis as an alternative measure of cardiac function and systemic perfusion as it quantifies the amount of blood flow leaving the ventricle into systemic circulation, measured in liters per minute (L/min). When LVEF and Q were compared within a patient sample over the age of 55 with prevalent cardiovascular disease, patients with clinically normal LVEF had low Q values 43% of the time. Furthermore, the two measurements were in agreement less than half the time (see Appendix A) (Jefferson, 2010). This finding supports the fact that the two measurements, Q and LVEF, are incompatible measures representing distinct parameters of cardiac function and Q may better represent systemic perfusion as it is free of the confounding factors that influence LVEF. When investigated as an indicator of systemic perfusion, evidence suggests that Q is associated with cognitive test scores and neuroimaging, although studies in this area remain scarce. In an aging cohort with stable CVD, low Q (<4.0 L/min) was related to impairments in neuropsychological tests, mainly in executive function, compared to normal Q (>4.0 L/min)

(Jefferson *et al.*, 2007a). Additionally, CVD patients with a lower Q experience a faster rate of decline on an Attention-Executive-Psychomotor composite score when followed for 36 months (Okonkwo *et al.*, 2011). Neuroimaging abnormalities have also been inversely linked to Q values. White matter hyperintensities (WMH) are areas of high intensity within the cerebral white matter of the brain that are made visible by a magnetic resonance imaging scan and are indicative of ischemia or lesions in that area (Fernando *et al.*, 2006). They become increasingly prevalent with age and are associated with reduced mean flow velocity (MFV) and lower cognitive performance (de Groot *et al.*, 2001; de Leeuw *et al.*, 2001; Tzourio *et al.*, 2001). As the result of work by Jefferson and colleagues, systemic blood flow measured by Q has also been found to be inversely associated with WMH's independent of age and hypertension (Jefferson *et al.*, 2007b). When scaled to body surface area, Q has furthermore been correlated to systolic blood velocity through the middle cerebral artery (MCA) (Saha *et al.*, 1993). Therefore, as an indicator of systemic perfusion, Q has been found to be associated with cognitive test scores, neuroimaging abnormalities and cerebral hemodynamics through the MCA. In spite of this, future studies are needed to elucidate the relationship in a heart failure cohort, Q values as a reflection of systemic perfusion may better identify those at risk for cerebral hypoperfusion and cognitive decline than LVEF.

1.3.2 Direct Evidence

In addition to the aforementioned indirect evidence suggesting cerebral hypoperfusion as the mechanistic link between heart failure and cognitive decline, CBF has also been directly measured using a variety of techniques. In 2006, Choi and colleagues found that resting supine global CBF, measured by radionuclide angiography, was reduced by 19% in advanced heart

failure compared to healthy controls (Choi *et al.*, 2006). This finding has been duplicated in an elderly male sample (age 68 ± 7 years) where a 14% reduction was found through the utilization of ultrasound to quantify global supine CBF by summing bilateral internal and vertebral artery blood flow (Loncar *et al.*, 2011). In both of these studies, the degree of CBF decline was related to the New York Heart Association (NYHA) functional class (Appendix B). Reductions, some as high as 30%, have also been reported by other researchers (Vogels *et al.*, 2008; Gruhn *et al.*, 2001; Massaro *et al.*, 2006). Cerebral hypoperfusion observed in hypertensive patients is strongly associated with later cognitive decline (Kitagawa, 2010) but in heart failure, investigations where neurological testing is performed in addition to CBF are scarce. In one report, Alves and others report a direct correlation between cognitive scores and resting CBF values (Alves *et al.*, 2005). In contrast, when MFV measured at the MCA was compared to a mean cognitive z-score in mild to moderate heart failure patients no correlation was reported (Vogels *et al.*, 2008). It is possible that the use of MFV as a surrogate for CBF could partly explain the lack of relationship found in this study. Furthermore, reductions in CBF were mild so the specific sample in this study may have still been able to compensate through cerebral autoregulation mechanisms. Many observations provide strong arguments for the heart-brain connection and the cerebral hypoperfusion hypothesis for cognitive dysfunction. Findings from the Rotterdam study suggest that cerebral hypoperfusion precedes clinical onset dementia (Ruitenberg *et al.*, 2005). When heart function is improved with transplantation or cardiac resynchronization therapy, CBF can be restored and cognition improvements have been noted (Gruhn *et al.*, 2001; Dixit *et al.*, 2010; van Bommel *et al.*, 2010). These results suggest a role for heart dysfunction in cognitive decline which acts through cerebral hypoperfusion.

All of the studies that have directly measured CBF have had an inclusion criterion of LVEF<50%. The average LVEF for the patients in these studies was 26.7 ± 7.67 %, therefore being inclusive to HFrEF. The relationship between HFpEF and cognitive decline has not yet received much attention because of the belief that since LVEF is preserved, output of blood to the rest of the body, including the brain, is also preserved. However, as previously mentioned, normal LVEF might not be a reliable indicator of normal Q. The definition of heart failure is the inability of the heart to pump sufficient blood to the rest of the body, identifying low Q as the main pathophysiologic abnormality (Libby *et al.*, 2008). While depressed Q is a key element of the heart failure definition, it is rarely used in clinical practice. Although LVEF shows discrepancies between the two forms of heart failure, Q is the same if not lower in patients with HFpEF (Andrew, 2003). The previous discussion on Q as a predictor of cognitive decline, suggests that low Q is associated with irregular neuropsychological test scores and imaging. Therefore, even though LVEF is preserved, low Q values may also predispose this subset of the population to cognitive dysfunction. In CVD patients with normal LVEF, diastolic dysfunction was significantly correlated with cognitive impairment (Suwa & Ito, 2009). While resting CBF is well documented to be reduced in HFrEF it remains unknown whether the same is true for HFpEF and how this relates to cognitive state. Arterial stiffness, which is reported prevalent in this population subset, has been linked to lower CBF and may act as a contributor alongside the depressed Q (Robertson *et al.*, 2010). A better understanding of cognition and CBF in both HFrEF and HFpEF will become increasingly important in the coming years with the rising prevalence and associated complications that contribute to significant morbidity and mortality.

1.4 Atrial Fibrillation, Cognition and Hypoperfusion

Heart failure and atrial fibrillation have the tendency to co-exist as they share many risk factors but also because the existence of one may predispose you to the other (Wang *et al.*, 2003). The co-existence may render the brain more vulnerable to lower CBF and cognitive decline. In atrial fibrillation, the sinoatrial node does not trigger the atrial contractions resulting in uncoordinated, low voltage, high frequency depolarizations with no discernable P wave. With this condition, the rate of atrial contractions greatly exceeds that rate of ventricular contraction leading to improper ventricular filling and reduced Q (Daoud *et al.*, 1996). The incidence of atrial fibrillation rises sharply with age and was estimated in 1997 to affect 6% of the Canadian population aged 65 years and older (Sacco *et al.*, 1997). The Framingham heart study estimated the lifetime risk for atrial fibrillation to be 1 in 4 for men and women aged 40 years and older and 1 in 6 in the absence of heart failure or myocardial infarction (Lloyd-Jones *et al.*, 2004). The Rotterdam study identified cognitive dysfunction as being twice as common in atrial fibrillation patients compared to those without atrial fibrillation (Ott *et al.*, 1997). Stroke has been recognized as a major cause of cognitive impairment in atrial fibrillation (Mizrahi *et al.*, 2011; Zhou *et al.*, 2004). Atrial fibrillation increases the risk of ischemic stroke 5-fold (Wolf *et al.*, 1991). The increased risk is attributed mainly to the high occurrence of thromboembolic events that are the result of stagnant blood in the left atrium and left atrial appendage. In addition to ischemic strokes, thromboembolic events can also lead to silent strokes and transient ischemic attacks (TIAs); which both increase the risk of eventually having an ischemic stroke. Silent strokes, those present on CT scans but with no previous medical documentation, are prevalent in an estimated 15-26% of atrial fibrillation patients (Ezekowitz *et al.*, 1995). Cognitive impairment in atrial fibrillation has been primarily attributed to thromboembolic events leading to ischemic

stroke with little focus on cerebral hypoperfusion. There are three ways in which cerebral hypoperfusion may be contributing to cognitive impairments in atrial fibrillation; two through stroke-dependent mechanisms and one through a stroke-independent mechanism. First, cerebral hypoperfusion may lead to hemodynamic TIA and stroke (stroke not caused by emboli). Second, hypoperfusion and embolic mechanisms may be linked, rather than being two separate entities. Cerebral hypoperfusion increases the quantity of arterial thromboemboli and reduces washout and clearance of emboli that have entered the vascular bed of the under perfused regions (Caplan & Hennerici, 1998). Last, cerebral hypoperfusion can lead to hypoxic brain damage resulting in cognitive impairments. This offers an explanation for studies that have detected cognitive impairments in atrial fibrillation patients with no clinical evidence of stroke (stoke-independent cognitive impairments) (Ott *et al.*, 1997; Marzona *et al.*, 2012). Cerebral hypoperfusion may be further exaggerated by underlying CVD, such as heart failure. A flow diagram depicting the potential pathways involved in atrial fibrillation related cognitive impairment is included in figure 1.1

In spite of the potential importance of cerebral hypoperfusion, few studies have investigated CBF in atrial fibrillation. Petersen et al. found CBF improvement after cardioversion therapy suggesting impairment at baseline; however there was no comparison to a healthy control group before the therapy and the patients had atrial fibrillation for less than three months in duration (Petersen *et al.*, 1989). In contrast, Porebska and colleagues compared MFV in controls versus those with paroxysmal (temporary) atrial fibrillation and found no difference, likely because patients with this form of atrial fibrillation have more efficient heart function (Porebska *et al.*, 2007). In both of the aforementioned studies, patients did not have coexisting heart failure. Cerebral hypoperfusion might be even more pronounced in heart failure patients

with atrial fibrillation as heart failure alone is well-documented to be associated with a reduction in CBF. One study sought to identify factors associated with CBF in heart failure patients. Using a linear regression analysis, the researchers found atrial fibrillation to be a significant negative determinant of CBF (β= -0.445, p<0.01) (Choi *et al.*, 2006). Further research is needed to confirm these findings. Another area requiring further investigation is the variability in Q and CBF that is associated with the beat-to-beat variability inherent to atrial fibrillation. While this relationship has been previously suggested, evidence has yet to be documented in the literature. The brain requires a continuous blood supply to maintain function and is particularly sensitive to pulsatile flow. High flow can penetrate and damage the microvascular bed while periods of low flow contribute to microvascular ischemia (Mitchell *et al.*, 2011). Thus it is important to determine if the irregular HR in atrial fibrillation translates to variability in CBF which has the potential to cause damage and impair cognitive functions (added in Figure 1.1)
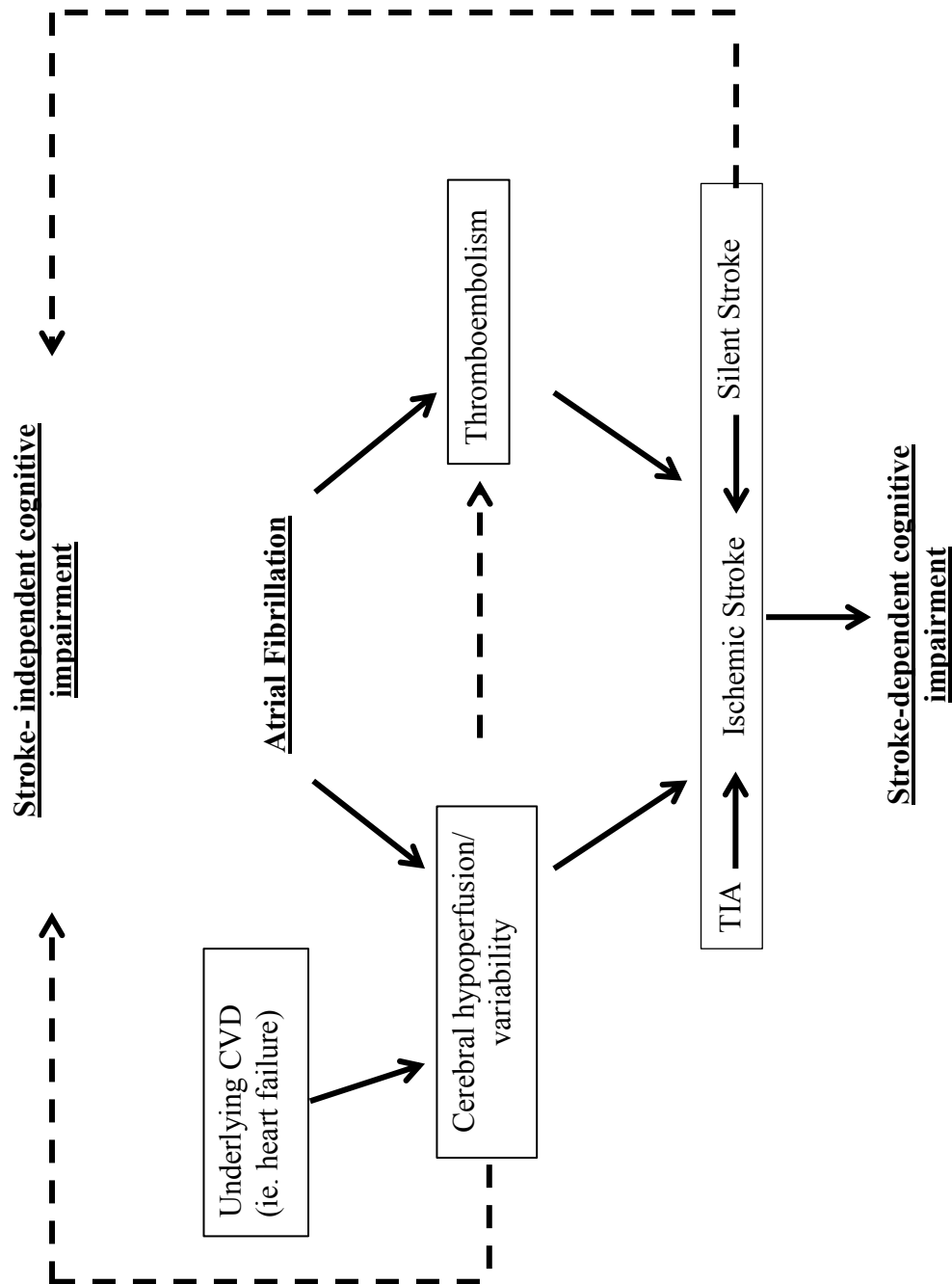
Figure 1.1 Flow chart of mechanisms leading to cognitive impairment in atrial fibrillation

Atrial fibrillation is associated with cognitive impairments. This association is either independent or dependent on a clinical documented stroke. Most cognitive impairments in atrial fibrillation are attributed to ischemic strokes caused by thromboembolism. However cerebral hypoperfusion may also be an important issue as cognitive impairments are documented in the absence of a stroke. Dashed lines indicate that less research has been performed versus solid lines representing a lot of attention has been paid to this area. TIA—transient ischemic attack; CVD—cardiovascular disease

1.5 Normal Physiologic Response to Upright Posture

When assuming an upright posture from lying flat, several adjustments are required. In a supine position, gravitational forces are evenly distributed throughout the body. However, standing up creates pressure gradients due to gravity and blood pools in the abdomen and lower extremities resulting in a decreased venous return to the heart (Silverthorn, 2007). Consequently, less blood is in the ventricle for the next contraction and arterial blood pressure (ABP) falls due to reduced Q. Necessary adjustments include increases in HR and total peripheral resistance to restore Q and ABP (Perlmuter & Greenberg, 1996). These are achieved in the short-term primarily by the baroreceptor reflex. Arterial baroreceptors, located in the aortic arch and carotid sinus, are stretch-sensitive mechanoreceptors (Silverthorn, 2007). A fall in ABP and filling pressures during an upright posture is detected by a decreased stretch of the receptors that then relay this information to the cardiovascular control centre in the medulla resulting in alterations to the activation levels of the sympathetic and parasympathetic nervous systems. Vagal withdrawal from the parasympathetic nervous system acts first increasing HR. Sympathetic nervous system activation further augments HR, increases stroke volume (SV) and leads to vasoconstriction (Silverthorn, 2007; Klabunde, 2005). Together, these alterations lead to increased Q and total peripheral resistance and ultimately to restored ABP. Hormonal responses normally have little to do with the initial response to standing upright but they may have a more important role during prolonged orthostatic stress. The renin-angiotensin-aldosterone system (RAAS) is activated by low ABP which it acts to restore through vasoconstriction and water retention (Silverthorn, 2007). If these neurovascular and hormonal adjustments are inadequate, ABP cannot be brought back up and remains depressed while upright; this is referred to as orthostatic hypotension (Perlmuter & Greenberg, 1996). Guidelines define orthostatic

hypotension as a decrease in systolic blood pressure of at least 20mmHg and/or diastolic blood pressure of at least 10mmHg within the first three minutes of assuming an upright posture (Freeman *et al.*, 2011).

In addition to the drop in ABP, orthostasis causes a reduction in CBF due to a documented fall in both the arterial partial pressure of carbon dioxide ($PaCO_2$) and cerebral perfusion pressure (Edgell *et al.*, 2012). The cerebral circulation is very sensitive to changes in CO_2, a potent vasodilator (Vavilala *et al.*, 2002). $PaCO_2$ decreases when upright resulting in cerebrovascular constriction and a subsequent reduction in CBF. Furthermore, cerebral perfusion pressure falls due to the drop in ABP at the level of the brain, contributing to the lessened CBF. However, CBF is quickly restored by cerebrovascular autoregulatory mechanisms. As mentioned earlier, this mechanism ensures stable CBF in the face of fluctuating ABP. This is achieved by changing the resistance of small cerebral arteries and arterioles accordingly, that is, the vessels constrict and resistance increases as ABP rises and dilate as ABP falls (Vavilala *et al.*, 2002). When ABP approaches the lower limit of 50mmHg and the upper limit of 150mmHg these vasomotor adjustments become exhausted and cerebrovascular resistance cannot increase or decrease any further to regulate CBF (see Appendix C)(Panerai, 1998). Importantly, the autoregulatory limits can be altered during pathological states; for example, the upper and lower limits are shifted to higher values during chronic hypertension (Iadecola & Davisson, 2008). If ABP is inadequately restored during an orthostatic stress and falls beyond the lower limit then CBF becomes pressure-dependent and the homeostatic protection of cerebral autoregulation is lost, ultimately resulting in reduced CBF that can lead to syncope (Silverthorn, 2007).

Cerebral autoregulation can be assessed by methods that cause simultaneous changes in ABP and CBF; however no gold standard is available. A commonly used technique is bilateral

thigh cuffs, which employs cuff inflation and subsequent deflation to induce significant and rapid changes in ABP (Aaslid *et al.*, 1989). This method has been criticized for being painful and not representative of the physiological stresses of everyday life. Posture changes throughout the day threaten CBF and therefore a sit-to-stand method has been used to evaluate autoregulation for its realistic implications of daily living (Sorond *et al.*, 2009; Lipsitz *et al.*, 2000). The assessment of cerebral autoregulation is important because it may expose cerebrovascular abnormalities that only become apparent when the system is challenged. Additionally, it provides valuable clinical information by identifying those at risk for cerebral ischemia or secondary brain damage due to hypoperfusion or hyperperfusion, respectively (Panerai, 1998). To prevent these complications, the identified patients require tight control of fluctuating ABP so to avoid changes in CBF.

1.6 Implications of Orthostatic Hypotension

The prevalence of orthostatic hypotension (OH) increases with advancing age (Rutan *et al.*, 1992; Rose *et al.*, 2000). However the prevalence reported in the literature varies greatly, from 5 to 30%, depending on the composition of the population being studied and the experimental conditions such as the time of day and the type of orthostatic test performed (Low, 2008). Age-related physiological changes responsible for the higher prevalence of OH include vascular stiffening, decreased baroreflex sensitivity, reduced responsiveness to sympathetic stimulation and reduced parasympathetic tone (Benvenuto & Krakoff, 2011). Additionally, there are a number of risk factors for OH that accompany older age including dehydration, the number and type of medications prescribed, hypertension and diabetes (Benvenuto & Krakoff, 2011). Several longitudinal studies have been performed in order to determine if OH is a secondary by-product phenomenon of other disease states or if it is a serious independent risk factor. These

investigations have uncovered that the presence of OH predicts future risk for CVD and overall mortality (Rose *et al.*, 2000; Masaki *et al.*, 1998; Verwoert *et al.*, 2008).

Interestingly, OH has also been found to be associated with cognitive dysfunction in an elderly cohort (age 76 ± 8 years) (Mehrabian *et al.*, 2010). Cerebral hypoperfusion resulting from OH represents a mechanistic link to cognitive impairment. It can acutely affect many cognitive domains due to reduced delivery of nutrients and oxygen, and when repeated or sustained can cause more permanent damage, such as WMH, that are implicated in the pathogenesis of cognitive decline (de Groot *et al.*, 2001; Tzourio *et al.*, 2001). The cerebral circulation is challenged during orthostasis and thus cognitive deficits may become more pronounced in an upright position. Patient populations that are susceptible to OH and thus recurrent falls in ABP are at a high risk for this postural cognitive loss. For example, patients diagnosed with neurogenic OH had significantly worse global cognitive function and performance on specific tasks that mainly involved executive function during head up tilt compared to supine (Poda *et al.*, 2012). However, this study was limited in that CBF was not assessed in the different postures or during the cognitive tests. Postural cognitive loss has also been studied in patients with chronic fatigue syndrome (CFS) which is associated distinctly with orthostatic intolerance and cognitive impairment (Stewart *et al.*, 2012). Patients along with age- and sex-matched controls were tested supine and at five incremental tilt angles (15, 30, 45, 60 and 75 degrees) while MFV was measured continuously with transcranial Doppler (TCD). An n-back test (n=0 to 4) was administered in each tilt angle and required the participants to monitor a series of stimuli and respond when the stimulus was the same as the one presented n-trials previously. The number of correct responses and the reaction time progressively worsened for each n-back level as tilt angle increased from supine in the CFS patients while performance

remained the same in the control subjects (Stewart *et al.*, 2012). Additionally, MFV decreased as tilt angle increased within each n-back level for CFS while MFV in controls was unaffected by orthostasis (Stewart *et al.*, 2012). Taken together these results suggest that orthostatic stress can reveal neurocognitive impairment and reduced MFV in CFS subjects compared to control subjects. These studies unveil some important considerations. In clinical populations with OH, cognitive posture testing exposes impairments that are not apparent in the supine position. Postural cognitive loss is a significant problem as the majority of daily activities are not performed while supine. Therefore cognitive loss while upright may interfere with the ability to independently perform activities of daily living, highlighting the importance of early identification and treatment.

