

**Cerebral Autoregulatory Response to Postural Changes and Walking in Older  
Adults with Heart Failure**

by

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### **Author's Declaration**

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

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

## **Statement of Contributions**

I clarify that the data for my thesis were collected in unison with another master's student, Kevin Murray. While shared data are acknowledged throughout this thesis by "(Murray, see Declaration)", unique variables from the data set were calculated independently for the purpose of hypotheses included in this thesis.

I hereby declare that I am the sole author of this thesis.

## **Abstract**

Individuals with heart failure (HF) have reduced cerebral blood flow (CBF) compared to age-matched older adults. This might be related to an impairment in cerebral autoregulation (CA), or an impairment in the CA mechanisms to respond. Previous research has shown impairment in dynamic CA in HF at rest, and during isometric exercise however, the cerebrovascular response to real world conditions, such as transition to upright posture and walking, remains unknown. We recruited 10 individuals with HF and 13 age-matched controls to investigate the effects of posture transitions and walking on the dynamic regulation of CBF in individuals with HF. On a plot of mean flow velocity and mean arterial pressure, we found static CA to be potentially impaired in individuals with HF compared to age-matched controls, when challenged by ambulatory stressors. A potential explanation for the difference observed between groups could be ascribed to lower cardiac output, leading to potential changes in the CA curve, coupled with a greater difference in the CBF response to fluctuations in carbon dioxide throughout standing and walking. Understanding cerebral hypoperfusion and changes in CA may help explain perceptions of fatigue during exertion and elevated rates of cognitive impairment seen in patients with HF. It is equally important to investigate the cerebrovascular effects of exercise training and therapy in the setting of HF therefore, introducing techniques for the assessment of CA into clinical practice should be seen as a priority.

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## List of Acronyms

**A $\beta$** : amyloid-beta  
**AD**: Alzheimer's Disease  
**ADL**: activities of daily living  
**ARI**: autoregulation index  
**ATP**: adenosine triphosphate  
**BP**: blood pressure  
**BP<sub>MCA</sub>**: middle cerebral artery blood pressure  
**CA**: cerebral autoregulation  
**CBF**: cerebral blood flow  
**CBFV**: cerebral blood flow velocity  
**CCA**: common carotid artery  
**CO**: cardiac output  
**CO<sub>2</sub>**: carbon dioxide  
**CPP**: cerebral perfusion pressure  
**CrCP**: critical closing pressure  
**CVD**: cardiovascular disease  
**CVR**: cerebrovascular resistance  
**CVRI**: cerebrovascular resistance index  
**DBP**: diastolic blood pressure  
**DFV**: diastolic flow velocity  
**ECG**: electrocardiogram  
**EF**: ejection fraction  
**EOV**: exercise oscillatory ventilation  
**HF**: heart failure  
**HFmEF**: heart failure with mid ejection fraction  
**HFpEF**: heart failure with preserved ejection fraction  
**HFrEF**: heart failure with reduced ejection fraction  
**HR**: heart rate  
**LV**: left ventricle  
**LVEF**: left ventricular ejection fraction  
**MAP**: mean arterial pressure  
**MCA**: middle cerebral artery  
**MCI**: mild cognitive impairment  
**MFV**: mean flow velocity  
**NO**: nitric oxide  
**NYHA**: New York Heart Association  
**O<sub>2</sub>**: oxygen  
**OH**: orthostatic hypotension  
**Paco<sub>2</sub>**: partial pressure of carbon dioxide  
**PP**: pulse pressure  
**PI**: pulsatility index  
**RAAS**: renin-angiotensin-aldosterone system  
**RI**: resistance index  
**SBP**: systolic blood pressure

**SFV:** systolic flow velocity  
**SV:** stroke volume  
**TCD:** transcranial Doppler  
**TPR:** total peripheral resistance  
**US:** ultrasound  
**WMH:** white matter hyperintensities

## **1.0 Literature Review**

### **1.1 Preamble**

The proportion of adults aged 65 years and older is increasing worldwide. The aging demographic is attributed to increased longevity of the older adult population. Globally, it is estimated that >37.7 million people worldwide are affected by heart failure (HF) (Ziaecian & Fonarow, 2016), a number that is expected to rise due to improved HF management and increased longevity (Ambrosy et al., 2014; Stewart, MacIntyre, Capewell, & McMurray, 2003). In general, HF is characterized by low cardiac output (CO) that is unable to meet the demands of the body (Kemp & Conte, 2012) , as a result of pathological remodelling to cardiac tissue.

Although there are many physiological consequences associated with this cardiac pathology, previous work has found cerebral blood flow (CBF) is lower in supine baseline in patients with HF, and the reduction in CBF on moving to the upright posture is greater in patients with HF, compared to healthy-matched controls (Fraser et al., 2015). These findings suggest a direct link between HF and cerebral ischemia, due to the inability to effectively regulate CBF and perfusion to the brain. The inability of these patients to maintain adequate blood flow to the brain suggests the impairment of cerebral autoregulation (CA), or the impairment in the capability of cerebral autoregulatory mechanisms to respond. Previous research has shown dynamic CA is impaired in patients with HF at rest (Caldas et al., 2017), and during isometric exercise (Caldas et al., 2018); however, the cerebrovascular hemodynamic alterations in response to orthostatic stress within the HF population is unknown. The purpose of this thesis is to investigate the effects of posture transitions and walking on the dynamic regulation of CBF in individuals with HF.

### **1.2 Epidemiology of Heart Failure**

The rising global epidemic of heart failure (HF) is a major clinical and public health issue. HF is a chronic phase of functional cardiac impairment secondary to many aetiologies, and presents with numerous signs and symptoms including fatigue, dyspnoea, fluid retention, and poor exercise tolerance (Ziaieian & Fonarow, 2016). Symptom severity is systematically organized by the New York Heart Association (NYHA) Classification system. This system documents functional cardiac status and places patients in groups I through IV based upon their symptoms and physical limitations as a result of their HF (Kemp & Conte, 2012). HF is associated with reduced quality of life, reduced longevity, and a significant burden by way of health care expenditures. The costs associated with this syndrome include long-term pharmacological treatment and frequent hospitalizations, particularly among those aged 65 and older (Roger, 2013).

There are several risk factors that impact the HF cascade however, multiple risk factors may co-exist and interact with each other, making the disease both complex and multifactorial. Despite advances in the control of cardiovascular disease (CVD), the incidence and prevalence of HF continues to increase with advancing age (McCullough et al., 2002). Results from the Global Burden of Disease Study indicate that the number of deaths attributed to CVD in 2013 reached a staggering high of 17.3 million, an increase of 41% since 1990 (Collaborators, 2015). The number of hospitalizations for HF in the United States has tripled since 1979 to reach 3.86 million in 2004 (Fang, Mensah, Croft, & Keenan, 2008), signifying a substantial economic burden to the health-care system. These increases are driven largely by the aging of the population (Stewart, MacIntyre, Capewell, & McMurray, 2003), with a lifetime risk for developing HF of approximately 20% between the ages of 40 and 80 years old (Lloyd-Jones et al., 2002). Detraining associated with obesity, is increasingly becoming recognized as an

independent risk factor for HF as the excess weight has been associated with negative effects on cardiac structure and ventricular function (Oga & Eseyin, 2016).

Many cardiovascular conditions, such as arrhythmias and valvular heart disease, may ultimately progress to the development of HF as a consequence of their pathophysiology (Ramani, Uber, & Mehra, 2010). More than one-third of patients will develop HF after a myocardial infarction (MI) (Hellermann et al., 2003), making ischemic heart disease a primary risk factor in the development of HF (Loehr, Rosamond, Chang, Folsom, & Chambless, 2008). Arterial hypertension plays a key role in the evolution of CVD, predisposing to acute MI (Pedrinelli et al., 2012) and increasing the risk of HF by 2- to 3-fold (Vasan & Levy, 1996). Although the risk of HF associated with hypertension is less than that associated with MI, hypertension has a higher contribution to the burden of HF because of its greater prevalence (Mosterd & Hoes, 2007). Data from the Framingham Heart Study found that hypertension antedated 91% of new HF cases (Levy, Larson, Vasan, & Kannel, 1996). This cohort revealed the median blood pressure (BP) for patients who developed HF was 150/90 mmHg, emphasizing that even moderate uncontrolled hypertension can significantly contribute to the development of HF (Levy et al., 1996). High blood pressure is easily diagnosed and treated, therefore, preventative strategies directed toward earlier and more aggressive BP control are likely to offer the greatest effect in reducing the incidence of HF and its associated mortality (Levy et al., 1996). Physical activity and regular exercise are emphasized for promoting general cardiovascular health (Eckel et al., 2014) however, recent evidence suggests they are associated with reduced incidence of HF and slower disease progression (Nayor & Vasan, 2015). Training induces a variety of important positive changes to the cardiac muscle including increases in myocardial function (Sullivan, Higginbotham, & Cobb, 1988), exercise time, stroke volume, as



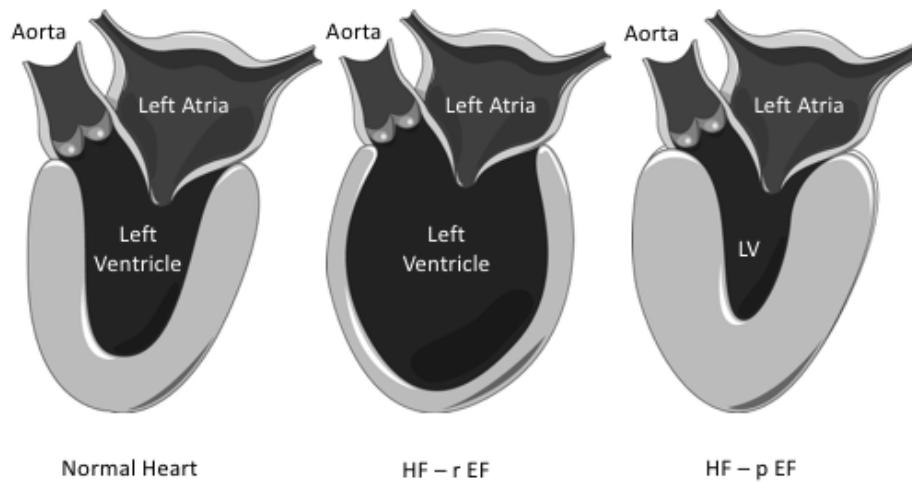
well as reduces cardiac hypertrophy (Hambrecht et al., 2000). Exercise training in individuals with HF serves as a potential cost-effective form of HF therapy and increases overall quality of life in patients suffering from a failing heart (reviewed in Pedersen & Saltin, 2015). While a number of risk factors including age, obesity, cardiac and vascular abnormalities, among others, have been associated with increased risk of HF, there have been modest improvements in HF survival reported over the past decades (Roger et al., 2004).

### *1.2.2 One Disease or Many?*

Traditionally, HF was seen as the inability of the heart to provide sufficient blood flow to meet metabolic requirements during systole (i.e., left ventricular systolic function) (Mosterd & Hoes, 2007). Systolic function is defined as the measurement of the beat-to-beat proportion of blood ejected out of the left ventricle (LV) relative to total ventricular volume, also known as left ventricular ejection fraction (LVEF). While HF is typically classified by LVEF (Alagiakrishnan et al., 2013), different thresholds for EF have been recommended (Roger, 2013): a LVEF of  $\leq 40\%$  by transthoracic echocardiogram indicates impaired left ventricular systolic function (Mosterd & Hoes, 2007) or, “systolic” HF. Systolic HF is clinically associated with left ventricular failure due to poor LV contraction and cardiac insufficiency, with an average annual mortality rate of approximately 19% (Vasan et al., 1999).