1.7 Orthostasis in Heart Failure

As described above, the baroreceptor reflex is an important mechanism for restoring ABP during an orthostatic challenge. Abnormalities in this reflex have been reported in heart failure through utilization of a neck chamber. By changing the pressure in the neck chamber inverse pressure changes are produced in the carotid arteries, thus stimulating or unloading the baroreceptors. Sopher and colleagues utilized this method and caused step-wise changes in pressure while simultaneously measuring HR at each step. They found that the sensitivity of the baroreceptor reflex was impaired in heart failure patients compared to controls (Sopher *et al.*, 1990).

The fluid shifts and elevated peripheral resistance associated with moving to an upright posture result in decreased preload and increased afterload of the heart, respectively (Mehagnoul-Schipper *et al.*, 2003). These changes mean there is less blood available for

pumping and increased work demands placed on the heart; both of which are less than ideal conditions for a failing heart and increase the likelihood of orthostatic cerebral symptoms. In 1951, an initial report was published suggesting that individuals with heart failure respond irregularly to upright tilt (Howard & Leathart, 1951) , a finding that was investigated further in following studies. The increase in HR normally associated with upright posture is diminished in heart failure (Levine *et al.*, 1983). Vasodilation occurring in the forearm and calf during orthostasis has been documented in contrast to the expected vasoconstriction (Wroblewski, 1994; Goldsmith *et al.*, 1983a). Additionally, neurohumoral factors, such as norepinephrine, renin and arginine vasopressin are elevated at rest in heart failure but have attenuated increases in response to upright tilt (Goldsmith *et al.*, 1983b; Levine *et al.*, 1983). Due to this irregular orthostatic response, one would expect the prevalence of OH be higher in heart failure patients. In a group of elderly women, the diagnosis of OH was warranted in 83% of patients compared to 53% of controls (Potocka-Plazak & Plazak, 2001). Additionally, symptomatic OH was not present in any controls but was present in 36% of heart failure patients which was likely related to the larger drop in systolic blood pressure and reduced ability to compensate with HR in this group (Potocka-Plazak & Plazak, 2001). In sum, heart failure patients typically respond abnormally to orthostatic challenges and have a higher prevalence of OH that is more likely to be symptomatic than age-matched controls.

2.0 Study Rationale

Although a reduced resting CBF in heart failure is generally well-accepted, it is unknown how CBF is affected by daily challenges that threaten cerebral perfusion, such as upright posture. Since a large proportion of the day is spent vertical, investigating CBF in positions other than supine is highly relevant. If CBF is not maintained upright it can lead to hypoxic regions and ischemia resulting in a compromised cognitive status. Some heart failure patients experience orthostatic hypotension that can be attributed to a blunted HR or Q response and/or to a paradoxical vasodilation to peripheral vascular beds such as to the calf or forearm (Levine *et al.*, 1983; Goldsmith *et al.*, 1983a; Wroblewski, 1994). This abnormal response to orthostasis can lead to decreased CBF and postural cognitive deficits. Thus, it is of interest to determine the CBF and cognitive response to upright positions in heart failure patients.

Past studies have suggested the main pathophysiological link responsible for cognitive impairment in heart failure to be cerebral hypoperfusion (Loncar *et al.*, 2011; Zuccala *et al.*, 1997). This relationship has primarily been investigated in heart failure patients who have a reduced LVEF since preserved LVEF patients are typically excluded from clinical studies. Badano et al. investigated the clinical characteristics of patients with chronic heart failure enrolled in clinical trials to those seen in the real world as characterized by epidemiology studies. Their results confirm that patients characterized by epidemiology research have an ejection fraction approximately 12% higher than patients enrolled in clinical trials (Badano *et al.*, 2003). Furthermore, from the trials included in their analysis, 0% had an ejection fraction >40% compared to 34% real world patients existing in this subgroup (Appendix D). Since normal LVEF does not necessarily imply normal Q, this significant portion of the population may also have reduced CBF threatening cognitive status. Therefore we will include a spectrum of LVEF

to investigate whether LVEF is related to cognitive scores or CBF. Furthermore, Q will be investigated as a potentially better predictor of CBF. Since atrial fibrillation and heart failure frequently co-exist, we will investigate CBF in heart failure with coexisting atrial fibrillation, specifically to determine if the variability in HR that is innate to atrial fibrillation translates to Q and MFV variability.

In sum, reduced Q and CBF have been reported in the supine position although it remains to be known how these variables respond to upright positions common to daily living. A lower upright CBF might further insult the low supine CBF and contribute to cognitive decline. Including a patient population that is representative to those seen in clinical practice is beneficial in the translation of research. Specifically, little information exists on cerebral hemodynamics for those with HFpEF or atrial fibrillation with coexisting heart failure. The following section outlines the specific objectives and hypotheses of this thesis.

3.0 Study Objectives and Hypotheses

Primary Objectives

1) Assess the influence of orthostatic stress on CBF in heart failure patients compared to a healthy age and sex-matched control population.

2) Ascertain whether cognitive performance and cognitive-activated hemodynamics worsen in the upright position in heart failure

Secondary Objectives

3) Include a spectrum of LVEFs, from preserved to reduced, in the overall heart failure sample. Determine whether LVEF is correlated with CBF or cognitive scores. Further assess if Q is correlated with LVEF or CBF.

4) Assess Q and MFV variability in heart failure patients who also have atrial fibrillation

Hypotheses

1) Seated CBF will be reduced compared to supine more so in the heart failure patients.

2) Cognitive performance will be worse in the seated position compared to supine. The hemodynamic response to the cognitive task will be attenuated when seated compared to supine.

3) LVEF will not be correlated with cognitive score, CBF or Q suggesting HFpEF will have similar hemodynamic and cognitive characteristics as HFrEF. Q will better predict CBF than LVEF.

4) Q and MFV variability will be greater in patients with atrial fibrillation

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 #18543). All patients volunteered freely after reading and signing an information-consent form. They were aware of their rights to withdraw from the study at any time.

4.2 Recruitment

4.2.1 Heart Failure Patients

Twenty-two independently-living, stable heart failure patients participated in this study between April 2013 and October 2013. Inclusion and exclusion criteria for this study are listed in Table 4.1. Recruited occurred at two family practices (New Vision family health care team and Dr. Jagas' practice at the Frederick Street Medical Center), a cardiology clinic (Dr. Fowlis) in the Kitchener-Waterloo region and from the Heart Function Clinic at the Hamilton General Hospital. Patients were first approached about the study by a health care professional within the patient's circle of care from each clinic. They were provided a short description of what the study entailed and asked if they would be willing to receive a phone call with more information. Thirty-two patients agreed to be contacted by phone. The reasons for exclusion and arrival at the final sample of twenty-two are presented in Figure 4.1. Data collection took place at the University of Waterloo (n=6) or on-site at one of the specified clinics (n=16) based on preference of the recruiting doctor and convenience for the patient. LVEF and NYHA class were performed by different medical professionals and were obtained from patient's health record. The NYHA is an

index of severity and the breakdown of each class is included in Appendix B. A list of current medications was provided by the patient on the day of the testing.

4.2.2 Controls

Fifteen heart failure patients were age- and sex-matched with healthy control subjects from a previously collected sample. In general, this sample was high-functioning older adults ($\geq$ 65 years old) that were recruited from the community. A detailed description of these participants can be found in Dr. A. Robertson's thesis dissertation (Robertson, 2013). In order to match heart failure patients who were <65 years old, seven additional control subjects were collected from the community. Data collection techniques for all control subjects were the same as those described below.

4.3 Experimental Protocol Overview

When the heart failure patients first arrived for testing they read and signed the information-consent form. The protocol and equipment were described until they were comfortable and all questions and concerns were addressed. Additionally, they were encouraged to ask any further questions that arose as the test progressed. Following this initial familiarization and orientation, a global cognitive test (Montreal Cognitive Assessment-MoCA) was administered and the n-back test was explained and practiced. Two 8-meter timed walking tests were then completed. After obtaining height and weight measurements, the patients were assisted into a comfortable supine position on a bed, where they were instrumented with equipment for continuous beat-by-beat monitoring of HR, blood pressure and MFV and breath-by-breath monitoring of exhaled CO_2. Once the patient had rested supine for 10 minutes and all signals

were optimized and stable, carotid pulse pressure (PP_{car}) was measured using applanation tonometry and right common carotid artery (CCA) and bilateral internal carotid artery (ICA) ultrasound imaging was performed. Patients then completed the n-back test in the supine position before being assisted to a seated position. Following a stabilization period in the sitting position of 5-10 minutes, a Q rebreathing trial was done followed by ultrasound imaging on the right ICA. A second rebreathing trial was completed and the n-back test was repeated while seated. Information about the rebreathing technique and results can be found in appendix E. Before leaving, hip and waist circumferences were measured half way between the top of the iliac crest and the lower rib and at the widest part of the buttocks, respectively. A questionnaire was described and distributed to be completed at home and mailed back in the pre-posted envelope. The test duration was between 1.5 and 2 hours depending on the ease of signal acquisition. A more in-depth description of each data collection technique discussed in this overview is included below.

4.4 Data Collection

4.4.1 Cognitive Testing

Global cognition was assessed with the MoCA. The MoCA is a rapid 30-item cognitive screening tool that takes approximately 10 minutes to administer and was developed as a tool sensitive enough to screen older adults who present with MCI (Nasreddine *et al.*, 2005). It includes the assessment of eight different domains; attention and concentration, executive function, memory, language, visual/constructional skills, conceptual thinking, calculations and orientations (Harkness *et al.*, 2011). A MoCA score of <26 out of a maximal possible score of 30 warrants a diagnosis of MCI and further neurocognitive investigation. Although the MMSE is

frequently used to screen for dementia and track cognitive changes over time, it is not sensitive enough to detect subtle cognitive impairments. The MoCA has been increasingly used in the heart failure population and was applied in this study because it tests many of the cognitive domains most often affected by this disease and it is highly sensitive in detecting MCI compared to the MMSE in older patients with heart failure (Cameron *et al.*, 2013; Harkness *et al.*, 2011).

The n-back test is a frequently used instrument to measure working memory, attention and reaction time (Stewart *et al.*, 2012). This test has the ability to be delivered rapidly and in an auditory fashion in a supine and seated position and therefore was chosen to assess cognition in these two positions. Additionally, the area of the brain activated by the n-back is supplied by the MCA which was monitored non-invasively and continuously using TCD (Stewart *et al.*, 2012). The n-back test was administered through an audio computer program where the patients listened to a series of numbers and responded by clicking a trigger button in their right hand when the number was the same as the one presented n-trials previously. Two n-back levels were presented (n=1 and n=2) subsequent to a control 0-back condition where patients responded to a pre-determined number. Patients became familiarized and practiced each n-back level with different, condensed number sequences prior to the start of data collection. All of the numbers consisted of two syllables with an interstimulus duration of one second and a ten second pause between each level. Different number sequences (total numbers=29) were used in each level with the potential for six correct responses per level. The number sequences also differed when receiving the test supine versus seated, which was randomized between patients. The numbers of correct responses as well as the reaction times were recorded for later analysis.

4.4.2 8-Meter Walk Test

An 8-meter walk test was performed to assess gait speed as a single indicator of frailty (Fried *et al.*, 2001). Patients were instructed to walk at a normal pace as if they were walking down the street to the bank. If walking aids such as canes or walkers were required, they were used. Following a short count down, they started walking on the 'go' command. Timing was stopped at the 8-meter mark but patients continued walking past this point to prevent the time required to slow down and stop from influencing the timing outcome.

4.4.3 Continuous Measurements

Measures of ABP, HR, CO_2 and MFV were collected continuously at 1kHz using data acquisition hardware (Powerlab, AD Instruments, Colorado Springs, CO, USA) and recorded to a computer using associated software (Chart v.5.5.6, AD Instruments) for later analysis.

ABP was measured by sphygmomanometry in the supine and seated position then beat-by-beat throughout the test using finger-cuff plethysmography (Finometer Pro, Finapres Medical Systems, Amsterdam, the Netherlands). In this technique the finger is wrapped with an inflatable cuff that uses infrared plethysmography to monitor and adjust the cuff pressure to the arterial finger pressure during each heartbeat. Internal corrections then adjust the shape and amplitude of the finger pressure waveform to that of the brachial waveform. This correction is supported by accounting for the vertical height difference between the finger and heart that is measured by a fluid filled tube attached to the finger cuff which travels to a pressure transducer secured at heart level. A brachial cuff calibration before data collection further validates the finger pressure as a representation of blood pressure at heart level.

Electrocardiography was recorded beat-by-beat and the R-R intervals were later used for the determination of HR (ECG module, Finapres Medical Systems, Amsterdam, the Netherlands).

Breath-by-breath exhaled CO_2 was sampled through a nasal cannula and analyzed by infrared spectroscopy (Ohmeda 5200 CO_2 Monitor, Madison, WI).

MFV from the MCA (MFV_{MCA}) was collected beat-by-beat using TCD. A 2MHz transducer (Neurovision Transcranial Doppler System Model 500M, Multigon Industries Inc., Yonkers, NY, USA) was placed over the right temporal window with a slight forward orientation to track the sphenoidal segment (M1) of the MCA, which runs horizontally from nose to ear. The temporal window is the thinnest portion of the temporal bone that allows for the vessels of the circle of Willis to be exposed to ultrasound. Insonation of the MCA was confirmed with the velocity profile, strength of the signal, auditory pitch, signal depth and probe angle. The outer envelope of the power spectrum from the MCA was recorded for later analysis. An adjustable headpiece was used to hold the transducer in place (Marc 600, Spencer Technologies, Seattle, WA USA) to ensure stable probe positioning across the different postures.

4.4.4 Applanation Tonometry

Applanation tonometry (SPT-301, Millar Instruments, Houston TX USA) was used to measure the pulse pressure in the CCA (PP_{car}). Once the blood pressure reading from the Finometer had stabilized, the tonometer was held to the left CCA for 20-30 consecutive cardiac cycles. The tonometer was calibrated using a two-point calibration with the mean and diastolic brachial pressures as there is <3mmHg difference in these measures between the two sites (O'Rourke *et al.*, 2001).

4.4.5 Ultrasound

While TCD measures blood velocity, it is commonly used as an index of flow under the assumption that the diameter of the MCA remains constant. Studies have been conducted to verify an unchanging MCA diameter (Serrador *et al.*, 2000) however others have reported changing diameter under extreme conditions (Valdueza *et al.*, 1999). Furthermore, in this study population, variation in diameters due to sex or genetic differences, age and/or atherosclerosis between subjects will almost certainly influence individual CBF values therefore limiting the between subject comparison. With the inability to determine MCA diameter, TCD will be used to indicate MFV_{MCA} and not CBF. While it is not appropriate for TCD to be used as an absolute indicator of CBF, it can help determine changes over time in MFV_{MCA}, which in the absence of changes in conditions can reflect changes in CBF within a person. In this study, CBF was quantified by measuring bilateral ICA using ultrasound while supine. To investigate the change in CBF when upright, the right ICA was measured while seated. An 8-12 MHz linear array transducer (L14-6s with M5 system, Mindray, Shenzhen, China) was used to image the ICA diameter 1-2cm distal to the carotid bifurcation while the Doppler function of the same probe permitted measurement of MFV of the ICA (MFV_{ICA}). To obtain a measure of intima media thickness (IMT), the walls of the right CCA were imaged supine.

4.4.6 Cardiac Output

There were two ways in which Q was obtained for this thesis: estimated from the Finometer device (Q_Fin) and measured directly with a foreign gas rebreathing method (Q_Inn) (Appendix E). The Q_Fin estimate makes use of an internal algorithm. The algorithm uses the finger arterial pressure waveform as well as the age and sex of the patient to estimate the aortic

flow waveform. The shape of the aortic waveform is then used to calculate SV and subsequently Q. The benefit of this method is that is gives an estimate of Q, non-invasively, with each heart beat. However, variables are not directly measured and some have questioned its accuracy in providing absolute values (Azabji *et al.*, 2004).

4.4.7 Take-home Questionnaire

Patients were given a questionnaire to fill out at home and mail back to the University in a pre-posted envelope (see Appendix F). They were asked questions regarding their cultural background, marital status, education and previous work experiences. Sleep and physical activity patterns along with smoking and alcohol use were also questioned. Lastly, the Geriatric Depression Scale short form (GDS-SF) was included at the end of the questionnaire which is a self-reported 15 item questionnaire to be used specifically on older adults where patients answer "yes" or "no" to each question. The GDS-SF has been validated against the 30-question GDS for the evaluation of depressive symptoms (Sheikh JI & Yesavage JA, 1986).

4.5 Data Analysis

4.5.1 Anthropometric Calculations

Waist to hip ratio (WHR) was calculated as the ratio of the circumference of the waist to that of the hips. WHR has been used as a measure of health as those with 'apple-shaped' bodies who carry more weight around the waist are at increased risk for health risks whereas those with 'pear-shaped' bodies with more weight around the hips are at a lower risk.

$$WHR = waist/hip$$
Equation 4.1 Waist-Hip Ratio

Body mass index (BMI) is a measure of body size based on height and weight.

$$BMI\ (kg/m^2) = mass\ (kg)\ /\ (height(m))^2$$
Equation 4.2 Body Mass Index

Body surface area (BSA) is a calculated surface area of the human body. The Dubois and Dubois formula for the calculation of BSA was used (Du Bois & Du Bois, 1989). Due to the variations in body size between participants and between groups (heart failure and control), BSA was used to correct for volume measures, SV and Q (see below).

$$BSA\ (m^2) = 0.007184 * w(kg)^{0.425} * ht(cm)^{0.725}$$
Equation 4.3 Body Surface Area

4.5.2 Cardiovascular Variable Calculations

The continuous blood pressure tracing from the Finometer was compared to traditional manual sphygmomanometer measurements. When the Finometer brachial artery pressure differed from the manual sphygmomanometer method by >5mmHg, the Finometer values were corrected for by using the manual blood pressure values.

Beat-by-beat SV and total peripheral resistance (TPR) were calculated with the following formulas:

$$SV\ (mL/beat) = Q\ (L/min)\ /\ HR\ (bpm)*1000$$
Equation 4.4 Stroke Volume

$$TPR\ (mmHg/L/min) = MAP\ (mmHg)\ /\ Q\ (L/min)$$
Equation 4.5 Total Peripheral Resistance

As mentioned previously, Q and SV were corrected for body size by dividing by the calculated BSA for the individual. The resulting variables are cardiac index (Qi) and stroke volume index (SVi) and are reported for the remainder of this thesis.

4.5.3 Carbon Dioxide

Breath-by-breath values for end-tidal CO_2 concentration were obtained and time-matched to the beat-by-beat data for analysis. The maximum % CO_2 concentration from each breath was identified on the capnographic output and then used in the conversion to end-tidal P_{CO2} (ETCO$_2$) with units of mmHg. ETCO$_2$ values were obtained by using ambient temperature and barometric pressure to convert the recorded percent CO_2 values to mmHg.

4.5.4 Transcranial Doppler

TCD monitoring of the MFV$_{MCA}$ was successful in 18 of the 22 heart failure patients and 22 of the 22 control subjects. Traditionally, TCD is limited in about 25% of older adults because of anatomical limitations, notably, with age, the structure of the temporal bone changes and the ultrasound signal cannot return to the transducer (Itoh *et al.*, 1993). TCD is beneficial in that its temporal resolution (10-100Hz) allows for examination of blood flow and resistance index calculations within a cardiac cycle. Cerebrovascular resistance at the level of the MCA was examined using three indices. Cerebrovascular resistance index (CVRi) is calculated by the rearrangement of Ohm's law (equation 4.6). Describing flow using this relationship is associated with a few assumptions: flow is assumed constant and laminar (Rowell, 1993), intracranial pressure (ICP) is constant and close to zero (Aaslid *et al.*, 1989) and the drop in ABP with posture change is dominant to ICP fluctuations (Hughson *et al.*, 2001). By rearranging equation 4.6 and applying appropriate local factors we can calculate CVRi (equation 4.7). Of note, ABP must be corrected to brain level to account for the orthostatic pressure gradient between the brain and the heart when in an upright posture (distance (cm) - 0.78mmHg/cm).   Within a single cardiac cycle the systolic (SFV) and diastolic (DFV) flow velocities were isolated lending to the

calculation of a pulsatility index (PI) and resistance index (RI) (equation 4.8 and 4.9, respectively).

$$CBF= (ABP-ICP)/resistance$$
Equation 4.6 Ohm's Law for Cerebrovascular Circulation

$$CVRi= ABP_{brain}/MFV$$
Equation 4.7 Cerebrovascular Resistance Index

$$PI= (systolic\ velocity-diastolic\ velocity)/\ MFV$$
Equation 4.8 Pulsatility Index

$$RI= (systolic\ velocity-diastolic\ velocity)/\ systolic\ velocity$$
Equation 4.9 Resistance Index

4.5.5 Supine and Seated Averages of Continuous Variables

Once hemodynamic variables were stabilized and optimized supine and seated, a minute average was calculated for all of the continuous variables.

4.5.6 Brachial and Carotid Pulse Pressure

Brachial pulse pressure (PP_{brach}) provides an estimate of peripheral artery stiffness and was calculated by subtracting diastolic blood pressure from systolic blood pressure. The arterial pulse in more distal muscular arteries, such as the brachial, is influenced less by relative increases in stiffness in comparison to more central elastic arteries (O'Rourke & Hashimoto, 2008). Thus, the PP_{car} in a more central elastic artery was examined using applanation tonometry as previously discussed. Once calibrated, PP_{car} was calculated in the same way as PP_{brach}.

4.5.7 Ultrasound Analysis

ICA diameter was measured during the diastolic phase by electronic calipers in triplicate and MFV was time-averaged using the Doppler function of the same probe. A peak SFV above

125cm/s is recognized as a good indicator of significant (>50%) narrowing of the ICA (Polak, 2004); all peak SFV were <125 cm/s in this patient sample. CBF through each vessel (RICA and LICA) was computed from the diastolic diameter and time-averaged MFV (Equation 4.9). ICA flow was measured at least 1 cm distal to the carotid bifurcation to minimize the influence of turbulent flow in the carotid bulb. Global anterior CBF (aCBF) was estimated as the sum of bilateral ICA flow in the supine position.

$$CBF = MFV \cdot \pi \cdot diameter^2 / 4$$

Equation 4.10 Cerebral Blood Flow

IMT was computed on frozen longitudinal right CCA images during diastole. Eight distinct sets of electronic calipers were placed at the intima and media of the far walls. The calipers were equally distributed over a vessel segment of approximately 1cm in length and mean values were calculated (IMT_{mean}).