Heart failure can also occur in patients with normal left ventricular systolic function. Originally referred to as ‘diastolic’ HF (Mosterd & Hoes, 2007), these patients present with a LVEF of  $>40\%$  and instead have impairments in the filling characteristics of the LV. Historically, as the physiology of diastolic HF developed, it was discovered that diastolic dysfunction was not unique to diastolic HF, but also present in systolic HF (Borlaug & Paulus, 2011). As depicted in Figure 1.1, the current terminology classifies HF as either HF with reduced

ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) as a better reflection of the pathophysiology behind the disease. While it has not been established whether these terms represent different forms of HF or exist as part of one ‘HF spectrum’, distinct patterns of ventricular and myocellular remodeling coupled with differences in evidence-based therapies for HF, would suggest they are significantly different disease processes (Nadruz et al., 2016). However, it should be noted that a diagnosis of mid-range LVEF was proposed to clinicians in 2016 supporting the ‘HF spectrum’ (Andronic, Mihaila, & Cinteza, 2016).



**Figure 1.1** Schematic representation of HFrEF and HFpEF. Modified from: <http://smart.servier.com/>

### 1.3 Pathophysiology of Heart Failure

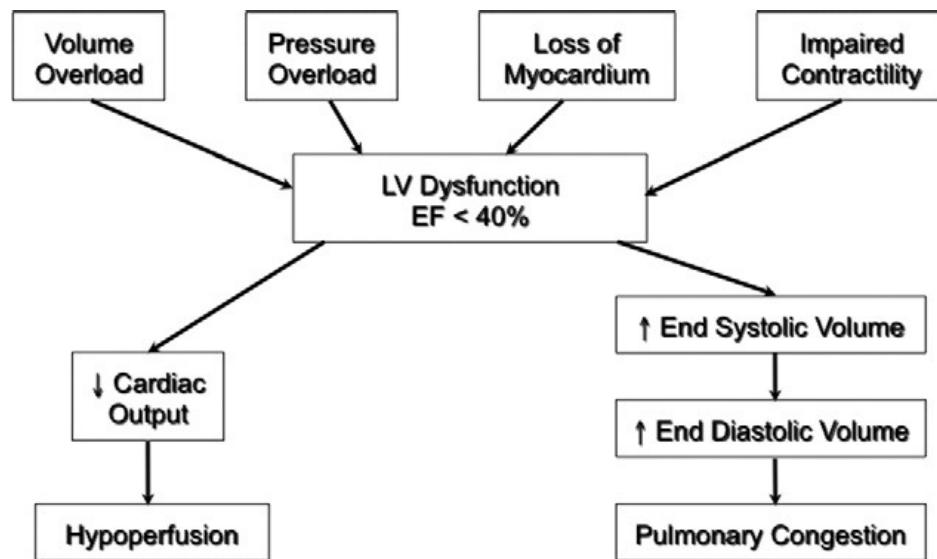
#### 1.3.1 Systolic Dysfunction

LV systolic dysfunction is defined as a LVEF of <40%, or HFrEF. The root problem underlying HFrEF is the inability of the LV to actively eject blood into the systemic circulation. A common cause of LV systolic dysfunction is loss of functional myocardium due to ischemic heart disease and MI. Infarcted tissue does not contribute to the generation of mechanical activity so overall, cardiac performance is decreased. Excessive pressure overload caused by arterial

hypertension is another major factor (Kemp & Conte, 2012), however, the predominant mechanism of reduced LVEF is through concentric remodeling of the cardiac muscle, leading to reduced contractility and ultimately, a reduction in stroke volume (SV) and cardiac output (CO) (Borlaug & Redfield, 2011). SV is defined as the amount of blood ejected by the ventricle per heartbeat, while CO refers to the amount of blood pumped by the heart over a given period of time. CO is the product of heart rate (HR) and SV and is typically 4-8 L/min in normal physiological function. In HF, values are reported as low as <4 L/min at rest (Jefferson, Poppas, Paul, & Cohen, 2007), leading to activity and exercise limitations as a consequence of the cardiac pathology. The Frank-Starling mechanism plays an important compensatory role in response to reduced SV in an attempt to attenuate the fall in CO and preserve sufficient blood flow to vital organs. This reduction in SV leads to an increase in both end-systolic and end-diastolic volumes. Initially, this increase leads to ventricular stretch and induces a greater SV with the next contraction, preserving CO (Delicce & Makaryus, 2018). However, there are limited benefits of the Frank-Starling mechanism in HFrEF. In turn, the elevated ventricular volumes cause an increase of pressure in the pulmonary circulation and right atria. As cardiac insufficiency develops, this increased pressure leads to pulmonary congestion and elevated jugular venous pressure, both independently associated with progression of HF (Damy et al., 2011; Drazner, Rame, Phil, Stevenson, & Dries, 2001). HR will also increase in attempt to rescue CO, resulting in a faster and weaker contraction of the myocardium that can ultimately lead to an impaired heart rate response to stress.

There are substantial changes in the geometry of the LV that contribute to reduced LVEF. Ventricular wall thickness may decrease or remain unchanged. Pathological remodelling of the LV causes misalignment of the papillary muscles and mitral valve leaflets (Chatterjee, 2012),

augmenting chronic volume overload and decreased mechanical efficiency. The decreased wall thickness together with increased volume is associated with increased ventricular wall stress. Cardiac hypertrophy occurs in response to increased wall stress in patients with HFrEF. An inverse relationship exists between wall stress and EF, as prolonged stress-induced hypertrophy can lead to ventricular failure and further contribute to reduced LVEF (Chatterjee, 2012). The complex physiological mechanisms that result in reduced CO in the setting of LV systolic dysfunction are summarized in Figure 1.2.



**Figure 1.2** Summary of LV systolic dysfunction.  
Figure from: (Kemp & Conte, 2012)

### 1.3.2 Diastolic Dysfunction

In contrast, HFpEF is characterized as HF in the presence of diastolic LV dysfunction with normal LV systolic function and thus, normal EF (Borlaug & Paulus, 2011). HFpEF is characterized by prolonged isovolumetric LV relaxation and increased diastolic stiffness (Borlaug & Paulus, 2011). The alterations in cardiac stiffness increases LV hypertrophy and shifts toward a reliance of atrial filling of the ventricle. Restricted filling leads to increased

ventricular diastolic pressure required to obtain normal end-diastolic volume (Chatterjee, 2012). In the setting of HFpEF, increased LV wall thickness is the predominant mechanism underlying normal LVEF. The LV cavity size is reduced due to concentric cardiac remodeling resulting in decreased CO, despite normal LVEF. Chronic volume overload, pulmonary congestion, and impaired heart rate response have also been identified as casual or contributing factors to the development of this HF subtype (Bench et al., 2009). Many clinical investigations to date have excluded HFpEF, resulting in large gaps in knowledge in this subset of the population. An additional goal of this thesis is therefore to include patients with HFpEF and aid in understanding the consequences of this cardiac pathology.