4.5.8 Cognitive Tests

MoCA

Formal educational achievements of ≤ 12 years were corrected for by providing an extra point to the overall MoCA score. The six individual cognitive domains present in the MoCA were isolated and a score was determined for each. The domains are: short-term memory, visuospatial function, executive function, attention, concentration and working memory, language and orientation.

N-back Outcomes

The number of omissions and number of commissions were calculated for each n-back level. Omissions refer to the number of times the patient didn't correctly respond and commissions are the number incorrect responses. Reaction times for incorrect responses were not included in the analysis. Accuracy was calculated based on a previously reported algorithm and is shown in equation 4.10 (Miller *et al.*, 2009).

Accuracy (%) = [1-((number of commissions +number of omissions)/total possible correct)]
*100

Equation 4.11 Response Accuracy

N-back Hemodynamics

In order to investigate how the cognitive task influenced hemodynamics in supine and seated positions, a baseline 1-min average was taken immediately before the start of the n-back test for all of the continuous collected and calculated variables. The same variables were then averaged for each n-back level and the change relative to the baseline value was calculated for each level supine and seated within the heart failure sample.

4.5.9 Self-reported Variables

Two heart failure patients did not return the questionnaire in the mail and physical activity questionnaire data were missing for one control subject. A score of >5 on the GDS was suggestive of depression. Scoring for the GDS and self-reported physical activity are included in appendix G and appendix H, respectively.

4.5.10 Atrial Fibrillation

There were four heart failure patients who were identified as having atrial fibrillation by their medical charts and this was confirmed by the electrocardiogram. These four patients were then age and sex matched to heart failure patients without any evidence of atrial fibrillation. The standard deviation from each patient's one minute supine average was calculated and then averaged for each group.

4.6 Statistical Analysis

The comparisons between heart failure and control characteristics were conducted using the non-parametric Mann-Whitney Rank Sum tests for continuous variables and z-tests for categorical variables. To investigate the various cognitive domain sub-scores between heart failure patients with normal and abnormal MoCA scores, Mann-Whitney Rank Sum tests were also used. The same statistical test investigated supine, seated and delta differences between control and heart failure patients. The outcome measures for the n-back were evaluated with Friedman repeated measures ANOVA on Ranks and a Tukey post-hoc test was used to isolate where the differences occurred. Supine and seated differences for n-back hemodynamic delta's from baseline to cognitive tasks were assessed with Signed Rank tests in each level (0, 1 and 2 back). Spearman correlations (r_s) were used to assess relationships between variables. Due to the fact that statistical significance depends heavily on sample size, effect sizes were calculated to determine the size of effect in the atrial fibrillation group versus the heart failure group with no atrial fibrillation. Glass's Δ effect size calculations were performed on the average standard deviations for Qi_Fin and MFV_{MCA} (Ellis, 2009). Sample size calculations were also performed on these variables. Categorical variables are represented as frequency (%) and continuous

variables are represented as median (interquartile range). Statistical tests were considered statistically significant at $p \leq 0.05$. Due to the small sample statistical trends were also reported at $p \leq 0.10$. Data were analyzed using SigmaStat 11.0 (Systat Software Inc., Chicago, IL).

The decision to use nonparametric tests was made due to the fact that the assumptions of normality and equal variance for parametric tests were not being met for most variables. The sample size in this study is small and we believe a more conservative approach of non-parametric statistics in these early stages is warranted.

4.7 Methodological Considerations

TCD was monitored unilaterally, on the right side only. Assumptions were made about bilateral symmetry. Similar assumptions were made about the IMT, and the change in ICA flow with posture. In a young, healthy population TCD on the left and right sides were found to be highly correlated; however, these results cannot be assumed to translate to the population in this study (Schmidt *et al.*, 2003). To address this assumption bilateral ICA CBF was compared supine (see section 5.2.1) and no differences were found. Only the right ICA was measured seated and because supine values were the same it is presumed the change to this upright position is also the same.

It should also be considered that the positions were not randomized; participants always began in the supine position and moved to the seated position second. With this in mind, results from the n-back test should be interpreted cautiously. Despite practicing the n-back before the test began, it is still possible that learning influenced cognitive outcomes in the seated position. Common symptoms reported by the heart failure patients in this study were fatigue, weakness and pain. While extreme attention was taken during testing to ensure patient comfort and

awareness of time it should still be considered that seated blood pressure may have been influenced by discomfort and/or fatigue.

Also, posterior CBF through the vertebral arteries (VA) was not collected for this study. Vertebral arteries contribute about 25% to global CBF at rest. However, Loncar and colleagues reported no differences in VA flow between healthy subjects and heart failure patients (Loncar *et al.*, 2011). Additionally, VA flow is well maintained in response to an orthostatic stress in young healthy subjects (Sato *et al.*, 2012).

The accuracy of the Finometer has been reported by some (Raamat *et al.*, 2006), but others have questioned its ability to provide reliable values in special populations or when a stress is applied (Stok *et al.*, 2006; Azabji *et al.*, 2004). A high level of vasoconstriction, such as when sympathetic activity is elevated, decreases the accuracy of the measurement (Raamat *et al.*, 2000). Further, stiffer arteries are accompanied by a smaller change in arterial cross-sectional area. This change in the pressure-diameter relationship can result in less accurate readings (Langewouters *et al.*, 1986). Elevated sympathetic nervous system activity and arterial stiffness are both commonly associated with heart failure. This raises questions about the reliability of the Finometer results in the current study. Using the Finometer for non-invasive monitoring of cardiovascular variables in heart failure sample requires further examination.

Table 4.1 Heart failure patient inclusion/ exclusion criteria

Inclusion criteria	Exclusion criteria
• No recent major changes to medical regime • No history of myocardial infarction within the past 1 month	• Transplant recipients • NYHA functional class IV • Hospital admission that required an overnight stay within the past 1 month • Stroke in the past 10 years • Known significant ICA stenosis >50% • Uncontrolled hypertension ($\geq$ 160/90) • Documented diagnosis of dementia • Uncontrolled sleep apnea

NYHA—New York heart association

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                    ┌─────────────────────┐
                    │     32 patients     │
                    │  contacted by phone │
                    └─────────────────────┘
                                │
┌─────────────────────┐         │
│ 2 patients declined to│       │
│   participate (6%)   ├────────┤
└─────────────────────┘         │
                                │   ┌─────────────────────┐
                                │   │   5 patients were   │
                                ├───┤  unable to be reached│
                                │   │   by phone (16%)    │
                                │   └─────────────────────┘
┌─────────────────────┐         │
│ 3 patients cancelled │        │
│    prior to their    ├────────┤
│ scheduled test (9%)  │        │
└─────────────────────┘         │
                                │
                    ┌─────────────────────┐
                    │ 22 patients included │
                    │ in final sample (69%)│
                    └─────────────────────┘
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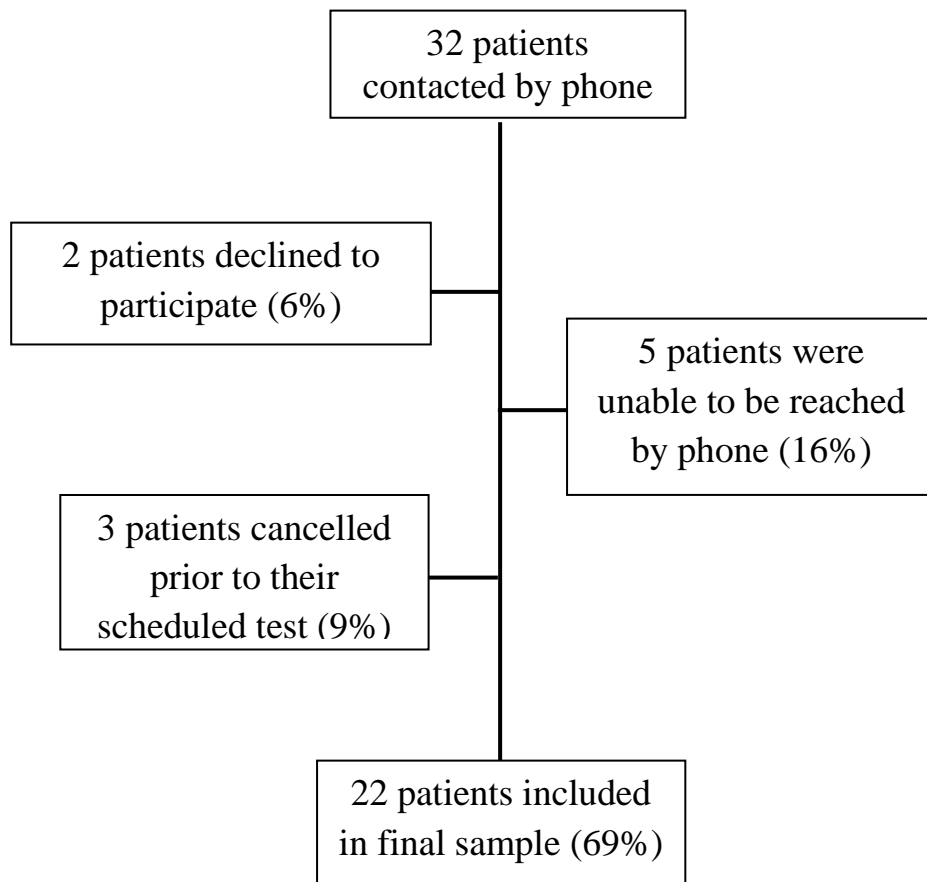
Figure 4.1 Heart failure patient recruitment

5.0 Results

5.1 Characteristics

The characteristics of the 22 heart failure patients and 22 age- and sex-matched healthy controls are presented in Table 5.1 and medical characteristics in Table 5.2; all patients and controls were community-dwelling. There was a trend for heart failure patients to have a larger BMI (p=0.062) than controls, but no other differences were detected statistically for height, weight or WHR. Heart failure patients had higher scores on the GDS (p<0.001). Three heart failure patients and one control subject scored >5 on the GDS. Heart failure patients also had a slower gait speed (p<0.001), had lower scores on the MoCA (p<0.001), had a lower education (p<0.001), and a higher history of smoking (p<0.001). With regards to the medical characteristics, a higher proportion of heart failure group had a pacemaker or implanted cardiac defibrillator (ICD) (p<0.001) and diabetes (p=0.001) than the control group. Heart failure patients were more likely to be on the following medications: β-blockers (p<0.001), ACE-inhibitors (p<0.001), Diuretics (p<0.001), Statins (p=0.015) and Plavix (p=0.013). There was a trend for Warfarin (p=0.055) to be higher in the heart failure group. Three heart failure patients were on anti-depressants (one person was on two).

The NYHA class and LVEF of each heart failure patient are listed in Table 5.3. The average LVEF for the study sample was 33 ± 11%. Four patients had an LVEF of >45%. The NYHA classification breakdown was: 18% NYHA I-II, 55% NYHA II, 9% NYHA II-III and 18% NYHA III.

Physical activity levels as determined from the self-reported questionnaire are presented in Table 5.4. There was a trend for a greater proportion of the heart failure sample to be

sedentary (55%) compared to their control counterparts (24%) (p=0.087). The proportion of control participants who were highly active (43%) was significantly different from the heart failure patients (5%) (p=0.014).

Mild or moderate cognitive impairment (MoCA<26) was observed in 64% of heart failure patients, with no score <19. Comparisons in sub-scores for various cognitive domains between patients with normal and abnormal MoCA scores are presented in Table 5.5. There was no age difference between patients with normal and versus abnormal MoCA scores. Cognitive domains showing significant differences in sub-scores are short term memory (p=0.001), visuospatial function (p=0.002), executive function (p=0.025) and language (p=0.011).

5.2 Posture Influence on Hemodynamics

5.2.1 Supine

The supine cardiovascular and cerebrovascular variables for heart failure and control groups are presented in Figures 5.1 and 5.2, with statistical comparisons in Table 5.6. While HR, mean arterial pressure (MAP) and TPR were not different between groups, Qi_Fin (p<0.001) and SVi (p<0.001) were significantly lower in the heart failure patients. No differences were detected in MFV_{MCA}, SFV_{MCA} or CVRi, although DFV_{MCA} was lower (p=0.026) and RI (p=0.001) and PI (p=0.001) were higher in the heart failure patients. The CBF through the LICA and RICA were compared within heart failure (243 mL/min versus 269 mL/min) and within controls (293 mL/min versus 296 mL/min) and no differences were detected in either group (p=0.451 and p=0.872, respectively). Total blood flow through the right plus left ICA (aCBF) was lower (p=0.013) in heart failure (479 mL/min) compared to controls (627 mL/min). No differences between groups were detected in $ETCO_2$. A trend was detected for PP_{car} to be higher in heart

failure versus controls (p=0.065) and no differences were found for PP_{brach}. The IMT_{mean} was higher in heart failure (p=0.009).

5.2.2 Seated

The seated cardiovascular and cerebrovascular variables for heart failure and control groups are presented in Figures 5.1 and 5.2, with statistical comparisons in Table 5.7. Similar to the supine position, Qi_Fin (p<0.001) and SVi (p<0.001) were significantly lower in the heart failure group. There were no differences in MFV_{MCA} or SFV_{MCA} but DFV_{MCA} was significantly lower in heart failure (p=0.003). Additionally in this group, RI (p<0.001) and PI (p<0.001) were higher compared to the control group. In the seated position, CBF through the RICA was lower in heart failure patients compared to the control group (p=0.003). No differences in any other variables were detected.

5.2.3 Change from Supine to Seated (Deltas)

The cardiovascular responses to the change in posture for heart failure patients and controls are depicted in Figure 5.3. The heart failure group did not increase their HR and it actually decreased slightly (-0.4 bpm) from supine to seated in comparison to the control group who increased by 4 bpm (p=0.001). The decrease in SVi and Qi_Fin and increase in TPR from supine to seated was not significantly different between the groups. The change in MAP was not different.

Figure 5.4 illustrates the cerebrovascular responses to the change in posture for the heart failure and the control group. The MFV_{MCA}, SFV_{MCA} (not shown) and CVRi decreased similarly from supine to seated for the controls and heart failure patients. DFV_{MCA} decreased more in the

heart failure group (controls= -2.1cm/s; heart failure= -3.2cm/s), although this difference did not reach significance (p=0.090). The increase in RI was not different; although PI increased significantly more in the heart failure group (p=0.018). Heart failure patients had a significantly greater decrease in CBF_{RICA} (-29 mL/min) from supine to seated (p=0.001) compared to controls (-7 mL/min). The $ETCO_2$ decreased supine to seated but was not different between heart failure and control.

Appendix I shows the mean and standard deviation of the change in Qi_Fin and CBF_{RICA} from supine to seated for healthy controls and heart failure patients. Due to the small sample in this study along with normality and equal variance assumptions being violated, non-parametric tests were applied and median (interquartile range) values are reported. Inherent differences between median and mean values account for a divergence in the Qi change from supine to seated. The mean Qi_Fin value (Appendix I) and individual responses (Figure 5.1) suggest that the Qi_Fin decrease from supine to seated may be more pronounced in heart failure.

5.3 Postural N-back Outcomes and Hemodynamics in Heart Failure

5.3.1 Cognitive Outcome Measures

The 0-back and 1-back were completed by 21 heart failure patients supine and seated whereas only 10 patients completed the 2-back in each posture. Healthy control subjects did not complete this test. The average age of patients who completed the first two levels was 68.7 ± 9.2 years and 64.6 ± 8.8 years for those who completed all three levels. There were no differences in omissions, commissions, accuracy or reaction time when the first two levels were considered together (Table 5.8). Similar results were found when considering all three levels together (Table

5.9) except that accuracy decreased with the 2-back (p<0.001) in each posture with no differences between posture.

5.3.2 Change in Hemodynamics from Baseline to Cognitive Load

Figure 5.5 illustrates the change in MFV_{MCA} and MAP from baseline to the cognitive task for heart failure patients within the supine and seated positions for each cognitive load (0-back, 1-back and 2-back). The increase in MFV was significantly lower when seated for all levels (0-back p<0.001; 1-back p<0.001; 2-back p=0.014). There was also a trend for MAP to increase less in the seated position for the 1-back (p=0.056) and 2-back (p=0.064). The HR increase to the cognitive load tended to be lower seated in the 0-back (p=0.082), was significantly lower in the 1-back (p=0.004) and was not different in the 2-back (p=0.193). It should be noted that the changes in HR were small, even when reaching statistical significance. The changes in the remaining variables between postures were not different within each cognitive load. Since these variables are not shown graphically, the p-values are listed in Table 5.10.

5.4 Correlations

Figure 5.6 illustrates the relationship between age and aCBF in the heart failure sample. A moderate negative correlation was statistically detected (p=0.017), in that, greater age was associated with a lower aCBF (r_s=-0.58). However, there was no correlation between age and global cognition assessed by the MoCA (Figure 5.7; r_s=-0.18, p=0.423).

Four patients with HFpEF were included in this study; due to the small sample LVEF will be presented as a continuum rather than separating the subtypes of heart failure. The LVEF relationship to Qi_Fin, MoCA and aCBF are shown in Figure 5.8, 5.9 and 5.10, respectively.

Importantly, higher LVEF that typically define HFpEF patients are not commonly included in these types of associations. No significant correlation was found between LVEF and supine Qi_Fin (r_s=0.04, p=0.848). A low-moderate negative relationship was found between LVEF and MoCA score (r_s= -0.30) but was not statistically significant (p=0.240) and no correlation was found between LVEF and supine aCBF (r_s= 0.06, p= 0.805). A significant positive correlation was found between supine Qi_Fin and aCBF (rs=0.50, p=0.047) and is shown in Figure 5.11.

5.5 Atrial Fibrillation

Characteristics of matched heart failure patients to those with heart failure and atrial fibrillation are shown in Table 5.11 and medical characteristics in Figure 5.12. Of note, the patients with heart failure and atrial fibrillation appear to have scored lower on the MoCA. Additionally, three of the four patients had HFpEF according to a LVEF cut-off of ≥45% that has been used in previous clinical trials (Carson *et al.*, 2005). No patients with heart failure or heart failure and atrial fibrillation had a documented history of stroke. A beat-by-beat sample output from one individual heart failure patient (A) and heart failure patient with atrial fibrillation (B) is included in Figure 5.12. The atrial fibrillation in patient B is evident in the ECG tracing and the irregular HR results in subsequent variation in the ABP, MFV_{MCA} and Qi channels. Hemodynamic averages and variability (average standard deviations) are presented in table 5.13. Effect size calculations on the variation of Qi and MFV_{MCA} were performed and the results were 1.93 and 1.13, respectively. These effect sizes are considered large by Cohen's classification system (Cohen, 1962) suggesting statistical significance can be detected with a larger sample. Sample size calculations suggest statistical significance can already be detected with the sample of four for Qi variability and ten patients in each group would be required to detect significance

in the variation of MFV_{MCA}. Figure 5.13 shows the ICA MFV tracing from one representative

heart failure patient (A) and one heart failure patient with atrial fibrillation (note: same patients

illustrated in figure 5.12). While the MFV through the right ICA is lower in the patient with

atrial fibrillation, the diameter of the vessel is larger resulting in these particular patients having a

comparable CBF through the right ICA (325 mL/min vs. 322 mL/min). An additional example

comparing ICA flows is presented in Appendix J. The average MFV_{MCA} that is listed in Table

5.13 is lower in the atrial fibrillation group (49 cm/s versus 56 cm/s) but, as previously

discussed, we are unable to determine the diameter of this vessel with this technique. The

CBF_{RICA} for healthy controls was 296mL/min, compared to the four-matched heart failure and

heart failure with atrial fibrillation patients, 262mL/min and 246mL/min respectively

Table 5.1 Patient characteristics

	Control n=22	Heart Failure n=22
Age (years)	68 (64-77)	68 (63-78)
Sex males *n*(%)	18 (82)	18 (82)
Height (cm)	172 (168-177)	171 (165-182)
Weight (kg)	75 (73-84)	86 (73-94)
BMI (kg/m^2)	25 (23-28)	28 (25-32)#
Waist/hip ratio	0.93 (0.84-0.96)	0.97 (0.87-1.0)
GDS score	0 (0-1)	2.0 (1.5-3.5)*
Gait speed (m/s)	1.28 (1.20-1.50)	0.97 (0.91-1.13)*
MoCA score	28.5 (27.0-29.0)	24.5 (22.0-27.0)*
Education (years)	17 (15-18)	12 (10-14)*
History of smoking *n*(%)	4 (18)	17 (77)*

All values are median (interquartile range); *p<0.001; #p<0.10. BMI—body mass index; GDS—geriatric depression scale; MoCA—Montreal cognitive assessment. n=22 except for GDS-heart failure n=20; history of smoking- heart failure n= 20

Table 5.2 Medical characteristics

	Control	Heart Failure
Pacemaker/ICD	0 (0)	12 (54)*
Diabetes	0 (0)	10 (45)*
β-blocker	2 (9)	22 (100)*
ACE-inhibitor	0 (0)	13 (59)*
Diuretic	4 (18)	20 (91)*
ANGII receptor antagonist	3 (14)	7 (32)
Ca^{+2} channel blocker	0 (0)	3 (14)
Nitroglycerin spray	0 (0)	4 (18)
Statin	7 (32)	16 (73)*
Alpha-1 antagonist	3 (14)	4 (18)
Aspirin	4 (18)	7 (32)
Warfarin	1 (5)	7 (32)#
Plavix	0 (0)	7 (32)*
Antidepressant	0 (0)	4 (18)

All values are n (%); *p<0.05; #p<0.10

Table 5.3 Left ventricular ejection fraction and NYHA class of each heart failure patient

Patient	LVEF (%)	NYHA class
1	25-30	II
2	<40	II
3	25	III
4	23-27	II
5	40	I-II
6	25-30	II-III
7	38	III
8	40	II
9	55	I-II
10	55	I-II
11	25	I-II
12	20	II
13	27	II
14	24	II
15	35-40	II
16	30	II
17	25	II
18	45	II
19	30-32	III
20	56	III
21	31	II
22	<20	II-III

LVEF—left ventricular ejection fraction; NYHA— New York Heart Association

Table 5.4 Physical activity proportions

	Control	Heart Failure
Sedentary	5 (24)	11 (55)#
Active Lifestyle	7 (33)	8 (40)
Highly Active	9 (43)	1 (5)*

All values are n (%); *p<0.05; #p<0.10; control n=21; heart failure n=20

Table 5.5 Montreal cognitive assessment cognitive domain median scores for patients with normal and abnormal total scores