## **1.4 Direct Effects of Reduced Cardiac Output**

### *1.4.1 Neurohormonal Activation*

The signs, symptoms, hemodynamics, and outcomes may be identical or similar between the forms of HF, as reduced CO is the central issue. In the face of lowered CO, neurohormonal activation serves to increase total peripheral resistance (TPR) using several mechanisms in order to obtain normal mean arterial pressure (MAP) (as  $MAP = CO * TPR$ ) (Kemp & Conte, 2012). This includes activation of the renin-angiotensin-aldosterone system (RAAS) to increase sodium retention and thirst in an effort to maximize SV and MAP. The detrimental sustained activation of RAAS will eventually promote excessive vasoconstriction and cardiac hypertrophy, leading to central artery stiffening (Ma, Kam, Yan, & Lam, 2010). Central arteries become stiff as a consequence of aging however, this arterial property is accelerated by hypertension, which may ultimately alter hemodynamic pulsatility. The pulsatile energy that occurs when transitioning from a low impedance vessel (like the aorta) to downstream vessels is naturally reflected. As

central arteries become stiff, the reflected wave instead arrives earlier in the cardiac cycle, increasing pressure in the peripheral arteries during systole (instead of diastole), ultimately increasing pulse pressure and pressure amplification into the peripheral organs (Mitchell et al., 2011). While not unique to HF but present colinearly with the advanced age of patients with HF, these high pulsatile flow patterns can damage the microvascular bed of the cerebrum (Mitchell et al., 2001), which may give rise to both cerebrovascular remodeling and endothelial dysfunction, as well as increases in cerebrovascular resistance (CVR) and reductions in cerebral blood flow (CBF) (Tarumi et al., 2014), also observed in HF populations.

#### *1.4.2 Global Hypoperfusion*

A major consequence of reduced CO is the development of global hypoperfusion. Reduced cardiac efficiency in the setting of HF leads to a decreased outflow of blood from the heart resulting in a decline of perfusion to the rest of the body (Alosco & Hayes, 2015), clinically manifesting as end-organ dysfunction or damage. For example, despite the high-flow, low-resistance hemodynamic nature of the kidneys, renal dysfunction is frequently observed in patients with HF due to decreased renal perfusion (Damman et al., 2007). The literature also recognizes HF as a factor that may cause perfusion of the brain to drop below a critical threshold of oxygen and glucose delivery (De la Torre, 2000), increasing the risk cognitive impairment and Alzheimer's Disease (AD). Global reductions of CBF in the setting of HF has been reported as high as 30% (Gruhn et al., 2001). These periods of low flow can contribute to microvascular cerebral ischemia (Mitchell et al., 2011), which may ultimately manifest as "white matter hyperintensities" (WMH) and small focal brain infarcts (Mitchell et al., 2011). In 2013, Alosco and colleagues found an association between cerebral hypoperfusion in patients with HF, and greater WMH on magnetic resonance imaging of the brain (Alosco et al., 2013). This research

extends the reports of increased total and regional brain atrophy in patients with HF concluded by various neuroimaging studies (Almeida et al., 2012; Vogels et al., 2007). These neurological abnormalities have been suggested to be responsible for the burden of cognitive impairment diagnosed in 25-75% of patients with HF (Ampadu & Morley, 2015), colinear with HF progression (Harkness, Demers, Heckman, & McKelvie, 2011).

### **1.5 Activities of Daily Living & Exercise in Heart Failure**

The simple task of transitioning from supine rest to standing upright, to activities of daily living (ADL) and participating in regular exercise present as major challenges for patients with HF. In normal physiological function, the act of standing leads to a transient decrease in CBF and arterial BP that rapidly return to normal due to baroreflex-mediated cardioacceleration and vasoconstriction to increase TPR and maintain MAP. However, in older adults (Lipsitz, 1989), and frequently present concomitantly with HF (Gorelik, Feldman, & Cohen, 2016), is the inability to compensate for the excessive physiological challenge, resulting in reduced CBF (Fraser et al., 2015) and orthostatic hypotension (OH) in the upright posture. This thesis will be the first to examine the cerebral hemodynamic response upon transition to upright posture and walking in individuals with heart failure.

Exercise limitation is a hallmark of HF with complex cardiac and noncardiac mechanisms at play. Traditionally, it was thought that CBF, even in patients with severe HF, remained normal because of blood flow redistribution from splanchnic, renal, cutaneous, and skeletal muscle vascular beds (Zelis, Sinoway, Musch, Davis, & Just, 1988). There is accumulating evidence however, that suggests CBF, estimated by transcranial Doppler ultrasonography (Vogels et al., 2008), is reduced in patients with both mild and severe forms of HF. Exercise intolerance in

patients with HF was traditionally perceived as a direct consequence of insufficient CO to supply blood flow to the exercising muscles. Recent evidence however, suggests that reduced CBF induced by HF, likely represents a limiting factor in exercise tolerance in these patients (Fu et al., 2011). While the mechanisms involved in CBF reduction in HF remain unclear, they may be related to reduced CO or vasoconstriction of the cerebral vasculature induced by higher brain sympathetic nervous activity and increased RAAS (Francis, 1989; Packer, 1992). Furthermore, common comorbidities in patients with HF such as atrial fibrillation, hypertension, and obesity have been associated with reductions in cerebral perfusion (Alosco et al., 2015; Birdsill et al., 2013; Fujishima, Ibayashi, Fujii, & Mori, 1995), which in turn, could worsen the already compromised regulation of CBF in the setting of HF.