	MoCA items	Total possible score	Heart Failure	
			MoCA≥26	MoCA<26
Age	-	-	68.5 (63.0-77.0)	67.5 (63.0-78.0)
Overall score	-	30	27.0 (27.0-28.5)	22.5 (21.0-24.0)*
Short-term memory	delayed recall	5	4.0 (3.0-4.0)	1.0 (1.0-3.0)*
Visuospatial function	clock, cube	4	4.0 (4.0-4.0)	3.0 (3.0-4.0)*
Executive function	trails, fluency, abstraction	4	3.5 (3.0-4.0)	2.0 (1.0-3.0)*
Attention, Concentration, Working memory	digit, serial 7, letter	6	6.0 (5.0-6.0)	5.0 (5.0-6.0)
Language	naming, sentence repetition, fluency	6	6.0 (4.5-6.0)	4.0 (4.0-5.0)*
Orientation	orientation	6	6.0 (5.5-6.0)	6.0 (6.0-6.0)

All values are median (interquartile range); *p<0.05. MoCA—Montreal Cognitive Assessment; MoCA ≥ 26 n=8; MoCA < 26 n=14

Table 5.6 Median values for cardiovascular and cerebrovascular variables in control and heart failure patients in the supine position

	Control	Heart Failure
HR (bpm)	56 (50-65)	60 (54-69)
MAP (mmHg)	95 (87-102)	89 (83-99)
Qi_Fin (L/min/m^2)	4.8 (4.1-6.1)	2.7 (2.4-4.3)*
SVi (mL/beat/m^2)	80 (62-96)	48 (34-71)*
TPR (mmHg/L/min)	18 (16-22)	17 (11-24)
MFV$_{MCA}$ (cm/s)	51 (44-55)	43 (34-60)
SFV$_{MCA}$ (cm/s)	77 (69-82)	74 (61-94)
DFV$_{MCA}$ (cm/s)	31 (28-35)	24 (19-32)*
CVRi (mmHg/cm/s)	1.9 (1.7-2.1)	2.0 (1.7-2.3)
RI	0.6 (0.5-0.6)	0.7 (0.6-0.7)*
PI	0.9 (0.7-0.9)	1.2 (1.0-1.3)*
CBF$_{RICA}$ (mL/min)	296 (255-343)	264 (214-313)
CBF$_{LICA}$ (mL/min)	293 (250-333)	235 (224-267)*
aCBF (mL/min)	627 (546-679)	479 (447-590)*
ETCO$_2$ (mmHg)	37 (33-40)	35 (32-39)
PP$_{brach}$ (mmHg)	56 (45-66)	61 (47-77)
PP$_{car}$ (mmHg)	50 (41-53)	61 (48-64)#
IMT$_{mean}$ (mm)	0.60 (0.55-0.76)	0.78 (0.62-0.88)*

All values are median (interquartile range); *$p<0.05$; #$p<0.10$. HR—heart rate n=22; MAP—mean arterial pressure n=22; Qi_Fin—cardiac index estimated from the Finometer n=22; SVi—stroke index n=22; TPR—total peripheral resistance n=22; MFV$_{MCA}$—mean flow velocity through the middle cerebral artery n=18; SFV$_{MCA}$—systolic flow velocity through the middle cerebral artery n=18; DFV$_{MCA}$—diastolic flow velocity through the middle cerebral artery n=18; CVRi—cerebrovascular resistance index n=18; RI—resistance index n=18; PI—pulsatility index n=18; CBF$_{RICA}$—cerebral blood flow through the right internal carotid artery n=19; CBF$_{LICA}$—cerebral blood flow though the left internal carotid artery n=18; aCBF—anterior cerebral blood flow through bilateral internal carotid artery n=17; ETCO$_2$—end tidal carbon dioxide n=22; PP$_{brach}$—brachial pulse pressure n=22; PP$_{car}$—carotid pulse pressure n=15; IMT$_{mean}$—mean intima-media thickness n=19

Table 5.7 Median values for cardiovascular and cerebrovascular variables in control and heart failure patients in the seated position

	Control	Heart Failure
HR (bpm)	62 (56-66)	60 (53-69)
MAP (mmHg)	94 (90-104)	93 (84-96)
Qi_Fin (L/min/m^2)	5.3 (4.1-5.7)	2.6 (1.9-3.7)*
SVi (mL/beat/m^2)	77 (60-86)	45 (34-57)*
TPR (mmHg/L/min)	18 (16-21)	17 (13-24)
MFV_{MCA} (cm/s)	49 (41-54)	39 (32-53)
SFV_{MCA} (cm/s)	74 (67-80)	73 (56-93)
DFV_{MCA} (cm/s)	30 (26-35)	21 (17-29)*
CVRi (mmHg/cm/s)	1.3 (1.1-1.7)	1.5 (1.4-1.9)
RI	0.59 (0.56-0.63)	0.69 (0.66-0.72)*
PI	0.92 (0.83-1.01)	1.27 (1.14-1.31)*
CBF_{RICA} (mL/min)	282 (255-333)	217 (188-271)*
$ETCO_2$ (mmHg)	37 (34-38)	34 (32-37)

All values are median (interquartile range); *$p < 0.05$. HR—heart rate n=22; MAP—mean arterial pressure n=22; Qi_Fin—cardiac index estimated from the Finometer n=22; SVi—stroke index n=22; TPR—total peripheral resistance n=22; MFV_{MCA}—mean flow velocity through the middle cerebral artery n=18; SFV_{MCA}—systolic flow velocity through the middle cerebral artery n=18; DFV_{MCA}—diastolic flow velocity through the middle cerebral artery n=18; CVRi—cerebrovascular resistance index n=18; RI—resistance index n=18; PI—pulsatility index n=18; CBF_{RICA}—cerebral blood flow through the right internal carotid artery n=19; $ETCO_2$—end tidal carbon dioxide n=22
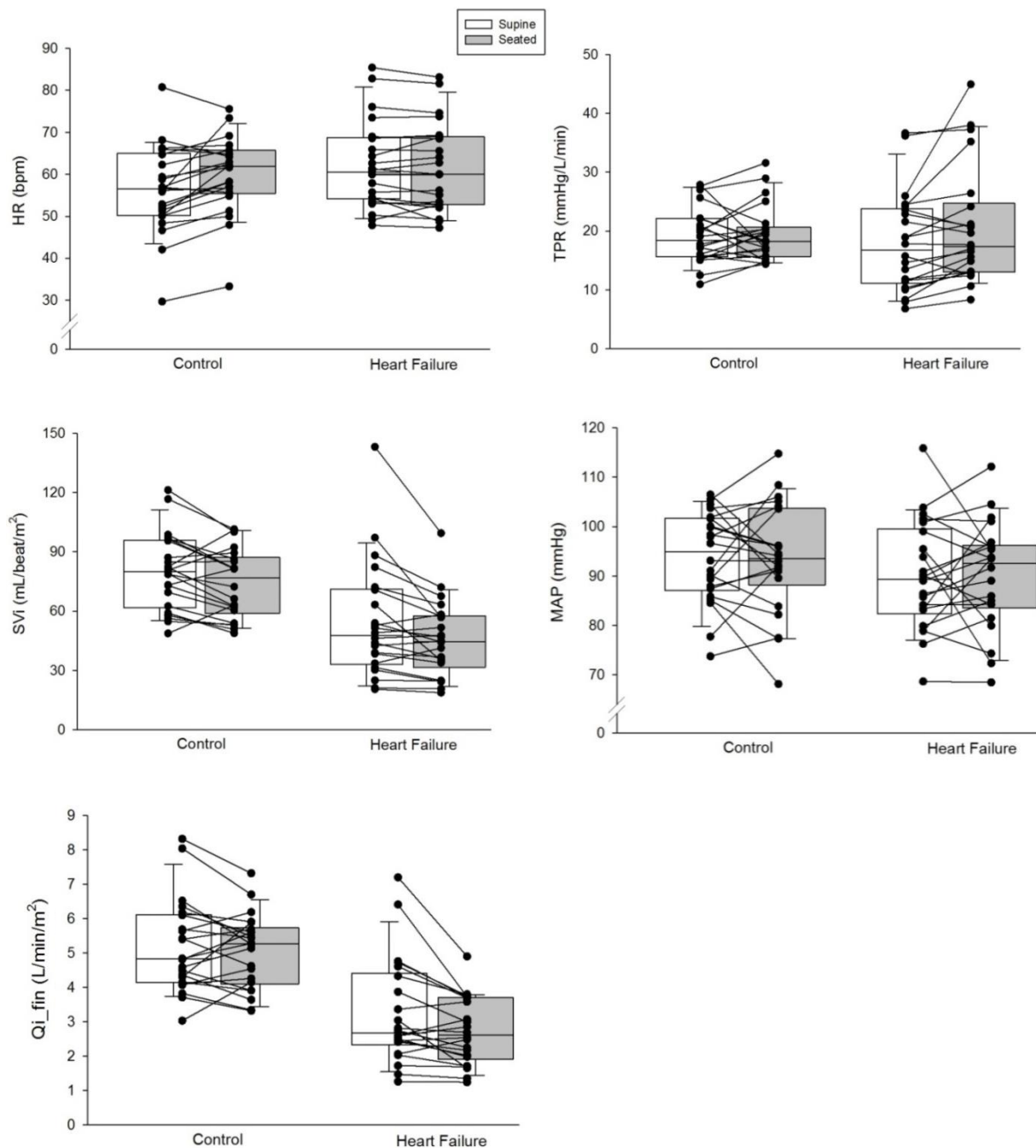
Figure 5.1 Absolute values and individual data for cardiovascular responses to supine and seated positions in control and heart failure patients White bars represent the supine position and grey bars represent the seated position. The boundary of the box closest to zero indicates the 25th percentile, a line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. The error bars above and below the box designate the 90th and 10th percentile. Each control and heart failure patient's response is displayed on the graph as the individual lines; n=22 for all variables; HR—heart rate; SVi—stroke volume index; Qi_Fin—cardiac index estimated from the Finometer; TPR—total peripheral pressure; MAP—mean arterial pressure
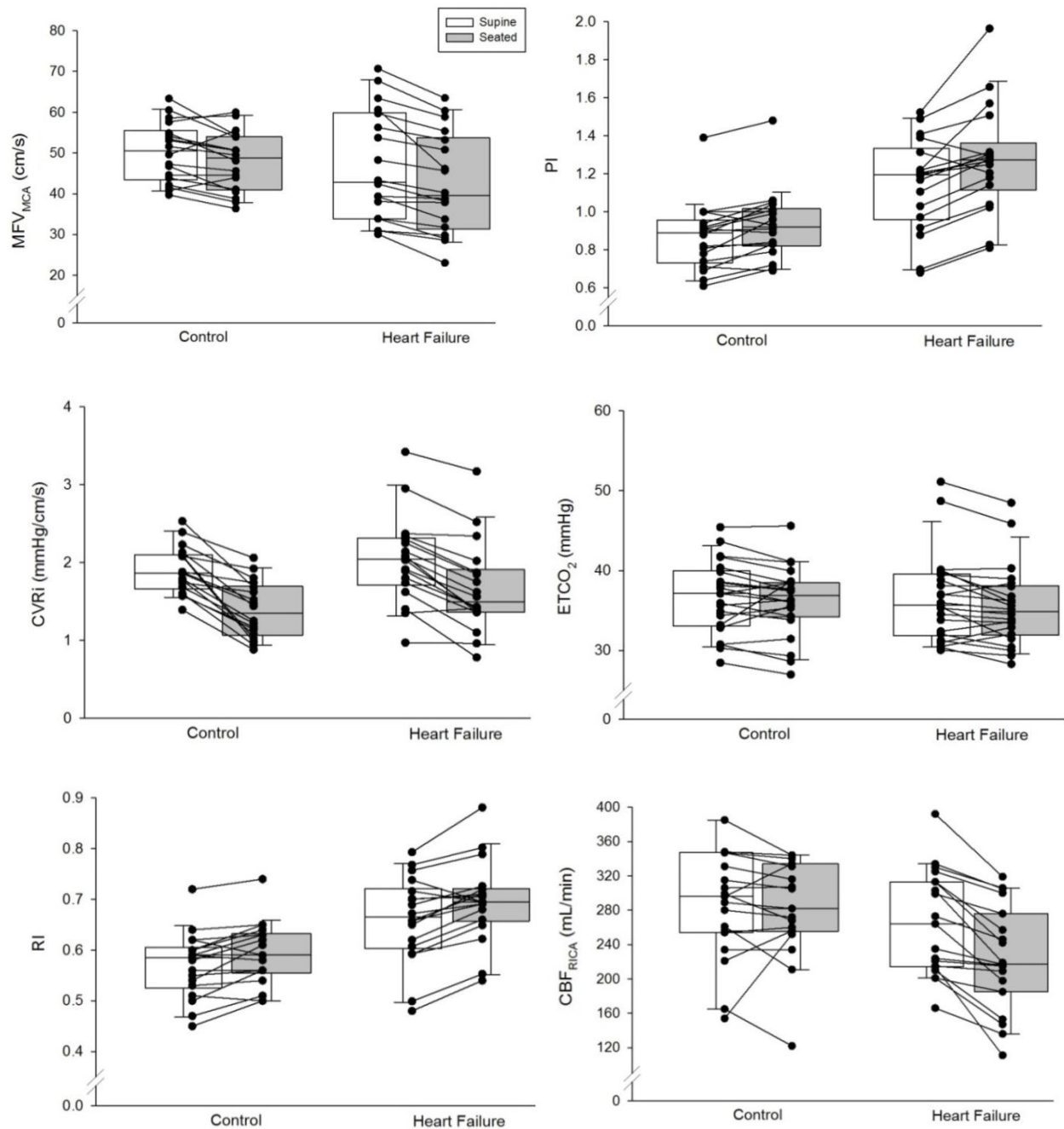
Figure 5.2 Absolute values and individual data for cerebrovascular responses to supine and seated positions in control and heart failure patients Graph format is the same as described in Figure 5.1. MFV_{MCA}—mean flow velocity from the middle cerebral artery n=18; CVRi—cerebrovascular resistance index n=18; RI—resistance index n=18; PI—pulsatility index n=18; $ETCO_2$—end tidal carbon dioxide n=22; CBF_{RICA}—cerebral blood flow through the right ICA n=19
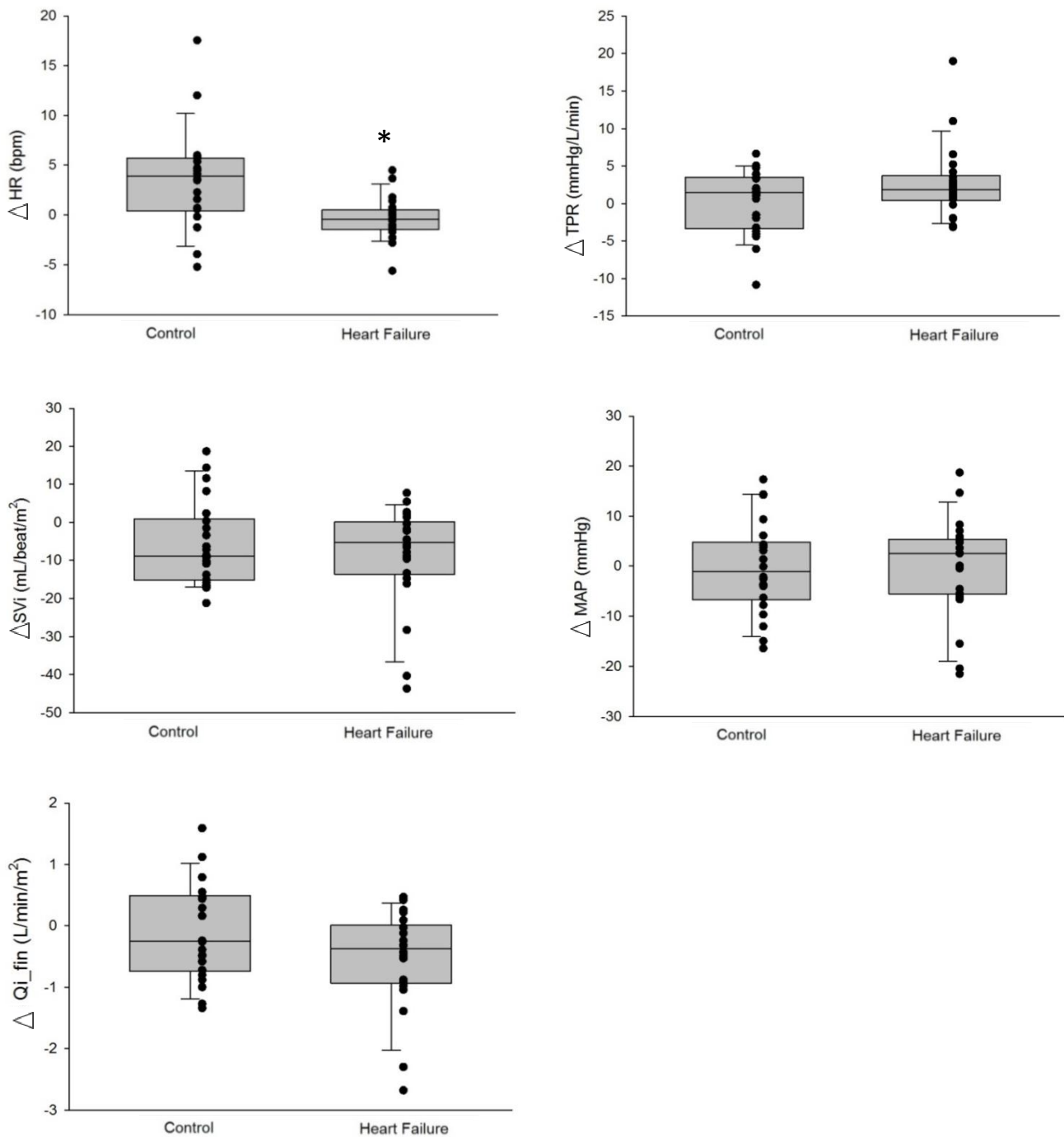
Figure 5.3 Change in cardiovascular responses from a supine to a seated position in controls and heart failure patients The boundary of the box closest to zero indicates the 25th percentile, a line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. The error bars above and below the box designate the 90th and 10th percentile. Each control and heart failure patient's response is displayed on the graph as individual dots; n=22 for all variables; HR—heart rate; SVi—stroke volume index; Qi_Fin—cardiac index estimated from the Finometer; TPR—total peripheral pressure; MAP—mean arterial pressure; * indicates significant difference from controls $p<0.05$
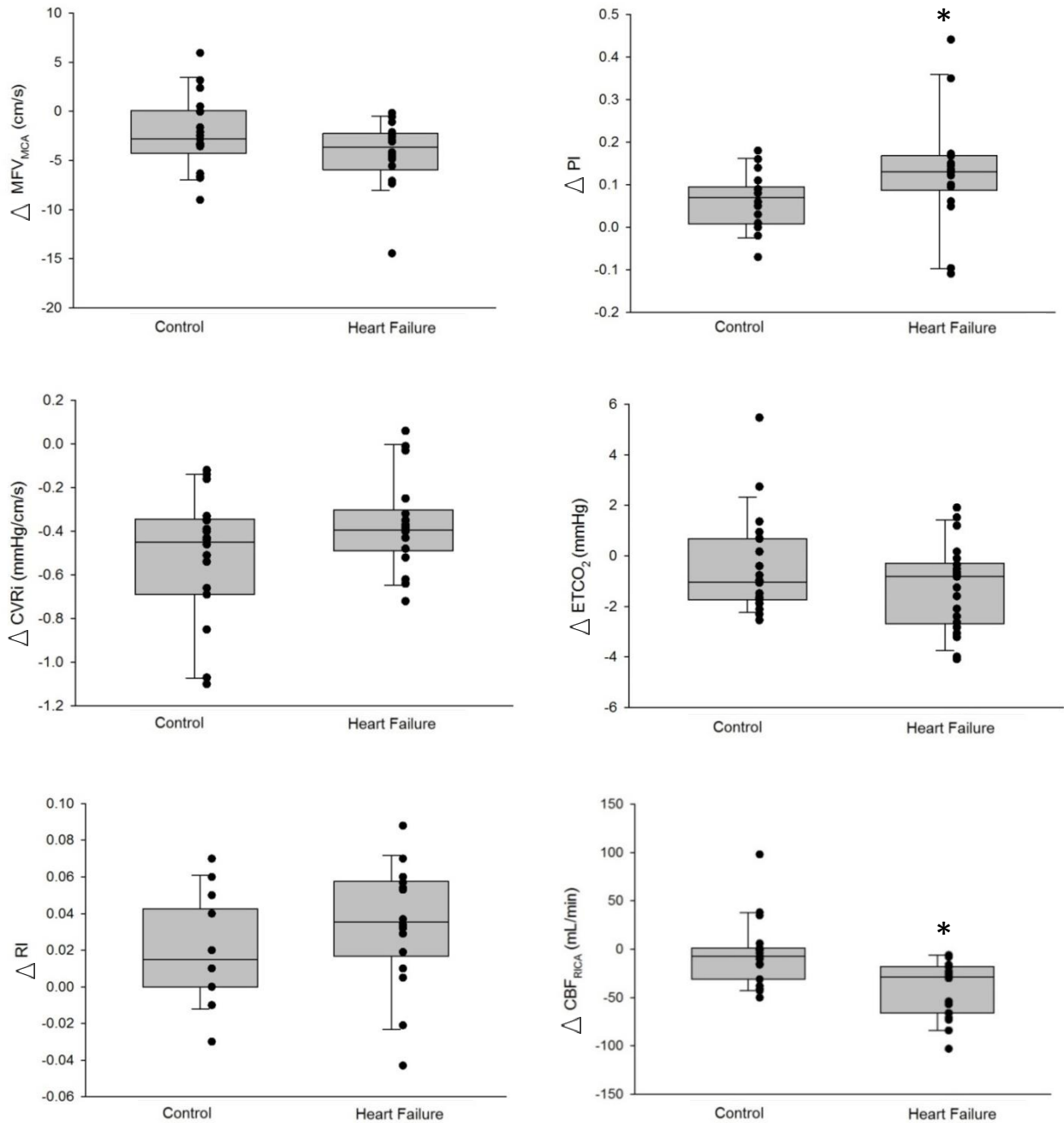
Figure 5.4 Change in cerebrovascular responses from a supine to a seated position in controls and heart failure patients Graph format is the same as described in Figure 5.3; MFV_{MCA}—mean flow velocity through the middle cerebral artery n=18; CVRi—cerebrovascular resistance index n=18; RI—resistance index n=18; PI—pulsatility index n=18; $ETCO_2$—end tidal carbon dioxide n=22; CBF_{RICA}—cerebral blood flow through the right ICA n=19. * indicates significant difference from controls $p < 0.05$

Table 5.8 Cognitive outcomes for the 0-back and 1-back in the supine and seated positions for heart failure patients

	0-back		1-back	
	Supine	Seated	Supine	Seated
Omissions	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Commissions	0 (1-0)	0 (0-0)	0 (0-0)	0 (0-0)
Accuracy (%)	100 (83-100)	100 (100-100)	100 (100-100)	100 (100-100)
Reaction time (ms)	1018 (921-1177)	1028 (938-1089)	1070 (993-1123)	1038 (910-1135)

All values are median (interquartile range); n=21

Table 5.9 Cognitive outcomes for the 0-back, 1-back and 2-back in the supine and seated positions for heart failure patients

	0-back		1-back		2-back	
	Supine	Sit	Supine	Sit	Supine	Sit
Omissions	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.5 (1-2)	1 (1-1)
Commissions	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1 (0-1)	0 (0-1)
Accuracy (%)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	67* (50-83)	83* (67-83)
Reaction time (ms)	961 (819-1170)	1002 (908-1141)	1053 (917-1089)	973 (903-1102)	1063 (968-1274)	1048 (1020-1318)

All values are median (interquartile range); n=10; *$p < 0.05$
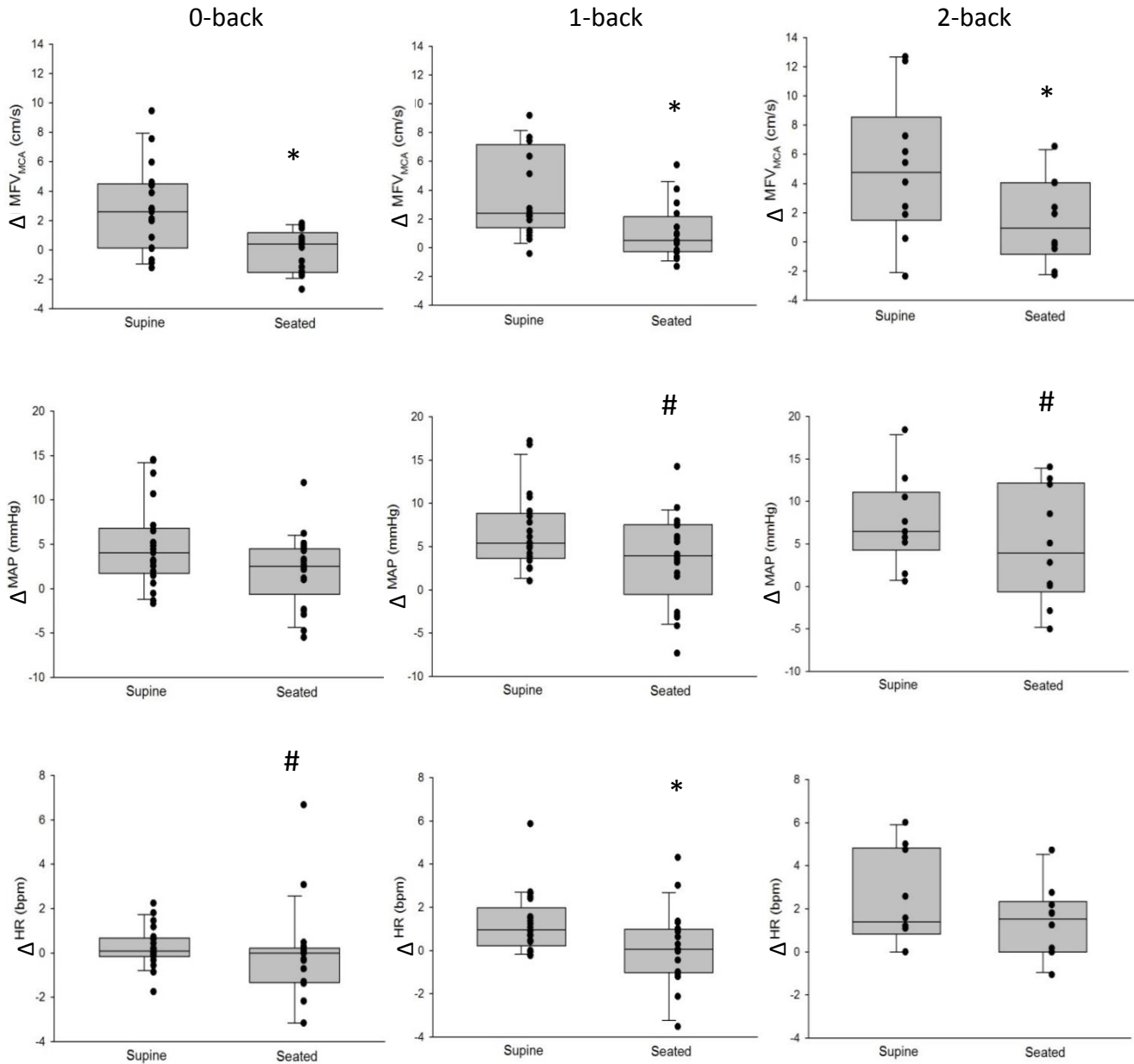
Figure 5.5 Change in mean flow velocity, mean arterial pressure and heart rate from baseline to cognitive load in supine and seated positions for heart failure patients The boundary of the box closest to zero indicates the 25th percentile, a line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. The error bars above and below the box designate the 90th and 10th percentile. Each heart failure patient's response is displayed on the graph as individual dots; MFV—mean flow velocity (0-back n=17, 1-back n=16, 2-back n=10); MAP—mean arterial pressure (0-back n=21, 1-back n=21, 2-back n=10); HR—heart rate (0-back n=21, 1-back n=21, 2-back n=10). * indicates significant difference from controls p<0.05; # indicates a trend to be different from controls p<0.10

Table 5.10 Statistical p-values for the comparison between supine and seated positions for various cognitive loads in heart failure patients

	0-back	1-back	2-back
Δ Qi_Fin (L/min/m^2)	0.289	0.414	0.910
Δ SVi (mL/beat/m^2)	0.140	0.348	0.232
Δ TPR (mmHg/L/min)	0.052 #	0.164	0.322
Δ CVRi (mmHg/cm/s)	0.263	0.712	0.250
Δ RI	0.144	0.715	0.129
Δ PI	0.304	0.900	0.232
Δ ETCO$_2$ (mmHg)	0.142	0.442	0.688

Values are p-values. #$p<0.10$. Qi_Fin—cardiac index estimated from the Finometer (0-back n=21, 1-back n=21, 2-back n=10); SVi –stroke index (0-back n=21, 1-back n=21, 2-back n=10); TPR—total peripheral resistance (0-back n=21, 1-back n=21, 2-back n=10); CVRi—cerebrovascular resistance index (0-back n=17, 1-back n=16, 2-back n=10); RI—resistance index (0-back n=17, 1-back n=16, 2-back n=10); PI—pulsatility index (0-back n=17, 1-back n=16, 2-back n=10); ETCO$_2$—end tidal carbon dioxide (0-back n=21, 1-back n=21, 2-back n=10)
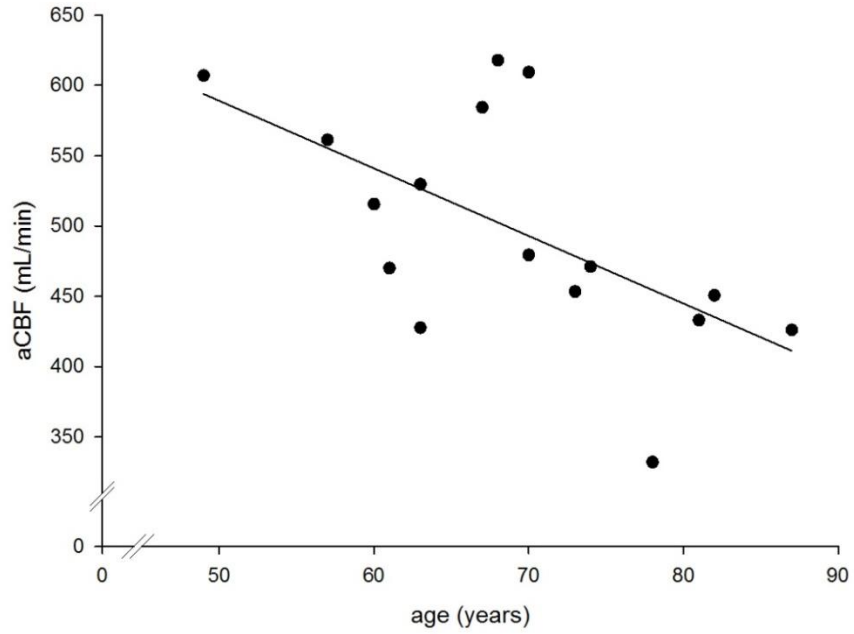
Figure 5.6 Relationship between age and supine anterior cerebral blood flow in heart failure patients

A greater age was inversely associated with a lower anterior cerebral blood flow (aCBF) through the bilateral internal carotid arteries. p=0.017; r_s=-0.58; n=16
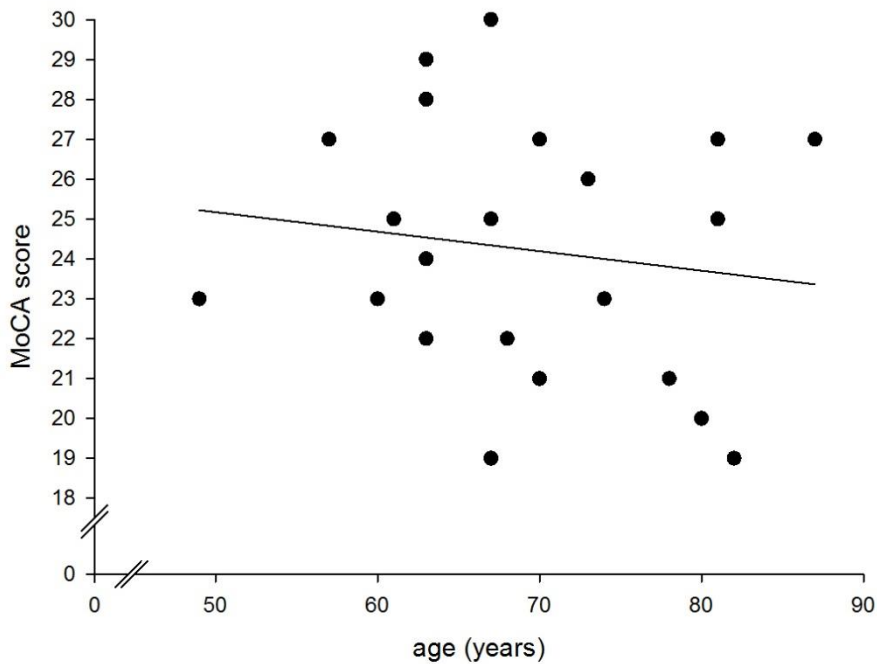
Figure 5.7 Relationship between age and MoCA score in heart failure patients

There was no relationship detected between MoCA score and age. p=0.423; r_s=-0.18; n=22
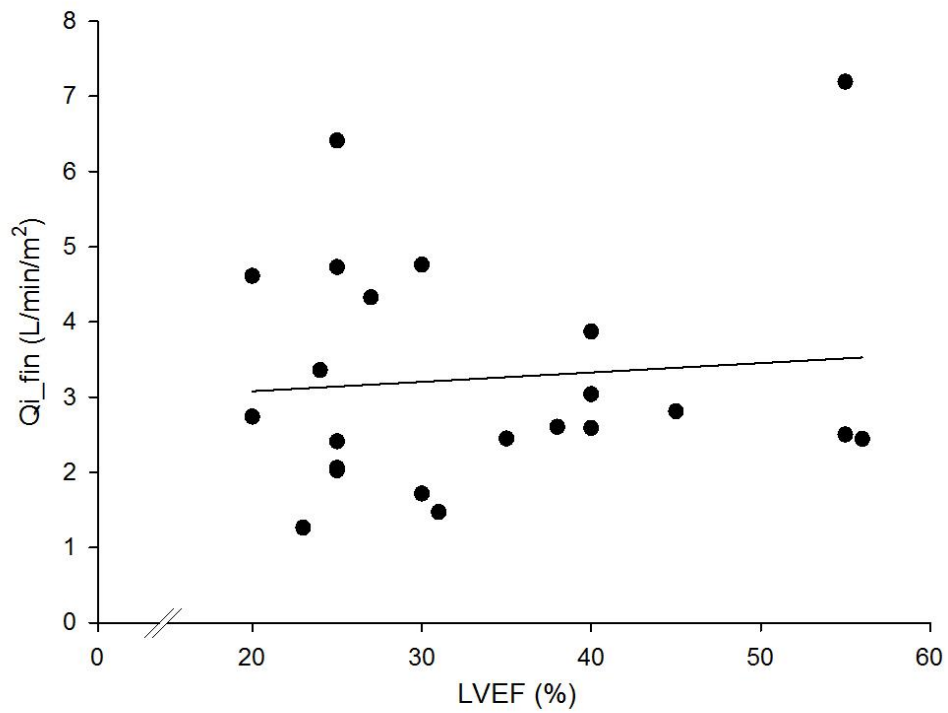
Figure 5.8 Relationship between left ventricular ejection fraction and supine cardiac index from the Finometer in heart failure patients
No relationship between supine left ventricular ejection fraction (LVEF) and supine cardiac index from the Finometer (Qi_Fin). p=0.848; r_s=0.0427; n=22
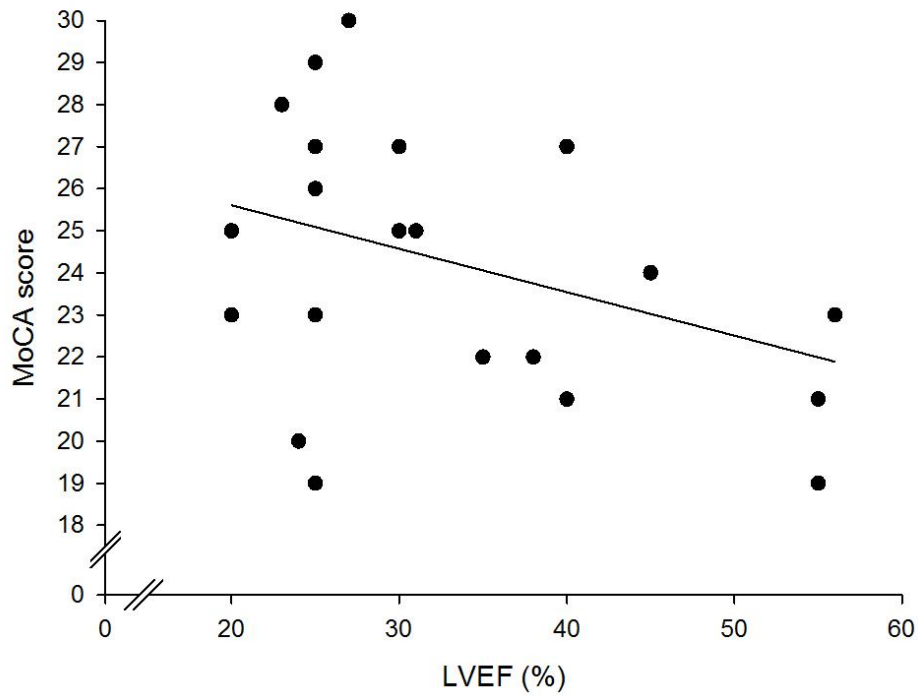
Figure 5.9 Relationship between left ventricular ejection fraction and MoCA score in heart failure patients

There was a low to moderate inverse relationship detected between left ventricular ejection fraction (LVEF) and MoCA score that did not reach statistical significance. p=0.240; r_s=-0.30; n=22
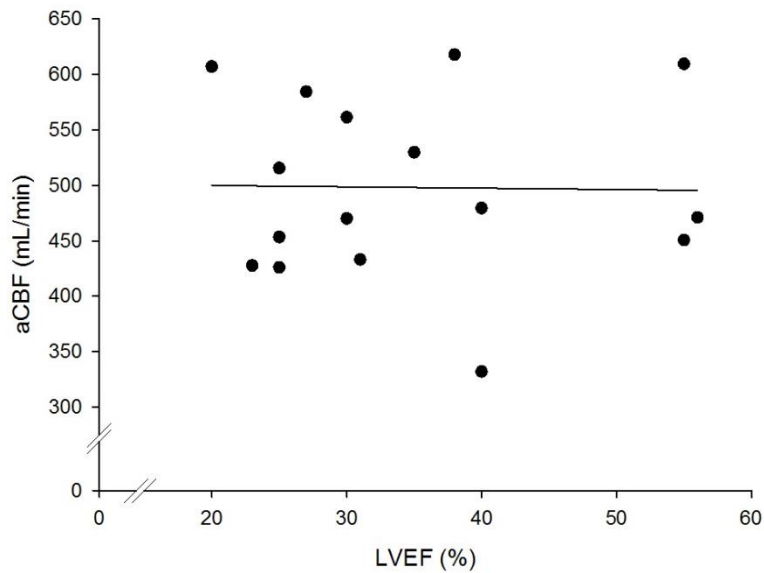
Figure 5.10 Relationship between left ventricular ejection fraction and supine anterior cerebral blood flow in heart failure patients

No relationship was identified between left ventricular ejection fraction (LVEF) and supine anterior cerebral blood flow (aCBF) through the bilateral internal carotid arteries. p=0.805; r_s=0.06; n=16
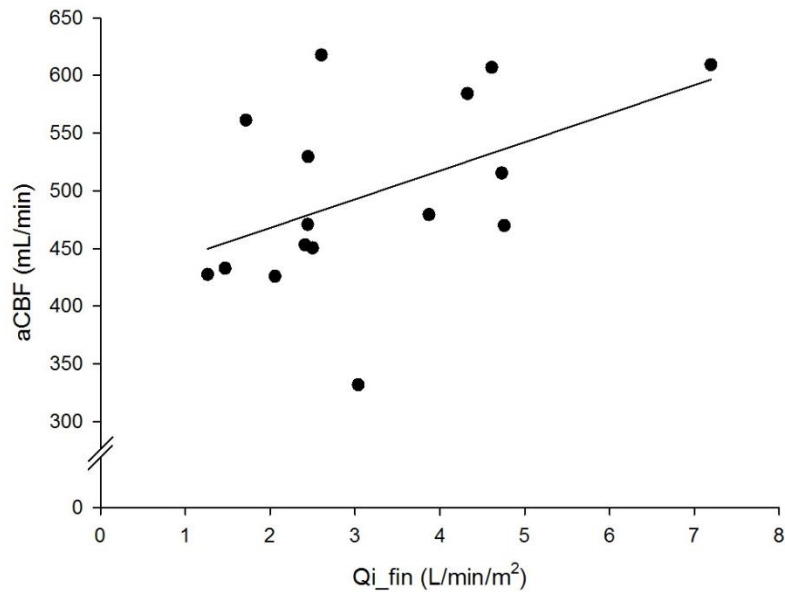
Figure 5.11 Relationship between supine cardiac output and supine anterior cerebral blood flow

A significant positive correlation was identified between supine cardiac output from the Finometer (Qi_Fin) and supine anterior cerebral blood flow through the bilateral internal carotid arteries. p=0.047; r_s=0.50; n=16

Table 5.11 Patient characteristics for heart failure patients matched to those with heart failure and atrial fibrillation

	Heart Failure	Heart Failure with Atrial Fibrillation
Age (years)	71±8	72±8
Sex males n(%)	3 (75)	3 (75)
Height (cm)	180±16	174±11
Weight (kg)	91±26	87±22
BMI (kg/m^2)	28±6	28±6
MoCA	26±3	23±3
[1]LVEF / NYHA	<40 / II	55 / I-II
[2]LVEF / NYHA	35-40 / II	45 / II
[3]LVEF / NYHA	25-30 / II	56 / III
[4]LVEF / NYHA	27 / II	<20 / II-III

Values are represented as mean ± standard deviation unless otherwise stated, n=4. BMI—body mass index; MoCA—Montreal Cognitive Assessment; LVEF—left ventricular ejection fraction; NYHA—New York heart association

Table 5.12 Medical characteristics for heart failure patients matched to those with heart failure and atrial fibrillation

	Heart Failure	Heart Failure with Atrial Fibrillation
Diabetes	1 (25)	1 (25)
β-blocker	4 (100)	4 (100)
Ace inhibitor	2 (50)	2 (50)
ANGII receptor blocker	2 (50)	1 (25)
Diuretic	3 (75)	4 (100)
Ca^{+2} Channel blocker	1 (25)	0 (0)
Statin	3 (75)	3 (75)
Warfarin	0 (0)	3 (75)
Aspirin	1 (25)	1 (25)
Plavix	3 (75)	0 (0)
Antiarrhythmic agent	0 (0)	2 (50)

Values are represented as n(%); n=4
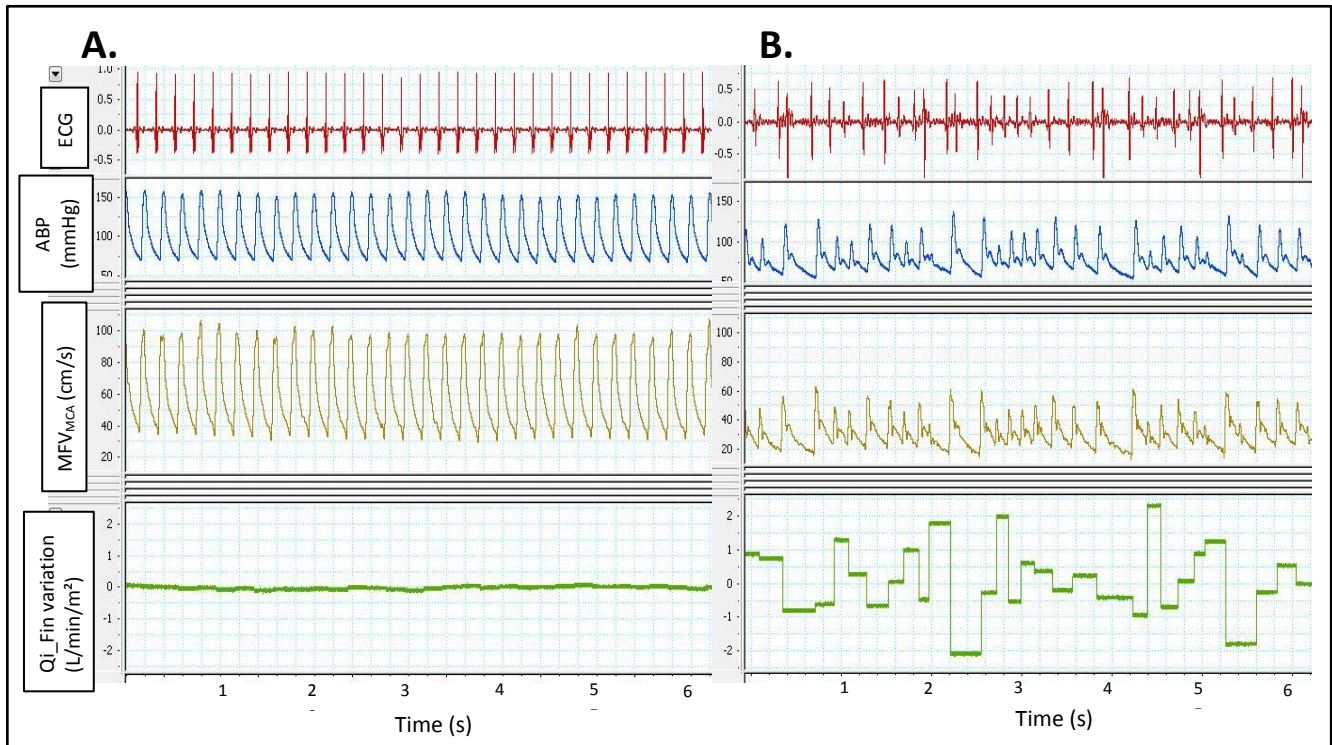
Figure 5.12 Representative beat-by-beat output in the supine position from a patient with heart failure and a patient with heart failure and atrial fibrillation