There is important research explaining the difficulty experienced with positional changes and reduced exercise tolerance in patients with HF, beyond that of impaired central and cerebral hemodynamics. Abnormalities in vascular endothelial function are responsible for the imbalance of BP regulation in advanced HF, due to the inability of the vasculature to physiologically respond to alterations in CO during ADL and exercise (Chung & Schulze, 2011). Mitochondrial oxidative capacity is impaired in HF due to decreased oxidative enzyme activity, mitochondrial volume, and capillary density (Chung & Schulze, 2011; Drexler et al., 1992), which correlates with decreased maximal oxygen consumption and total exercise time (Duscha et al., 1999). Elevated pulmonary pressure, deranged pulmonary mechanics, and patient deconditioning have been proposed as potential mechanisms underlying cardiorespiratory dysregulation seen in patients with HF (Abudiab et al., 2013; Chung & Schulze, 2011) however, exertional capacity is predominately constrained by abnormalities in cardiac function (Paulus, 2010). Under conditions of a failing heart, the cardiac muscle cannot easily respond to increases in physiological demand



as its resources are already stretched enough at rest. Patients with both HFrEF and HFpEF have a lower HR reserve and maximal HR, a higher HR at rest (Lele et al., 1996) and attenuated SV during exercise (Sullivan, Knight, Higginbotham, & Cobb, 1989) on account of limited LV end-diastolic reserve (Chattopadhyay et al., 2010). Accordingly, CO is decreased during exercise which may contribute to lowered CBF during exercise and ultimately contribute to reduced functional capacity (Fu et al., 2011).

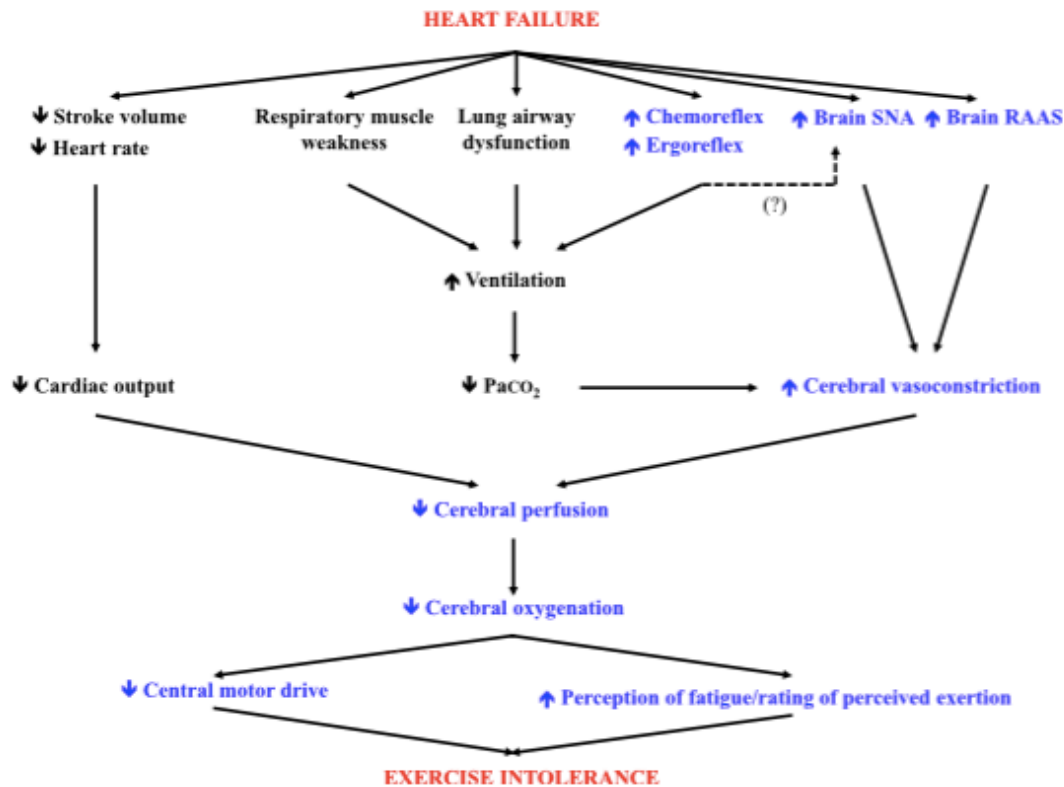
### *1.5.1 The Regulation of PaCO<sub>2</sub> During Exercise*

Patients with HF have increases in minute ventilation during exercise, disproportionate to the increase in CO<sub>2</sub> production (Sullivan et al., 1988), directly affecting cerebral perfusion through the reduction in arterial PCO<sub>2</sub>, and further contributing to cardiorespiratory dysregulation (Ponikowski et al., 2001). Instability of respiratory control can be recognized in both HFrEF and HFpEF, and clinically manifests as exercise oscillatory ventilation (EOV) (Dhakal & Lewis, 2016). EOV, detected by cardiopulmonary exercise testing, is characterized by periods of hyperpnea and hypopnea without interposed apnea (Olson, Arruda-olson, & Somers, 2009), which distinguishes it from other forms of periodic breathing observed in HF including Cheyne-Stokes respiration (Lorenzi-Filho, Genta, Figueiredo, & Inoue, 2005). Exaggerated ventilatory responses to exercise ( $V_E/V_{CO_2}$  slope) where  $V_E$  is minute ventilation and  $V_{CO_2}$  is carbon dioxide output, is also present in patients with HF (Malhotra, Bakken, & Lewis, 2016). Ventilatory efficiency and stability reflect HF severity, with a  $V_E/V_{CO_2}$  slope in excess of 34, and the presence of EOV, both consistently indicating 1-year mortality rates of  $\geq 20\%$  (Malhotra et al., 2016). Of note, in response to maximal graded exercise, one study found the  $V_E/V_{CO_2}$  slope in individuals with systolic HF to be significantly higher compared to individuals with diastolic HF ( $37 \pm 8$  vs.  $34 \pm 7$   $P=0.03$ ) and between healthy age-matched controls ( $37 \pm 8$  vs.  $32 \pm 5$

$P=0.02$ ) (Moore, Brubaker, Stewart, Kitzman, & Carolina, 2007). In this study, no differences were observed between DHF and control participants.