The heart failure patient (A) was male, 67 years old and had a left ventricular ejection fraction of 27%. The heart failure patient with atrial fibrillation (B) was male, 67 years old and had a left ventricular ejection fraction of <20%. As a consequence of the atrial fibrillation, evident in the electrocardiogram (ECG) in column B, the patient had much more variation in his arterial blood pressure (ABP), mean flow velocity from the middle cerebral artery (MFV_{MCA}) and cardiac index from the Finometer (Qi_Fin). Qi_Fin variation is illustrating the variation of Qi_Fin around the mean value

Table 5.13 Mean supine values and mean variation for heart failure patients and heart failure patients with atrial fibrillation

	Heart Failure		Heart Failure with Atrial Fibrillation	
	Average	Average standard deviation	Average	Average standard deviation
HR (bpm)	60	1.5	67	17.4
MAP (mmHg)	98	3.5	83	5.3
Qi_Fin (L/min/m^2)	2.9	0.1	2.6	0.7
SVi (mL/beat/m^2)	49	2.1	42	8.3
TPR (mmHg/L/min)	17	1.4	18	6.7
MFV$_{MCA}$ (cm/s)	56	2.8	49	4.9
CVRi (mmHg/cm/s)	1.9	0.09	1.8	0.17
RI	0.6	0.03	0.6	0.07
PI	1.0	0.08	1.1	0.22
ETCO$_2$ (mmHg)	36	1.6	34	2.1

Values are represented as means. HR—heart rate n=4; MAP—mean arterial pressure n=4; Qi_Fin—cardiac index estimated from the Finometer n=4; SVi—stroke index n=4; TPR—total peripheral resistance n=4; MFV$_{MCA}$—mean flow velocity through the middle cerebral artery n=3; CVRi—cerebrovascular resistance index n=3; RI—resistance index n=3; PI—pulsatility index n=3; ETCO$_2$—end tidal carbon dioxide n=4

A. MFV$_{RICA}$=29.9cm/s; d=0.48cm; CBF$_{RICA}$=325mL/min
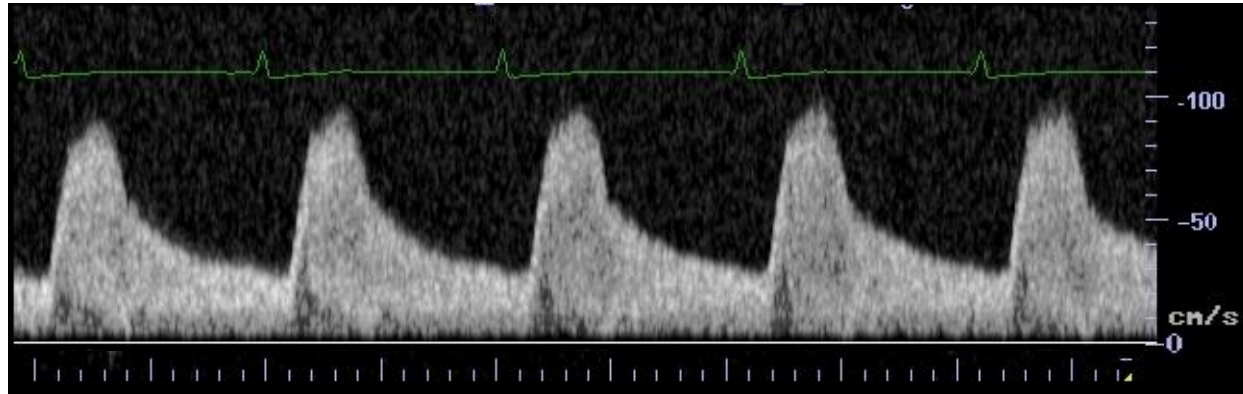
B. MFV$_{RICA}$=15.4cm/s; d=0.67cm; CBF$_{RICA}$=322mL/min
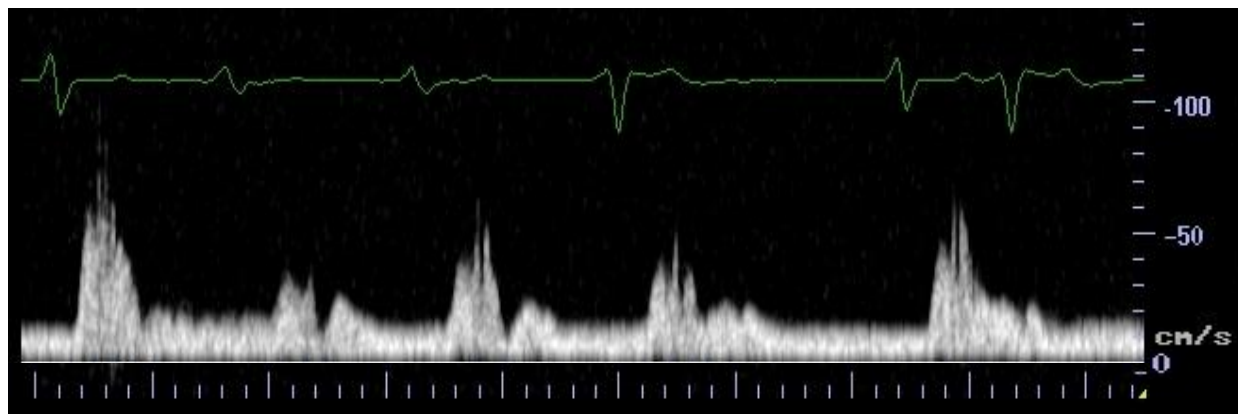
Figure 5.13 Representative supine velocity tracing from the right internal carotid artery in a patient with heart failure (A) and a patient with heart failure and atrial fibrillation (B)
These data are from the same patients described in figure 5.12. This illustrates that despite having a lower mean flow velocity, evident here through the internal carotid artery (MFV$_{RICA}$) and in Figure 5.12 through the middle cerebral artery, cerebral blood flow (CBF$_{RICA}$) through the ICA is maintained since the diameter (d) of the artery is larger

6.0 Discussion

The primary objective of this thesis were successfully met by (1) investigating how CBF changes in response to an upright posture in heart failure patients compared to age- and sex-matched controls and (2) comparing the difference in cognitive outcomes and cognitive-activated hemodynamics between supine and seated in the heart failure sample. Our hypothesis was confirmed by the finding that CBF decreased more in response to sitting upright in the heart failure group compared to healthy age- and sex-matched controls. Additionally, Q more consistently decreased in the heart failure patients in response to the orthostatic stress compared to controls. This intermittent cerebral hypoperfusion may further insult the already reduced supine CBF and contribute to cognitive impairments over time. Within the heart failure patients, performance outcomes on the n-back cognitive task were posture-independent, that is, they did not perform worse when upright, differing from our initial hypothesis. In contrast, the n-back or cognitive-activated hemodynamics were dependent on posture. Specifically, MFV_{MCA} increased significantly less in response to the cognitive task while seated; HR and MAP showed similar trends but were not significant. While this confirmed the original hypothesis, a learning effect is recognized as a potential confounding factor.

Furthermore, secondary hypotheses were verified through the inclusion of a spectrum of LVEF and patients with atrial fibrillation with coexisting heart failure. LVEF was low-moderately and inversely related to lower MoCA scores, although not reaching statistical significance. We further detected no correlation between LVEF and Qi_Fin or LVEF and supine aCBF in agreement with the hypothesis. A positive correlation was detected between supine Qi_Fin and supine aCBF suggesting that Q rather than LVEF may better predict those at risk for cerebral hypoperfusion that, over time, can contribute to cognitive decline. Last, the hypothesis

of high Qi and MFV variability in atrial fibrillation with co-existing heart failure was confirmed. This has important implications as a potential contributor to the cognitive impairments observed in atrial fibrillation.

6.1 Posture Effects on Hemodynamics in Heart Failure (Primary Objective 1)

The primary focus of the current thesis was to determine the effect of an upright posture on CBF in heart failure patients compared to age- and sex-matched healthy controls. It was hypothesized that the heart failure group would have a greater drop in CBF upon moving to an upright seated posture compared with a control group. This hypothesis was supported as the median CBF_{RICA} was reduced significantly more in the heart failure group (-29 mL/min) compared to the controls (-7 mL/min). In addition to the effect on upright CBF, the cerebrovascular and cardiovascular baseline supine measures in the heart failure patients differed from the controls in several ways. The following sections will address cerebrovascular (section 6.1.1) and cardiovascular (section 6.1.2) differences between the heart failure and control groups in the supine baseline condition as well as in response to an upright seated position. Differences in vascular structure and function will also be discussed (section 6.1.3). Also included are the proposed mechanisms linking cardiac dysfunction, cerebral hypoperfusion and cognitive impairments (section 6.1.4).

6.1.1 Cerebrovascular differences between heart failure and controls

Supine Baseline

Consistent with previous work (Loncar *et al.*, 2011) we confirmed a lower supine CBF in heart failure (479 mL/min) compared to controls (627 mL/min) when measured by ultrasound. In

contrast to the ultrasound flow measurement, MFV_{MCA} determined using TCD was not statistically different between the groups in spite of being lower by 8cm/s in the heart failure group compared to controls. Vogels and colleagues reported MFV_{MCA} to be 9cm/s lower in a heart failure group compared to controls, a difference which they reported to be significant (Vogels *et al.*, 2008). Small sample size, high variability and the large age range in our sample are likely candidates for the inability to detect significant differences. A further consideration is that TCD is a measure of MFV and not CBF due to the inability to quantify MCA diameter. In order to use TCD as a surrogate of CBF, MCA diameter must be assumed constant. However, under extreme conditions (prolonged hypoxia and maximum hypercapnia) and certain disease states, MCA diameter does change (Valdueza *et al.*, 1999; Willie *et al.*, 2012). While no reports exist on changing MCA diameter in heart failure, age and atherosclerosis related structural changes likely affect the intracranial vessels (Ozdogmus *et al.*, 2008). In fact, the PI of the MCA was elevated in heart failure as indicated by this study (discussion below) and others (Vogels *et al.*, 2008) and has been reported to be directly related to artery stiffness (Webb *et al.*, 2012). Thus, changes in MCA diameter may occur in heart failure and are unaccounted for by using TCD, although this remains speculative.

The indices of resistance (RI and PI) were higher in the heart failure patients compared to controls in the supine position. This may be partly explained by the lower supine DFV_{MCA} in the heart failure group, implying downstream vasoconstriction leading to higher cerebral resistance. It is important to note that these indices are independent of pressure so caution must be taken when making conclusions on resistance based solely on these indices (Richards *et al.*, 1998). The finding of higher resistance indices (RI and PI) could also be due to the elevated arterial stiffness or a smaller cross sectional area of the vessel. Utilization of PI and RI as estimates of resistance

in the cerebral circulation has been questioned for their ability to solely reflect changes in downstream resistance (Czosnyka *et al.*, 1996); rather, in addition to resistance, they represent a combination of cerebral perfusion pressure, compliance of the cerebral arterial bed and HR (de Riva *et al.*, 2012). CVRi is an alternate resistance index to RI and PI and was unchanged between groups in this study. Although this index is also limited as it assumes blood flow to continue at pressures approaching 0 mmHg. Alternatively, the calculation of critical closing pressure, a linear extrapolation to the pressure at which blood flow would theoretically cease, in the determination of cerebral perfusion pressure has been deemed more physiologically relevant (Weyland *et al.*, 2000; Carey *et al.*, 2001). A vascular resistance measure, resistance area product, can then be calculated by incorporating critical closing pressure. These measures have shown promise in understanding cerebral regulation (Weyland *et al.*, 2000). Future studies with this population should consider these calculations in order to gain more accurate estimates of cerebrovascular resistance changes.

Upright Posture

The seated position resulted in a greater increase in PI in the heart failure group compared to controls. PI has been found to increase in an elderly population compared to a young population upon moving to a seated position (Edgell *et al.*, 2012) and the results from this thesis suggest a further elevation in heart failure patients compared to the control group collected. A trend was detected for DFV_{MCA} to be reduced more when upright in the heart failure patients compared to controls and is a likely contributor to the elevated PI in this group.

For the first time, CBF_{RICA} was found to decrease more when upright in heart failure patients compared to healthy controls. The heart failure group also experienced a greater and

more consistent decrease in Q with the upright position compared to the controls. Previous reports have highlighted the reliance of CBF on Q, specifically by using exercise as a mechanism to increase Q. One study found that when Q was limited, such as with cardiac pathology, cerebral perfusion could not increase during moderate exercise (Ide *et al.*, 1998). This was further confirmed in another study that decreased or increased Q with LBNP or serum albumin, respectively, and observed concomitant changes in MFV_{MCA} during rest and during exercise (Ogoh *et al.*, 2005). Specifically in heart failure patients, one-legged exercise could not elicit the same 20% increase in MFV_{MCA} that was seen in controls (Hellstrom *et al.*, 1997). These results suggest that, when challenged, blood flow to the brain could not increase when Q was compromised. When heart function is improved, such as with a transplant, Q is increased along with CBF (Gruhn *et al.*, 2001). Taken together, results from this thesis along with previous findings suggest a dependency of CBF on Q especially when Q is lowered, such as with heart failure. Another possibility is the lack of cerebrovascular reserve capacity. The reduction in Q that is innate to heart failure may require dilation of brain arterioles while resting to maintain blood flow to the brain limiting the potential for further dilation when challenged. In fact, Georgiadis and colleagues have reported impaired cerebrovascular reactivity in patients with chronic heart failure (Georgiadis *et al.*, 2000). However it should be noted that cerebrovascular reactivity measures the response to a metabolic challenge, normally CO_2, rather than a pressure change. In response to the upright position, heart failure and controls exhibited a statistically similar decrease in $ETCO_2$. The decrease in $ETCO_2$ observed with the posture change was small and likely contributed little to the CBF response. Cerebral autoregulation, the built in mechanism to maintain CBF in the face of fluctuating pressure represents a research area to be explored in the heart failure population. Cerebral autoregulation limits are also known to change with

pathological states, such as hypertension (Iadecola & Davisson, 2008) and impairments have also been reported in diabetes (Bentsen *et al.*, 1975). More work is needed to determine cerebral autoregulation functioning in heart failure.

6.1.2 Cardiovascular differences between heart failure and controls

Supine Baseline

By definition, heart failure is associated with low Q due to impairment in the heart's ability to pump or fill. Heart failure patients had a significantly lower supine Qi_Fin (2.7 L/min/m^2) compared to healthy controls (4.8 L/min/m^2), a finding that has been reported by others (Carlsson *et al.*, 2012). Interestingly, a significant relationship was detected between Qi_fin and supine aCBF in the heart failure patients (Figure 5.11). The dependency of the brain on Q is highlighted by the fact that it receives 15-20% of Q at rest but only represents 2% of overall body mass (Silverthorn, 2007). Low Q (<4.0 L/min) has been previously associated with cognitive (Jefferson *et al.*, 2007a) and neuroimaging abnormalities (Jefferson *et al.*, 2007b). Significantly lower brain volumes are detected at Qi <2.9 L/min/m^2 and therefore this has been suggested as a possible clinical threshold associated with abnormal brain aging (Jefferson *et al.*, 2010). Absolute supine values of Qi obtained in this study were plotted against the change in CBF$_{RICA}$ from supine to seated for heart failure patients and controls. The relationship appears to be non-linear and fit better to an exponential non-linear model (non-linear r=0.53, linear r=0.35). Figure 6.1 suggests that beyond a Qi of ~3.0-4.0 L/min/m^2 there is an apparent smaller CBF change. Therefore, a lower hearts ability (indicated by low Qi) may increase the risk for a greater change in CBF when moving to an upright posture.
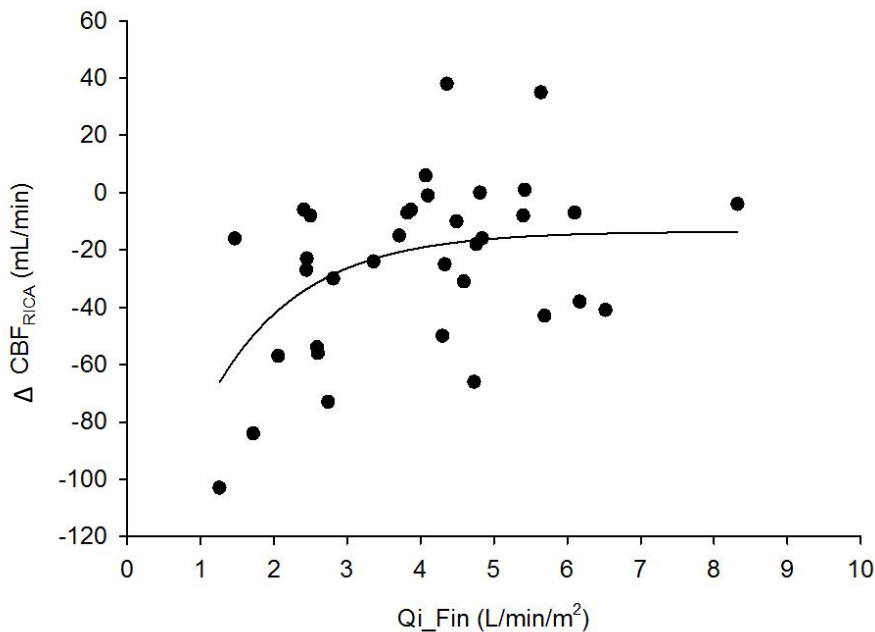
Figure 6.1 Comparison of absolute cardiac index from the Finometer to the change in cerebral blood flow through the right internal carotid artery A non-linear exponential relationship was detected (r=0.53, p=0.018, n=35). This suggests that a lower supine cardiac index (Qi_Fin) is associated with a greater drop in cerebral blood flow (CBF_{RICA}) when moving to an upright position.

Upright Posture

The healthy control group increased their HR significantly more than the heart failure group, which is consistent with previous literature (Levine *et al.*, 1983; Cody *et al.*, 1982). In the 1980's reports on the abnormal response to prolonged tilt in heart failure surfaced, since then little work has been done in this area. These early studies found attenuated neurohumoral compensatory responses to the passive, prolonged orthostatic stress. Heart failure patients exhibited no change in plasma norepinephrine and no increase in HR or plasma renin that were documented to increase in the healthy control group (Levine *et al.*, 1983). These irregular responses are speculated to be due to maximal stimulation of compensatory mechanisms while resting. To our knowledge, this is the first time a more active orthostatic challenge representative

of everyday postures has been investigated as well as the inclusion of CBF. In our study design, humoral responses from the RAAS are unlikely contributors to the initial posture response since there were only 5-10 minutes in the upright posture prior to data collection. Impairments would rather be attributed to the changes in the arterial and cardiopulmonary baroreceptors with heart failure (Creager & Creager, 1994). Both heart failure and control groups were able to maintain MAP in the upright position through an increase in TPR in order to compensate for the drop in Q. In spite of the smaller increase in HR with heart failure, MAP at heart level was maintained because of the sufficient increase in resistance. Although baroreflex function was not specifically tested, it appears the response was appropriate in this sample. A larger challenge to pressure such as during prolonged passive head up tilt may exposure insufficiencies in this system but importantly, the blood pressure response to a normal every day postural challenge seemed sufficient.

6.1.3 Vascular Structure and Function Differences while Supine between Heart Failure and Controls

Structural and functional differences were found between heart failure and control groups. The PP in the CCA (a central elastic artery) was greater in the heart failure group compared to the controls whereas PP in the brachial (a distal muscular artery) was comparable. Wall thickness, as indicated by IMT, was also found to be greater in the heart failure patients compared to healthy controls. Consistent with these results, heart failure has also been found to be associated with significant arterial wall thickening and decreased compliance measured at the CCA (Lage *et al.*, 1994). In the same study, norepinephrine was found correlated with arterial compliance, suggesting the sympathetic nervous system over activity in heart failure may

contribute to the arterial stiffening in heart failure (Lage *et al.*, 1994). Arterial stiffness and wall thickening have been associated with adverse outcomes in normal aging and pathological states. In well-functioning, community dwelling older adults, arterial stiffness is associated with higher CVD morbidity and mortality (Sutton-Tyrrell *et al.*, 2005). These findings are exacerbated in the setting of systemic hypertension (Laurent *et al.*, 2001). Arterial stiffness also predicts mortality and is a risk factor for hospital re-admission (Demir *et al.*, 2013; Meguro *et al.*, 2009). Arterial stiffness and carotid wall thickening have been reported to contribute to lower CBF (Tarumi *et al.*, 2011; Sojkova *et al.*, 2010)

6.1.4 Linking Heart Dysfunction and Cerebral Functioning

This study and others have documented cerebral hypoperfusion and cognitive decline in heart failure; but how are the two linked? The exact mechanism is yet to be determined. In 1993, de la Torre published a number of papers leading to the proposition of the CATCH hypothesis— critically attained threshold of cerebral hypoperfusion (de la Torre & Mussivand, 1993). Their model suggests that the presence of vascular risk factors further diminish CBF in individuals with already diminishing cerebral perfusion with advancing age (de la Torre & Mussivand, 1993). This two-fold burden on CBF leads to a neuronal energy crisis due to the reduced delivery of glucose associated with cerebral hypoperfusion. The energy starved neurons undergo oxidative and endoplasmic reticulum stress that ultimately reduces the main fuel for cells—ATP. The reduction in ATP impacts post-translational steps, namely protein synthesis, assembly and folding. Defects in any of these steps results in dysfunctional or non-functional proteins. Irregular protein cleavage and degradation ultimately leads to the build-up of beta-amyloid containing plaques, which are found in the brains of patients suffering from Alzheimer's disease.