An increased  $V_E/V_{CO_2}$  slope in HF may be the result of respiratory muscle weakness (Brassard & Gustafsson, 2016). The respiratory muscle pump is composed of skeletal muscles, where the strength of the muscles directly influences the strength of the pump. Reduced inspiratory and expiratory muscle strength has been found to correlate with dyspnea in response to daily activities in individuals with HF (McParland, Krishnan, Wanga, & Gallagher, 1992), and therefore, may reflect increased pulmonary congestion in these patients. Cardiac and noncardiac alterations in HF that may contribute to reduced exercise capacity are summarized in Figure 1.3.

While seated upright posture is associated with small reductions of CBF in patients with HF (Fraser et al., 2015), upright posture with walking might activate an important defense, the skeletal muscle pump. The skeletal muscle pump acts to increase venous return and CO, to ultimately protect from a drop in pressure (Van Lieshout, Pott, Madsen, Van Goudoever, & Secher, 2001) and subsequent CBF. This study will be the first to examine CBF during a transition to standing and a transition to walking in patients with HF.



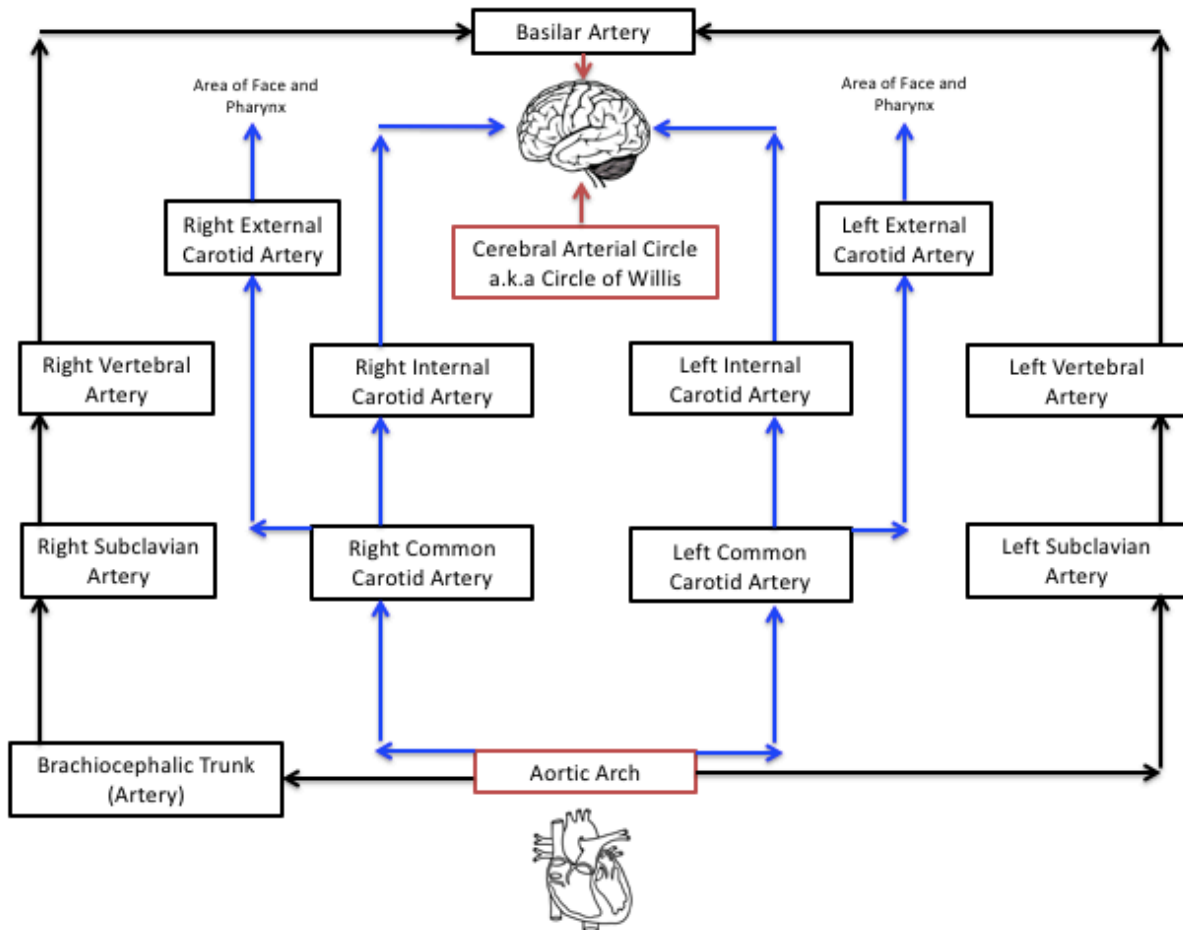
**Figure 1.3** Brain alterations in heart failure might reduce exercise tolerance. System input (heart failure) and output (exercise tolerance) are shown in red, and factors within or directly affecting the nervous system are shown in blue.

Figure from: (Brassard & Gustafsson, 2016)

## 1.6 Cerebral Hemodynamics

There is a close link between the heart and the brain to maintain a homeostatic balance between oxygen demand and delivery. Inherent to understanding perfusion of the brain is the understanding of the vast metabolic requirement of the organ. Normal function of the brain is obtained exclusively through aerobic metabolism. As such, this organ, which represents approximately 2% of total body weight, requires approximately 20% of resting oxygen consumption, making the brain especially vulnerable to interruption of oxygen, substrate delivery, and regulation of blood flow (Greene & Lee, 2012). In order to understand the compromised cerebral circulation in patients with HF, knowledge of normal cerebral

hemodynamics must first be acknowledged. The brain is a high-flow, low-resistance organ that relies on a constant supply of nutrients, despite any comorbid medical or clinical conditions (i.e. HF, hypertension, hypotension, exercise, bleeds etc.). In its most simple terms, arterial blood can travel to the brain through 2 basic pathways, described in Figure 1.4.



**Figure 1.4** Schematic representation of arterial blood flow from the heart to the cerebral arterial circle; often referred to as the Circle of Willis. The pathway through the right and left vertebral arteries, which combine to form the basilar artery, are shown in black. The pathway through the right and left internal carotid arteries are shown in blue.

The Circle of Willis is a circulatory network of collateral vessels that supplies blood to the brain and surrounding structures through the interconnections between branches of the internal carotid arteries and vertebrobasilar system (Greene & Lee, 2012). The circle is formed

by the anterior and posterior communicating artery that respectively connect the internal carotid system (between the anterior cerebral arteries), and the vertebrobasilar system (between the middle cerebral arteries (MCA) and posterior cerebral arteries) (Greene & Lee, 2012).

In a normal physiological state, CBF is regarded as being remarkably sustained at ~ 50 mL per 100 g of brain tissue per minute, provided that cerebral perfusion pressure (CPP) is in the range of ~ 60 to 160 mmHg (Paulson, Strandgaard, & Edvinsson, 1990), and arterial PCO<sub>2</sub> is constant (Battisti-Charbonney, Fisher, & Duffin, 2011). CPP represents the pressure gradient driving CBF and is defined as the difference between intra-arterial pressure and either venous pressure or intracranial pressure, whichever is greater, although both are challenging to measure (Cipolla, 2009). Brain blood flow can be represented with the assumption that flow is laminar and proportional to the difference in inflow and outflow pressures (CPP), divided by the resistance to flow (R) (Paulson et al., 1990):  $CBF = CPP/R$ . The hemodynamic determinants of average blood flow through an organ are typically understood through Poiseuille's law  $Q = \frac{\pi Pr^4}{8\eta l}$  which states that the flow (Q) of fluid is related to the pressure gradient across the tubing (P), the diameter (r) and length (l) of the tubing, and the viscosity (η) of the fluid, where even a small change in lumen diameter will have a significant effect on blood flow through the vessel. The flow of blood can also be understood by the hemodynamic equivalent of Ohm's law, known as Darcy's law:  $Q = \frac{\Delta P}{R}$  (Tzeng & Ainslie, 2014) where in the context of the brain, ΔP is the cerebral perfusion calculated from the difference between MAP and the effective downstream pressure of the cerebral circulation, and R is the cerebrovascular resistance. Given the exponential relationship between vessel radius and CBF, factors which influence the size of cerebral vessels are key to regulating flow within an acceptable range.

## 1.7 Cerebral Autoregulation

Although the study of HF is primarily concerned with function and therapies of the LV, there are important secondary considerations for high-flow organs such as the brain, and thus, cerebrovascular function. Autoregulation indicates the intrinsic ability of a vascular bed or organ to maintain relatively constant perfusion, despite fluctuations in MAP (Xiong et al., 2017). The brain's ability to regulate its own CBF over a range of MAP is well-described and serves as a protective mechanism referred to as cerebrovascular autoregulation (CA) (Aaslid, Lindegaard, Sorteberg, & Nornes, 1989). CA maintains relatively constant CBF however, the limits of CA are not entirely fixed and can be impacted by factors that either increase or decrease CBF (Paulson et al., 1990).

The definition of CA has been dichotomized as either “static”, or, “dynamic” (Cipolla, 2009). Static CA refers to the mean CBF changes relative to MAP fluctuations over the course of minutes or longer, in response to orthostatic stress (Xiong et al., 2017) and is a measure of the overall efficiency of the system. Dynamic CA reflects the transient response of CBF to rapid changes in BP (Caldas et al., 2017). Both definitions of CA are characterized by the relationship between mean flow and pressure, averaged across one or more cardiac cycles (Robertson, Edgell, & Hughson, 2014). Notably, quantitative assessment of CA is challenged by the methods used for measurement of CBF. While a gold standard for measuring CBF is not currently defined (Cipolla, 2009), the advent of high frequency, transcranial Doppler ultrasound (TCD), has made it possible to sample flow velocity in large cerebral vessels; cerebral blood flow velocity (CBFV) of the MCA is most commonly reported (Fantini, Sassaroli, Tgavalekos, & Kornbluth, 2016), and permits derivative calculations of standard resistivity (RI) and pulsatility (PI) indices (Greene, Yonan, Sharrar, Sibbitt, & Roldan, 2012). RI and PI correlate with physiologic factors

of cerebral hemispheric arterial tone, blood flow resistances, and impedances, all of which determine cerebral perfusion and thus, participate in the regulation of blood flow (Greene et al., 2012). Since TCD measures flow velocity, and not absolute values of CBF derived from simultaneous measurement of arterial diameters, only assessment of changes in flow can be made. Previous research has indicated that CBFV of the MCA is in fact a reliable and valid index of CBF (Kirkham et al., 1986; Valdueza et al., 1997), as changes in diameter of the MCA are not detected during simulated orthostatic stress (lower body negative pressure) (Serrador, Picot, Rutt, Shoemaker, & Bondar, 2000). These findings conclude that relative changes in CBF, or CBFV, are representative of changes in physiological stimuli (Serrador et al., 2000), including, but not limited to, the reduction in CO observed in HF patients.

Of note, this assumption of CBFV as an accurate surrogate of CBF may not be valid in situations of altered partial pressures of arterial carbon dioxide ( $P_{aCO_2}$ ) (Ainslie & Hoiland, 2014; Coverdale, Gati, Opalevych, Perrotta, & Shoemaker, 2014) therefore, caution should be taken when forming conclusions around TCD measures; CBFV values may be underestimated in the presence of manipulated arterial gas concentrations. Further, differences in blood viscosity may also influence CBF however, it remains unknown whether the change in CBF is due to blood viscosity, or the respective change in hematocrit levels (Rebel et al., 2001). Hematocrit levels and blood viscosity may decrease in individuals with HF (Ana-Silvia et al., 2003; Ozcan Cetin et al., 2019), resulting in increases in CBF. It is possible that CBFV does not follow CBF if hematocrit levels influence the diameter of the cerebral resistance vessels; a direct conclusion on TCD measures as CBF should be cautioned.