The under perfused state prevents washout further contributing to the build up of plaques and they eventually congregate to form senile plaques. The initial neuronal energy crisis presents initially as mild memory impairments but as time progresses and damage accumulates the cerebral hypometabolic state lends to the development of dementia and Alzheimer's disease. Support for this theory comes from a recent study that utilized right carotid artery permanent ligation to induce mild chronic hypoperfusion in mice (Elali *et al.*, 2013). The researchers found that chronic dysfunction of the neurovascular unit and early vascular deposition of beta-amyloid peptides. Further evidence of the importance of perfusion is that these alterations were essentially prevented by brain reperfusion or the administration of a high dose of glucose (Elali *et al.*, 2013). This thesis proposes that upright cerebral hypoperfusion further contributes to the declining cognitive state over time by causing intermittent hypoperfusion throughout the day.

6.2 Cognition (Primary Objective 2)

An additional focus of this thesis was to assess cognition and determine if changes could be detected in the different postures, supine and seated. It was hypothesized that performance outcomes and cognitive-activated hemodynamics in response to a n-back cognitive task would be lower in the seated position compared to supine for the heart failure group. The results partly disprove the hypothesis as performance on the task was unchanged between supine and seated. However, cognitive-activated MFV_{MCA} was lower in the seated position and HR and MAP showed similar trends. Moreover, global cognitive functioning was assessed by the MoCA and revealed that a high proportion of the heart failure group had some degree of cognitive deficits that were not clinically documented.

6.2.1 Global Cognition

Greater than 60% of the heart failure patients were found to have some degree of cognitive impairment as detected by a MoCA score of <26. This is slightly higher than previous literature which documented that 25-50% of heart failure patients suffer from cognitive deficits (Pressler, 2008). Importantly, no cognitive impairments in this sample were previously documented formally, suggesting a large portion of mild-moderate cognitive impairments go undetected in a clinical setting. This may interfere with the patient's ability to engage effectively in self-care practices and can lead to adverse outcomes. In a recent study, poor self-care was an independent risk factor for cardiac events, hospitalizations as well as length of hospital stay (Kato *et al.*, 2013). When individual cognitive domains assessed by the MoCA were isolated, those with mild-moderate cognitive impairments (MoCA<26) performed worse on the following domains: short term memory, visuospatial function, executive function and language. These results are consistent with previous literature (Harkness *et al.*, 2011).

The high prevalence of cognitive impairments contributes to the deterioration of quality of life in heart failure. The existence of cognitive impairments is an independent predictor of disability, morbidity and mortality and influences one's ability to perform instrumental activities of daily living (Alosco *et al.*, 2012; Zuccala *et al.*, 2003; Zuccala *et al.*, 2001). Moreover, depression and slow gait speed in heart failure may further insult outcomes and quality of life. Depression, as assessed by the GDS, was significantly greater in the heart failure patients than their healthy counterparts; this was conversely associated with a greater proportion of antidepressant usage. These results are in agreement with previous reports of high levels of depression or depressive symptoms associated with a heart failure diagnosis (Rutledge *et al.*,

2006). In addition to higher GDS scores, gait speed, assessed by the 8-m walk test, was lower in heart failure. Slow gait has been associated with functional decline in older adults (Cesari *et al.*, 2005) and has been indicated as a predictor for the onset of disability in patients newly diagnosed with heart failure (Chaudhry *et al.*, 2011). A high level of cognitive functioning is required to maintain gait with integration required from attention, planning, memory and other processes (Scherder *et al.*, 2007) and a decreased gait has been suggested to predict a decline in cognition (Marquis *et al.*, 2002). Gait speed has been suggested as a singular measure to assess frailty; defined as an increased vulnerability to stressors (Fried *et al.*, 2001). A frail phenotype correlates with loss of independence and other patient-centered outcomes (Cacciatore *et al.*, 2005). Frailty in heart failure is complex as they frequently co-occur and each condition can exacerbate the other (Dodson & Chaudhry, 2012). Therefore, in addition to the high prevalence of cognitive impairments in heart failure, depression and frail phenotypes may interact and contribute to a decline in quality of life, morbidity and mortality.

6.2.2 Postural Cognition Outcomes

Cognitive performance on the n-back task, indicated by the outcome measures of commissions, omissions, accuracy and reaction time, was independent of posture and load with the exception of accuracy worsening on the 2-back. These findings are distinct from those of Stewart et al. (2012) who found the responses to the n-back progressively worsened as orthostasis progressed from a tilt angle of 0 to 75 degrees. In this aforementioned study, no changes were detected between groups in the unloaded, 0-back condition and changes became more distinct with increasing n-back level. In contrast to our study, where the majority of patients only completed 0- and 1-back levels, Stewart et al. (2012) had patients and healthy

controls perform the n-back up to a cognitive load of 4. With this in mind, the lack of findings could be partly due to not administering high enough n-back loads.

6.2.3 Neurovascular Coupling

Neuronal activity requires the delivery of oxygen and glucose and therefore is tightly linked to increases in CBF (neurovascular coupling). Previous studies have found the n-back cognitive task to be sufficient in eliciting an increase in MFV_{MCA} (Stewart *et al.*, 2012; Sorond *et al.*, 2011). In a chronic fatigue syndrome patient population, the percent change in CBF decreased with increasing tilt angle (Stewart *et al.*, 2012). In comparison, healthy young adults (20-30 years old) can increase CBF in response to cognitive tasks independent of the orthostatic conditions (Stewart *et al.*, 2012; Azevedo *et al.*, 2007). We found that the neuronal-activated increases in MFV_{MCA} were posture-dependent in our heart failure sample, in that there was less of an increase in MFV_{MCA} in the seated position. This may be due to the low Q in heart failure limiting the absolute amount of blood available to the brain and the ability to increase when challenged (Ide *et al.*, 1998). Alternatively, since performance on the task did not change when seated, the demand for neuronal activation and consequently cerebral blood flow may have been lower due to performing a version of the task previously while supine.

6.3 Relationships between Measures of Systemic Perfusion, MoCA and Brain Blood Flow (Secondary Objective 1)

A secondary objective of this thesis was to include a spectrum of LVEF's to determine the relationship between LVEF and cognitive, assessed by the MoCA, and CBF. It was hypothesized that LVEF would not be correlated with MoCA scores or CBF. Results confirmed no significant relationship between LVEF and cognition, although a low-moderate, inverse

relationship appears to be present suggesting that higher LVEF may result in lower MoCA scores. Furthermore, no association was detected between LVEF and CBF, confirming the hypothesis. It is proposed that Q may better predict cerebral hypoperfusion and identify those at risk for cognitive decline.

LVEF versus Q

General cardiac function and systemic perfusion are frequently evaluated with LVEF, a ratio of ejected blood dependent on end diastolic volume. However, low Q is the main clinical outcome of heart failure and is rarely in agreement with LVEF values (Jefferson, 2010). In fact a weak correlation was found between Qi and LVEF in a sample of 157 heart failure patients with a LVEF of less than 40% (Carrlson, 2012). Similar, in patients with acute heart failure and a broad range of LVEF's, a weak correlation was also noted between LVEF and Qi (Uriel *et al.*, 2005). Our results are in agreement with these findings as no relationship was detected between LVEF and Qi (Figure 5.8) providing further evidence that a preserved LVEF does not necessarily translate to a higher Q.

Relationship between LVEF and cognition

A moderate, inverse but non-significant relationship between LVEF and MoCA scores was found in the heart failure sample (Figure 5.9). This finding suggests that those with a higher LVEF are equally at risk for cognitive deficits. Importantly, the HFpEF subgroup is poorly investigated in the literature and consequently has led to a lack of documented knowledge on their cognitive state. Recently published studies have found a higher LVEF to be associated with worse cognitive functioning in a cross-sectional design (Huijts *et al.*, 2013) and greater decline over time in a longitudinal design (Riegel *et al.*, 2012).

Systemic perfusion measures and CBF

No association was found between LVEF and supine aCBF (Figure 5.10) in the heart failure sample suggesting that a higher LVEF did not result in an improved CBF as values were similar across the LVEF spectrum. On the other hand, an alternative measure of systemic perfusion, Qi, showed a significant positive correlation with supine aCBF (Figure 5.11). Similar results were presented in a paper by Saha et al. (1993) who found SFV_{MCA} to be significantly related to Qi in a patient population pre or post open-heart surgery (Saha *et al.*, 1993). Therefore, Q may better predict those are risk of cognitive decline due to low CBF measures. In fact, Q has been related to executive dysfunction and WHM in an elderly population with prevalent CVD (Jefferson *et al.*, 2007a; Jefferson *et al.*, 2007b).

6.4 Atrial Fibrillation (Secondary Objective 2)

An additional secondary objective of this thesis was to isolate those patients that had clinically diagnosed atrial fibrillation in addition to heart failure and determine if they had greater variability in Q and brain blood flow due to inherent variations in HR compared to those with heart failure alone. High variability in Q and MFV_{MCA} confirmed the hypothesis. While the sample size was small, the utilization of effect size calculations suggests promising results with a larger sample. In fact, sample size calculations revealed that Qi variability was already significantly different between those with and without atrial fibrillation and MFV_{MCA} variability significance would be met with the addition of 8 patients to each group.

Heart failure and atrial fibrillation very often co-exist (Wang *et al.*, 2003) and each is known to be associated with cognitive impairments (Ott *et al.*, 1997; Trojano *et al.*, 2003). While much attention has been paid to cerebral hypoperfusion in heart failure, most cognitive

impairments are attributed to thromboembolic events leading to stroke in atrial fibrillation. Very few studies have documented CBF in atrial fibrillation with or without co-existing heart failure (Petersen *et al.*, 1989; Porebska *et al.*, 2007) and have yielded some conflicting results. The results from this thesis suggest that patients with heart failure and atrial fibrillation have a lower unilateral CBF through the RICA (246mL/min) compared to heart failure alone (262mL/min) and the healthy control group (296mL/min). The results from Choi and others suggest atrial fibrillation is a further insult to CBF in heart failure (Choi *et al.*, 2006). Perhaps just as important as the overall decrease in flow is the pulsatility or variability of blood through the cerebral vessels. In healthy, older adult population with no history of atrial fibrillation, higher CVD risk was associated not only with lower overall flow through the CCA and MCA but also with the pulsatility of flow (Pase *et al.*, 2012). Pulsatile flow creates a risk for cognitive impairments through cerebrovascular dysfunction due to shearing of the small cerebral vessel endothelium during high flow and ischemia during low flow. The variability in Qi and MFV_{MCA} represents an underappreciated pathway leading to cognitive impairments independent of stroke in atrial fibrillation.

7.0 Limitations

The entire heart failure sample was being actively treated with medications for heart failure, most notably β-blockers (100%), ACE-inhibitors (59%), angiotensin receptor blockers (32%) and diuretics (90%). Since it is unethical to take patients off their medications, it would be impossible to completely eliminate this potential confound in the setting of this study. However it should be noted that a goal of this research was to be inclusive of a sample representative of the actual clinical population. The medications listed above are the first line of defence in the treatment of heart failure in order to counteract the overactive sympathetic nervous system, increase vasodilation and reduce fluid retention. We did not obtain information such as duration of heart failure diagnosis or presence of certain co-morbidities. We were provided access to clinic space and patient records and made efforts to be as minimally disruptive as possible to daily clinic goings-on. Extended time with patient records and/or assistance from clinic staff would have been able to uncover more information about medical background of study participants. The relatively small sample size in this study needs to be acknowledged specifically in the subsets of HFpEF and atrial fibrillation. Application of the results to these populations needs to be made with caution; although promising results do warrant continued investigation. Methodological limitations are noted throughout this thesis and include the assumption of constant MCA diameter when utilizing the TCD technique (section 4.4.5), using Finometer estimates of Q (section 4.7), use of resistance indices (section 6.1) and the lack of posture randomization (section 4.7). Importantly, since the postures were not randomized, a learning effect on the n-back task cannot be discounted. We did not have data on the postural n-back response in a healthy control group (section 6.2) therefore the comparison is limited to between postures within the heart failure group. The NYHA class was obtained from patient records in

this study. This is a limitation as the classification system is subjective and poorly reproducible. Interoperator agreement has been reported to be only 54% even when the same patient was assessed on the same day (Raphael *et al.*, 2007). The common point of disagreement is between class II and III, the main groups in this study, as they require subjective interpretation of "ordinary physical activity" and "slight" and "marked" limitations (Appendix B).

8.0 Future Considerations

This thesis employed a cross-sectional, investigative design. While mechanisms can be speculated, further work is needed and warranted to replicate and build upon the results presented here. While we found lower supine CBF and a greater decrease in CBF with an upright position, an increased understanding of cerebral regulation can be gained in the future by incorporating the determination of critical closing pressure and resistance area product. Increases in sample size are necessary in all aspects of this study with specific attention to the groups with HFpEF and atrial fibrillation. Both of these subsets of the population present unique characteristics that require further investigation. Future studies should continue to consider a sample representative of the population encountered in every day practice to maximize the translatability of the results. Compared to heart failure patients seen in clinical practice defined by epidemiology studies, those enrolled in clinical trials are younger, more likely to be male, have lower LVEF and generally have fewer co-morbidities (Badano *et al.*, 2003). Women are only represented in 21% of heart failure intervention trials despite their rising prognosis of CVD (Heiat *et al.*, 2002). The heart failure sample in this thesis was younger and predominantly male compared to the 'real-world patient characteristics' presented by Badano et al. (2003). While the average LVEF in this study (33%) was higher than those from clinical trials (26%), it was still slightly lower than that of patients in epidemiology studies (38%). Additionally, the percentage of heart failure patients with NYHA class IV is suggested to be 62% (Badano *et al.*, 2003), however in this study and others, they have been excluded. These patients are likely hospitalized and/or have mobility issues that limit their ability to participant in research studies outside of a hospital setting. Therefore, future studies need to be considerate of the 'real-world' heart failure patient characteristics, specifically, an older age, greater proportion of females and higher LVEF.

The results from this study suggest a worsening impact of posture on CBF, raising the issue of prevention since heart failure patients are upright during normal daily activities. Exercise intolerance is a hallmark of heart failure and is associated with poor prognosis (Pardaens *et al.*, 2013). A heart failure patient's ability to increase Q during exercise is severely reduced as a consequence of the inability to augment SV as well as a lower maximum HR (Klabunde, 2005). Additionally, chronically high sympathetic nervous system activity in heart failure downregulates receptors in the heart that increase rate and contraction in response to acute sympathetic activation during exercise (Klabunde, 2005). Limited oxygen delivery to working muscles and muscle atrophy are further limiting factors (Klabunde, 2005). Together these factors contribute to the fatigue and dyspnea experienced by heart failure patients during exertion and limit exercise capacity. In this study, the heart failure sample was significantly more sedentary than their healthy counterparts when assessed with self-reported questionnaires (Table 5.4). The beneficial impact of physical activity in older adults on cardiovascular function is well-documented and positive effects are also noted in the brain, such as improved cognitive performance (Barnes *et al.*, 2003). Brain blood flow is reported to be higher in master athletes (Thomas *et al.*, 2013), to increase in response to short term exercise training in previously sedentary seniors (Chapman *et al.*, 2013) and even to increase in response to a single exercise bout in healthy young adults (MacIntosh *et al.*, 2014). In a study with healthy elderly, a physically active lifestyle was found to prevent cerebral vasoconstriction and hypoperfusion during an orthostatic challenge (Formes *et al.*, 2010). In CVD and specifically heart failure patients, exercise training shows promise at improvements in cognitive function although the effect on CBF in this population remain elusive (Tanne *et al.*, 2005; Garcia *et al.*, 2013). Taken together, physical activity represents a potential pathway for improving cerebrovascular

functioning in heart failure. Exercise intolerance along with other barriers in this population represents a significant limitation to research and clinical application in this population.

Furthermore, it needs to be investigated if this decline in CBF is related to heart failure severity. Heart failure patients with a higher NYHA class, a subjective globally used severity scale, have been found to have a lower CBF (Choi *et al.*, 2006; Georgiadis *et al.*, 2000). In future studies, due to the subjective nature of NYHA classification, the same researcher or clinician should classify each study patient. This will eliminate some error with this measurement and facilitate the ability to determine the effect of severity on important hemodynamic measures such as Q, CBF and functional outcomes such as gait speed. Utilizing Q represents an additional pathway to classify severity. A Qi $<$2.9 L/min/m^2 has been suggested as a potential clinical cut off of accelerated brain aging (Jefferson *et al.*, 2010). We found that an absolute supine Qi of $<$ 3.0-4.0 L/min/m^2 was associated with larger changes in CBF when moving to an upright posture. Therefore, future investigated into Q as an indicator of abnormal brain changes is justified; however, more reliable estimates of Q should be considered.

The Q estimates from the Finometer were overestimated according to the foreign gas rebreathing method obtained from the Innocor (Appendix E). While the Innocor has been suggested by some to be effective in a heart failure sample, we found that not all patients were able to successfully breathe at the appropriate rate or empty the rebreathing bag which contained the required gases to utilize this technique. The benefit to both the Innocor and the Finometer are their non-invasive nature in comparison to traditional invasive gold standard measures such as the Fick technique or thermodilution that require pulmonary or cardiac catheterization. Future consideration should be given to obtaining Q from cardiac ultrasound and/or aortic Doppler as a

potentially more reliable method. With dependable Q values we can begin to investigate its contribution to functional decline in this population. An important question that remains to be answered is whether a critical Qi cut-off (proposed around 3.0 L/min/m^2) is associated with markers of functional decline, such as slow gait speed. Impaired cerebrovascular regulation assessed by neurovascular coupling and cerebrovascular reactivity has been found to be associated with slow gait speed in community dwelling older adults (Sorond *et al.*, 2011; Sorond *et al.*, 2010), however investigation into the heart failure population remains elusive. The low CBF in the heart failure population may be related to slow gait and the addition of a cognitive task may further divert CBF needed for the complex motor task of walking and lead to falls. Research into the relationship between CBF and dual tasking while walking and the relationship to falls in heart failure is needed.

9.0 Conclusion/Summary

In conclusion, this thesis sought primarily to determine if CBF and cognition were lower in an upright position in a sample of heart failure patients compared to healthy age- and sex-matched controls. We found CBF_{RICA} decreased to a greater extent in heart failure patients than the controls. We speculate that this reduction is through a Q-dependent mechanism as supine Qi and aCBF were found to be correlated in this population. Furthermore, a low absolute supine Qi was associated with a greater drop in CBF from supine to seated, to a threshold of approximately 3.0-4.0 L/min/m^2. This intermittent cerebral hypoperfusion with upright postures may have important implications in contributing to cognitive impairments and Qi may represent an important predictive factor for abnormal brain changes. Previous studies have found arterial and cardiopulmonary baroreflexes are impaired in heart failure. In spite of a smaller increase in HR when moving upright in the heart failure group, MAP was maintained by increased TPR. Therefore in response to a normal everyday upright stress, the baroreflex appears sufficient in maintaining MAP. In order to assess cognition in different postures in the heart failure group, an auditory n-back test was administered while continuing to monitor cardiovascular and cerebrovascular hemodynamics. We found that posture had no influence on n-back outcomes but that the increase in MFV_{MCA} in response to the cognitive task was lower when upright.

The secondary objectives of this thesis were to include sub-groups of heart failure patients with higher LVEF and atrial fibrillation patients. Within the heart failure sample no significant relationship was found between LVEF and MoCA scores; although a low-moderate inverse relationship suggests that higher LVEF may be associated with lower MoCA scores in a larger sample. Rather than LVEF, resting supine Qi was found to be a better indicator of supine CBF. Taken together these results suggest HFpEF patients to be equally at risk for cognitive

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impairments and that resting supine cerebral hypoperfusion can be better predicted by Qi than LVEF in heart failure. In the patients that had atrial fibrillation and co-existing heart failure we found higher variability in Qi and MCA$_{MFV}$. Importantly, this variability in brain blood flow may contribute to cognitive decline by damaging the small cerebral vessels endothelium. Thromboembolism causing stroke has been primarily attributed for cognitive declines in atrial fibrillation, however, changing cerebral hemodynamics may represent an important alternative pathway.

The results from this thesis add novel insights about upright cerebral hemodynamics in heart failure. Furthermore, we presented evidence for increasing attention to be brought to cerebral hemodynamics and cognition in HFpEF and atrial fibrillation. Unquestionably, this research provides the foundation for future work to be done in this area, which will become increasingly important as the elderly population continues to rise in the coming years.

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Appendix A- Comparison of LVEF and Q

|	Normal ejection fraction	Low ejection fraction[‡]
Normal cardiac output	$n = 24$	$n = 18$
Low cardiac output[†]	$n = 18$	$n = 8$

This table taken from Jefferson (2010) illustrates that low ejection fraction does not always correspond with low cardiac output. Normal cardiac output was defined as ≥4.0 L/min and normal ejection fraction defined as ≥55% (Jefferson, 2010).

Appendix B- NYHA classification

Class	New York Heart Association 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

Table taken from Raphael et al. (2007) showing the NYHA classifications. This system uses four categories to describe the impact of heart failure on daily activities. It is a measure of disease severity related to exercise intolerance and is based on subjective measures made by clinicians and patients (Raphael *et al.*, 2007).

Appendix C- Cerebral Autoregulation
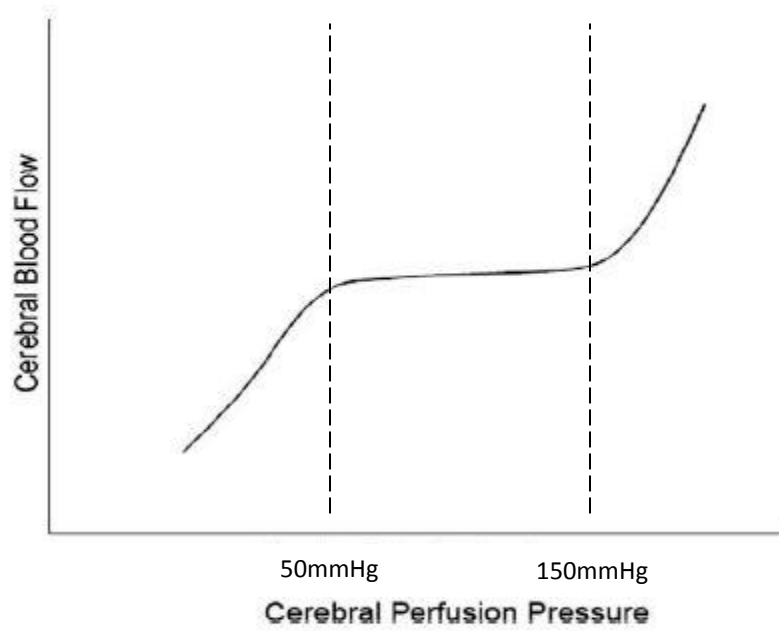
This figure from Bellapart and Fraser (2009) is an illustration of the cerebral autoregulation curve. Beyond the lower (50mmHg) and upper limit (150mmHg) the homeostatic protection is lost and cerebral blood flow changes with cerebral perfusion pressure (Bellapart & Fraser, 2009).

Appendix D- Comparison of LVEF between clinical trial and real-world patients
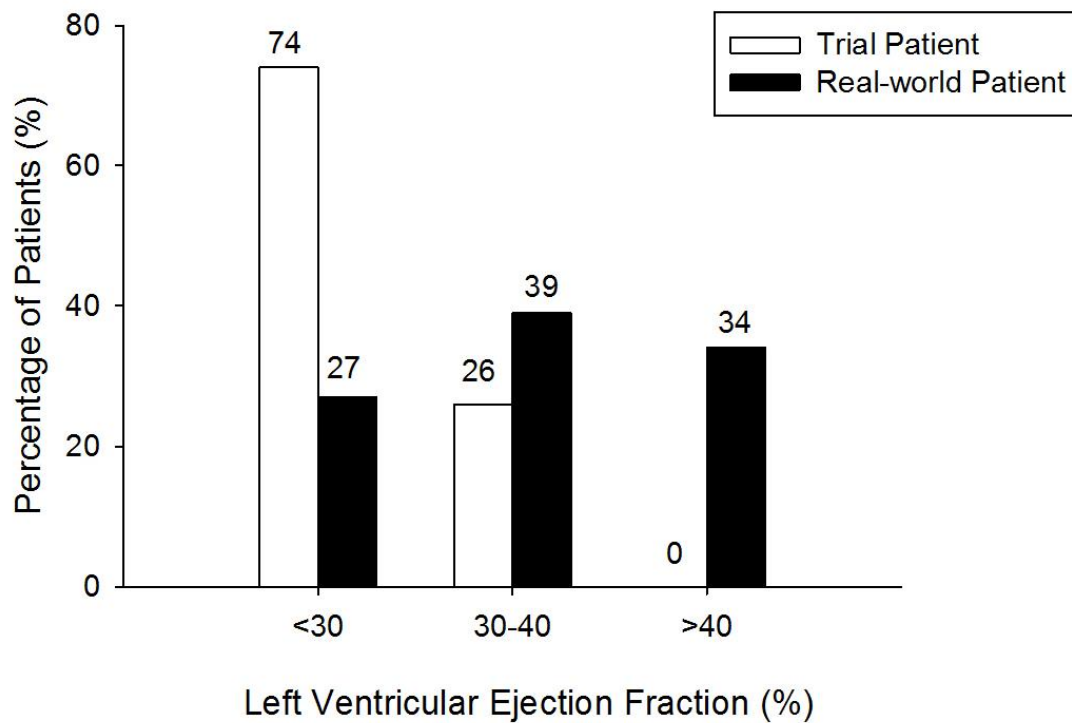
This figure was adapted from Badano and colleagues (Badano *et al.*, 2003). It shows that clinical trial patients tend to have a lower LVEF than those typically seen in clinical practice. Similarly, real world patients from epidemiology studies have a higher ejection fraction than those investigated in clinical trials.

Appendix E- Foreign gas rebreathing technique

A foreign gas rebreathe method using the Innocor device (Innovision A/S, Odense, Denmark) was also used to measure Q. The only requirement of this technique is that the patient be capable of understanding instructions from the operator when performing the breathing maneuver. Until recently, the foreign gas rebreathe method required a mass spectrometer which is expensive, non-portable and complicated for clinical use. The Innocor which uses an infrared photoacoustic gas analyzer has made this technique more clinically accessible by making it portable, less expensive and easier to operate. In a heart failure sample, the foreign gas rebreathe using the Innocor device has been found comparable to gold standard techniques that are invasive and timely such as the Fick and thermodilution methods (Dong *et al.*, 2005; Sobanski *et al.*, 2008). The Innocor measures the relative levels of two inert gases, one blood soluble and one blood insoluble component over approximately 5 respirations or 15 seconds. It is based on the principle that the rate of washout of the blood soluble gas from the alveolar space is proportional to pulmonary blood flow (PBF) which is equal to Q in the absence of a significant intrapulmonary shunt (Innovision, 2013). The insoluble gas is measured to account for the accuracy of mixing between the rebreathing bag and alveolar air and also factors that affect the distribution of the blood soluble gas including the lung volume from which it disappears.

In a seated position, the patient breathed an oxygen enriched mixture containing 0.5% nitrous oxide (N_2O; blood soluble gas) and 0.1% sulfur hexafluoride (SF_6; blood insoluble) into a respiratory valve using a single-use mask with a bacterial filter in a closed circuit system. The mask was adjusted to ensure a proper seal to the face with no leaks. A constant ventilation rate was ensured by having the patient breathe in synchrony to a metronome set at 15 breaths/min. Pulse oximetry was used to detect the presence of significant shunting (arterial oxygen saturation

(SpO_2) > 95%). The patients first practiced by breathing room air from the mask to the metronome for approximately 20-30 seconds to acclimatize to the breathing rate. Once the operator was confident the breathing rate could be maintained, the patients were switched into breathing the gas mixture from the rebreathing bag at the end of expiration. The ventilation volume was held constant by ensuring the patients emptied the rebreathing bag with each breath. The bag was monitored and verbal encouragement was given by the operator to breath deeper if the bag was not being completely emptied. The rebreathe protocol was repeated twice with at least 5 minutes between trials.

The Innocor rebreathing internal software uses the insoluble gas concentration to account for lung volume and incomplete mixing. The first two or three breaths are excluded from the analysis as gas mixing is not completely achieved at this point. The slope of the regression line through logarithmically transformed N_2O end expiration concentrations indicates PBF and thus Q. That is, the steeper the slope, the greater the rate of N_2O disappearance from the alveoli in the lung to the passing blood and the higher the PBF, which is used to indicate Q_{inn}. Height, weight, age and sex were entered into the Innocor and consequently a measure of Qi_{inn} was also provided in the output from the machine. Successful Innocor trials were performed on eleven patients. One person was excluded due to the detection of a pulmonary shunt ($SpO_2 = 92\%$), resulting in ten patients being included in the analysis.

A comparison between Qi values from the Finometer (Qi_Fin) and from the Innocor (Qi_Inn) is included in the figure below. The Finometer tended to overestimate Qi as the mean values from the Finometer and Innocor were 3.2 L/min/m^2 and 2.0L/min/m^2, respectively. The seated Qi_Inn was compared to the estimated seated value from Qi_Fin and no relationship was detected (figure 5.8; r_s=0.39, p=0.243). In this small sample, these results are suggestive of

inaccurate estimates from the Finometer in this population, although it appears a relationship may be detectable with a larger sample size. Further research is needed to make definite conclusions on the accuracy of the Finometer in a heart failure sample
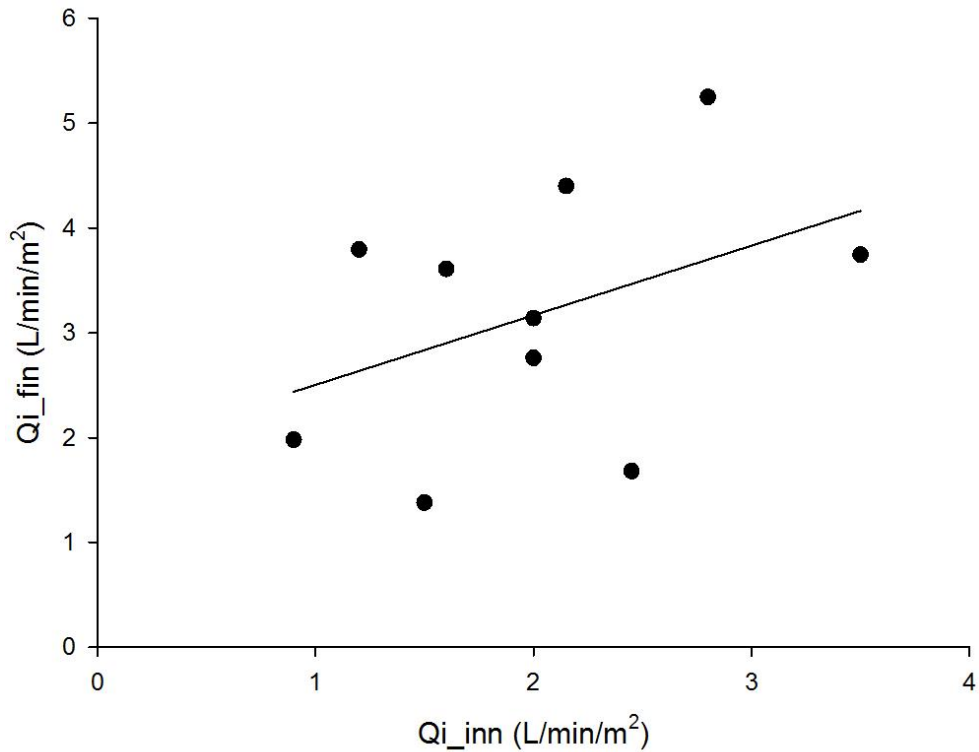
Relationship between seated cardiac index from the Innocor and seated cardiac index from the Finometer
No relationship between seated cardiac index from the Innocor (Qi_Inn) and seated cardiac index from the Finometer (Qi_Fin). p=0.243; r_s= 0.389; n=10

Appendix F- Take home questionnaire

Study ID:_____   Date:_____

1. Your Background

1.   People living in Canada come from many different cultural and racial backgrounds.

Are you? *(Check (√) all that apply)*

□ Aboriginal: □ 1st Nation   □ Inuit   □ Métis

□ White   □ Black   □ Southeast Asian i.e. Vietnamese

□ Filipino   □ Chinese   □ South Asian i.e. East Indian/Pakistan

□ Latin American   □ Other: _____

2. What language did **you** first learn to speak as a child? _____

3. In what languages can **you** conduct a conversation?   _____

4. What is **your** birthplace?   City/Town_____ Province_____

If born outside Canada,   Country _____ years in Canada: _____

5. What is **your mother's** birthplace? City/Town _____ Province_____

If born outside Canada,   Country _____

6. What is **your father's** birthplace?   City/Town_____ Province_____

If born outside Canada,   Country_____

2. Your Marital Status

□ never married

□ married or living with a partner

□ widowed, not currently married

□ divorced, not currently married

□ separated

3. Your Education

1. What are your total years of formal education (includes grades 1 and higher):

_____years

2. What diplomas, certificates or degrees have you obtained?
   (Check (√) all that apply)
   □ None   □ High School

   □ Trade certificate/diploma   □ Community college diploma

   □ University undergraduate degree   □ University graduate degree

4. Your Occupation

1. What kind of work did you do for most of your life?

_____

2. If you did not work for pay, what did your spouse do for most of their life?

_____

3. Are you working for pay now?

If yes,   please check (√):   □ casual

□ part time

□ full time

If no, year last worked _____   or   □ never worked

5. Sleep Hygiene

1. How many hours do you sleep within a **24-hour** period of time? Please exclude time awake overnight but include daytime naps.
    (Check (√) which time most frequently applies to you)
    ___6 hours or less

    ___7 hours

    ___8 hours

    ___9 hours or more

2. Have you had any of the following symptoms within the last **30 days**?

       Sleeping disorders or insomnia   Yes____   No____

       Fatigue and tiredness   Yes____   No____

6. Physical Activity

Physical activity is any form of body movement that requires effort, but does not include routine activities of daily living such as self-care and cooking. Physical activity can be required for work or transportation, or for pleasure.

The **intensity** of physical activity refers to the amount of effort you put into the activity. It can be judged on a 10-point scale, where '0' is sitting and '10' is all out effort, or it can be described in terms of how much you are sweating and breathing. To help us group activities together, we split intensity into 3 categories: **LIGHT, MODERATE** and **HARD.**

LIGHT: 2-4 on a scale from 0-10.

                     No sweating, but faster breathing, e.g. walking.

MODERATE: 5-6 on a scale from 0-10.

                     Some sweating and deeper breathing, but still able to talk comfortably, e.g. brisk walking or biking.

HARD: 7-8 on a scale from 0-10.

                     Heavy sweating and heavy breathing with difficulty talking, e.g. running or swimming.

---

1. This question asks you to list specific activities that you have regularly performed **during the past 4 months**. List any regular activity from gardening to running. Circle the appropriate **Frequency** and **Duration** for each **Activity** you list. **Intensity** might vary within the activity. Please indicate the percentage of time you spend at each **Intensity** for all the **Activities** you list. An example listing has been completed in the first row.

Activity Description	Frequency (# of sessions per week)	Duration (minutes per session)	Intensity (described above)
E.g. Cycling	1-2 (3-4) 5+	up to 20 (20-30) 30-60 60+	Light Moderate Hard 50% 50% 0%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ___% ___% ___%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ___% ___% ___%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ___% ___% ___%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ___% ___% ___%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ___% ___% ___%

2. This question asks you about the amount of regular physical activity you perform. Only consider activities you perform for at least 20 continuous minutes at a time. Please check <u>one box in each intensity category</u> that describes the frequency of your <u>average</u> physical activity habits **<u>during the past year.</u>**

   a) I have engaged in **LIGHT** physical activity:

   □ No days per week

   □ 1 to 4 days per week

   □ At least 5 days per week

   b) I have engaged in **MODERATE** physical activity:

   □ No days per week

   □ 1 or 2 days per week

   □ 3 or 4 days per week

   □ At least 5 days per week

   c) I have engaged in **HARD** physical activity:

   □ No days per week

   □ 1 or 2 days per week

   □ 3 days per week

   □ At least 4 days per week

d) I have engaged in activities to increase **muscle strength**, such as lifting weights:

        □ No days per week

        □ 1 or 2 days per week

        □ 3 days per week

        □ At least 4 days per week

e) I have engaged in activities to improve **flexibility**, such as stretching or yoga:

        □ No days per week

        □ 1 or 2 days per week

        □ 3 days per week

        □ At least 4 days per week

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt
over the <u>past week</u>.

1.	Are you basically satisfied with your life?	yes	no
2.	Have you dropped many of your activities and interests?	yes	no
3.	Do you feel that your life is empty?	yes	no
4.	Do you often get bored?	yes	no
5.	Are you in good spirits most of the time?	yes	no
6.	Are you afraid that something bad is going to happen to you?	yes	no
7.	Do you feel happy most of the time?	yes	no
8.	Do you often feel helpless?	yes	no
9.	Do you prefer to stay at home, rather than going out and doing things?	yes	no
10.	Do you feel that you have more problems with memory than most?	yes	no
11.	Do you think it is wonderful to be alive now?	yes	no
12.	Do you feel worthless the way you are now?	yes	no
13.	Do you feel full of energy?	yes	no
14.	Do you feel that your situation is hopeless?	yes	no
15.	Do you think that most people are better off than you are?	yes	no

Total Score _____

Appendix G: Geriatric Depression Scale Scoring

Instructions: Score 1 point for each bolded answer. A score of 5 or more suggests depression.

1. Are you basically satisfied with your life?   yes   **no**

2. Have you dropped many of your activities and interests?   **yes**   no

3. Do you feel that your life is empty?   **yes**   no

4. Do you often get bored?   **yes**   no

5. Are you in good spirits most of the time?   yes   **no**

6. Are you afraid that something bad is going to happen to you?   **yes**   no

7. Do you feel happy most of the time?   yes   **no**

8. Do you often feel helpless?   **yes**   no

9. Do you prefer to stay at home, rather than going out and doing things?   **yes**   no

10. Do you feel that you have more problems with memory than most?   **yes**   no

11. Do you think it is wonderful to be alive now?   yes   **no**

12. Do you feel worthless the way you are now?   **yes**   no

13. Do you feel full of energy?   yes   **no**

14. Do you feel that your situation is hopeless?   **yes**   no

15. Do you think that most people are better off than you are?   **yes**   no

A score of $\geq$ 5 suggests depression   **Total Score** _____

Ref. Yes average: The use of Rating Depression Series in the Elderly, in Poon (ed.): Clinical Memory Assessment of Older Adults, American Psychological Association, 1986

Appendix H: Self-reported physical activity scoring

a) I have engaged in **LIGHT** physical activity:

    ☐ No days per week ——————————→ **0 points**

    ☐ 1 to 4 days per week ——————→ **1 point**

    ☐ At least 5 days per week ————→ **2 points**

b) I have engaged in **MODERATE** physical activity:

    ☐ No days per week ————————→ **0 points**

    ☐ 1 or 2 days per week ——————→ **2 points**

    ☐ 3 or 4 days per week —————→ **3 points**

    ☐ At least 5 days per week ————→ **5 points**

c) I have engaged in **HARD** physical activity:

    ☐ No days per week ————————→ **0 points**

    ☐ 1 or 2 days per week ————→ **3 points**

    ☐ 3 days per week ————————→ **7 points**
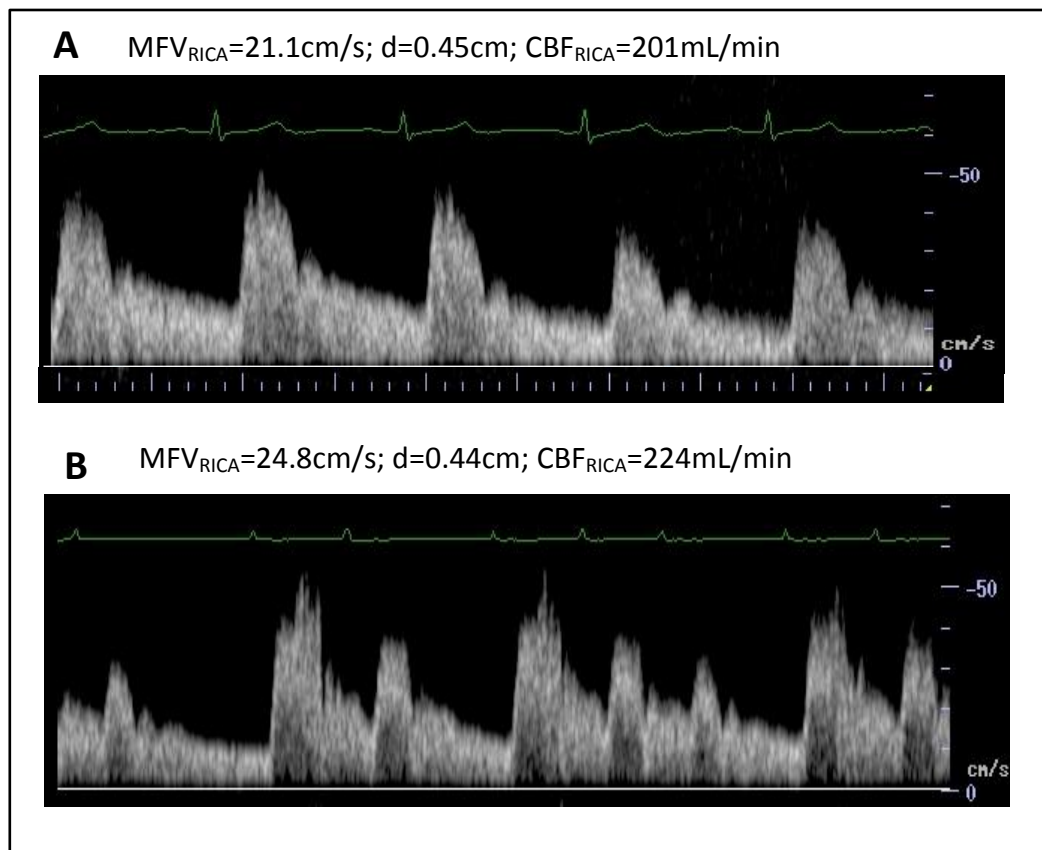
    ☐ At least 4 days per week ————→ **9 points**

Sedentary	0-2 points
Active Lifestyle	3-6 points
Highly Active	>7 points

Appendix I: Cerebral Blood Flow and Cardiac Output
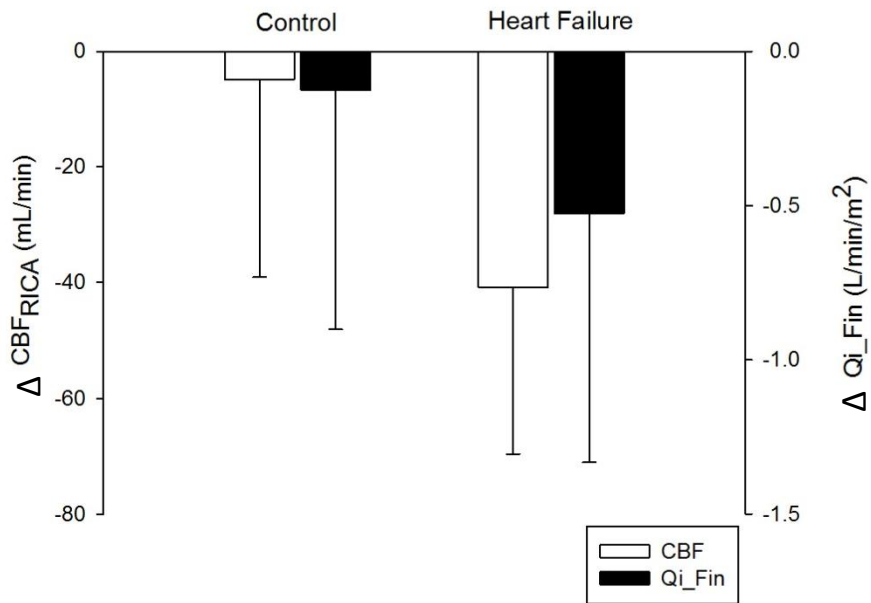
Change in cerebral blood flow in the right internal carotid artery (CBF$_{RICA}$) and cardiac index (Qi) from supine to seated for healthy control and heart failure groups. Graphical representation of mean and standard deviation. Heart failure group appears to have a larger drop in CBF and Qi from supine to seated; although the large variation is noted.

Appendix J: CBF in heart failure and heart failure with co-existing atrial fibrillation

A $MFV_{RICA}=21.1cm/s$; $d=0.45cm$; $CBF_{RICA}=201mL/min$

B $MFV_{RICA}=24.8cm/s$; $d=0.44cm$; $CBF_{RICA}=224mL/min$

The heart failure patient (A) was female, 81 years old and had a left ventricular ejection fraction defined as <40%. The heart failure patient with atrial fibrillation (B) was female, 82 years old and had a left ventricular ejection fraction defined as 55%. This figure illustrates the high variability in the velocity when atrial fibrillation is present. CBF_{RICA} in these particular patients was comparable.