### *1.7.1 Assessment of Cerebral Autoregulation*

The assessment of CA in both normal physiological function and that of a diseased state is important because it can expose cerebrovascular abnormalities that may only become apparent when the system is challenged. Assessing CA will also identify those at risk for cerebral ischemia or secondary brain damage due to hypoperfusion or hyperperfusion, respectively (Panerai, 1998). While it is common for CA to be impaired in HF, it should be noted several studies comparing CA in young and older adults report an intact autoregulatory system with age (Carey, Eames, Blake, Panerai, & Potter, 2000; Lipsitz, Mukai, Hamner, Gagnon, & Babikian, 2000; Sorond, Khavari, Serrador, & Lipsitz, 2005).

In general, assessments of static CA can be achieved by infusion of drugs such as trimetaphan and angiotensin II, which directly alter MAP, without inducing an effect on the cerebral vasculature or metabolism (Lassen, 1974). In this case, the change in CBF is only a result of the drug's effect on systemic blood pressure. There are a number of ways to assess dynamic CA, including inducing rapid MAP changes through sudden thigh cuff release (Aaslid et al., 1989), or studying the CBF responses to slow oscillations in MAP involving paced breathing (Reinhard et al., 2006) or head-up tilt (Cheng, Shang, Hayes, Saha, & Yu, 2012). The technique of bilateral thigh cuffs for the purpose of assessing dynamic CA has been criticized for being painful and not representative of the physiological demands that threaten cerebral perfusion upon a postural transition (Sorond, Serrador, Jones, Shaffer, & Lipsitz, 2009). To overcome these limitations, a simple sit-to-stand method that produces a transient decrease in BP has been developed for its ambulatory tolerability, and realistic implications of daily living (Lipsitz et al., 2000). Autoregulation in these cases is indicative of time to CBF recovery, where the faster CBF returns to its baseline value, the better the autoregulation index (ARI), thereby providing a feasible clinical tool in which to assess CA (Aaslid et al., 1989). The measurement of dynamic



CA offers the advantage of quantifying beat-to-beat variations of response time and pressure-flow in the cerebral circulation (changes in BP taking place over 5-10 seconds) (Eames, Blake, Dawson, Panerai, & Potter, 2002), which may have different physiological control mechanisms to static CA (Tiecks, Lam, Aaslid, & Newell, 1995). Dynamic CA is more commonly assessed by the change in CVR for a given change in pressure, where,  $CVR = MAP/CBF$  (Hughson, Edwards, O'Leary, & Shoemaker, 2001). In cases where direct measurements of CBF cannot be obtained, a measurement of CBFV is used, and cerebrovascular resistance index (CVRi) is estimated as  $CVRi = MAP/CBFV$  (Hughson et al., 2001; Liu et al., 2014). It should be noted that assessment of CA using CBFV (or CVRi) obtained with TCD in the MCA is likely to be underestimated when compared with the measurements of CBF or CVR in the internal carotid artery (Liu et al., 2013).

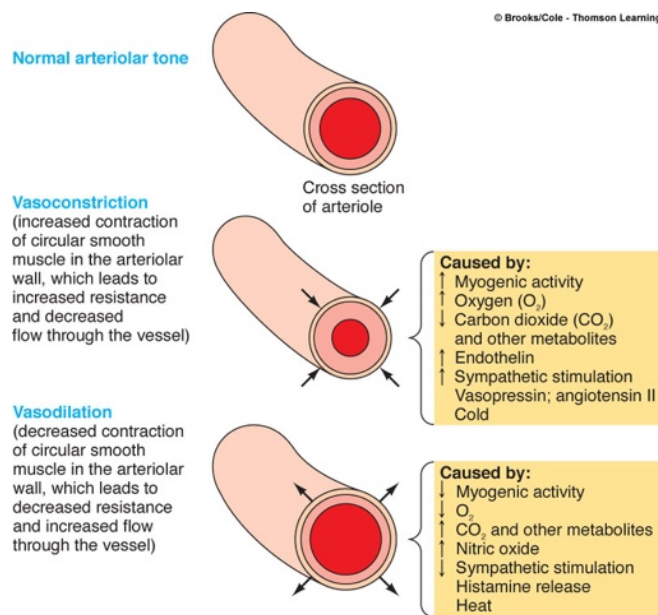
## **1.8 Physiological Mechanisms of Cerebral Autoregulation**

Despite the critical importance of the autoregulatory capacity of the cerebral vasculature, the physiological mechanisms of CA, and the state of altered CA in HF, remain unresolved (Hamner, Tan, Lee, Cohen, & Taylor, 2010). The term CA encompasses the integrated myogenic, metabolic, and autonomic adjustments needed to maintain CBF (Van der Scheer et al., 2018), by integrating at the level of the cerebral resistance vessels (Meng, Hou, Chui, Han, & Gelb, 2015). While much overlap exists, any of these systems can be altered, impacting cerebral perfusion, and thus, influencing the regulation of CA.

### *1.8.1 Myogenic Mechanisms*

The myogenic response, arising from the downstream arteries and arterioles, plays an important role in maintaining vascular resistance and autoregulation of blood flow in normal

cerebrovascular function (Yang & Liu, 2017). The cerebrovascular endothelium produces vasoactive mediators including endothelins, prostacyclin, nitric oxide (NO), and endothelium-derived hyperpolarization factor that control vascular tone and CA (Yang & Liu, 2017). The myogenic behaviour acts to protect downstream arterioles and capillaries from damaging high pressures associated with increased perfusion. In the face of increased MAP, vasoconstriction occurs in order to increase CVR and thus, decrease CBF. The associated decrease in CBF that occurs brings oxygen (O<sub>2</sub>) delivery and carbon dioxide (CO<sub>2</sub>) removal back towards normal. Conversely, myogenic behaviour also acts to ensure adequate tissue perfusion by means of vasodilation when MAP is decreased, in order to decrease CVR and increase CBF. Vasodilation restores the balance between O<sub>2</sub> supply and demand, primarily mediated through activation of NO in the arterial endothelium (Bor-Seng-Shu et al., 2012). The cascade of changes is summarized in Figure 1.5.



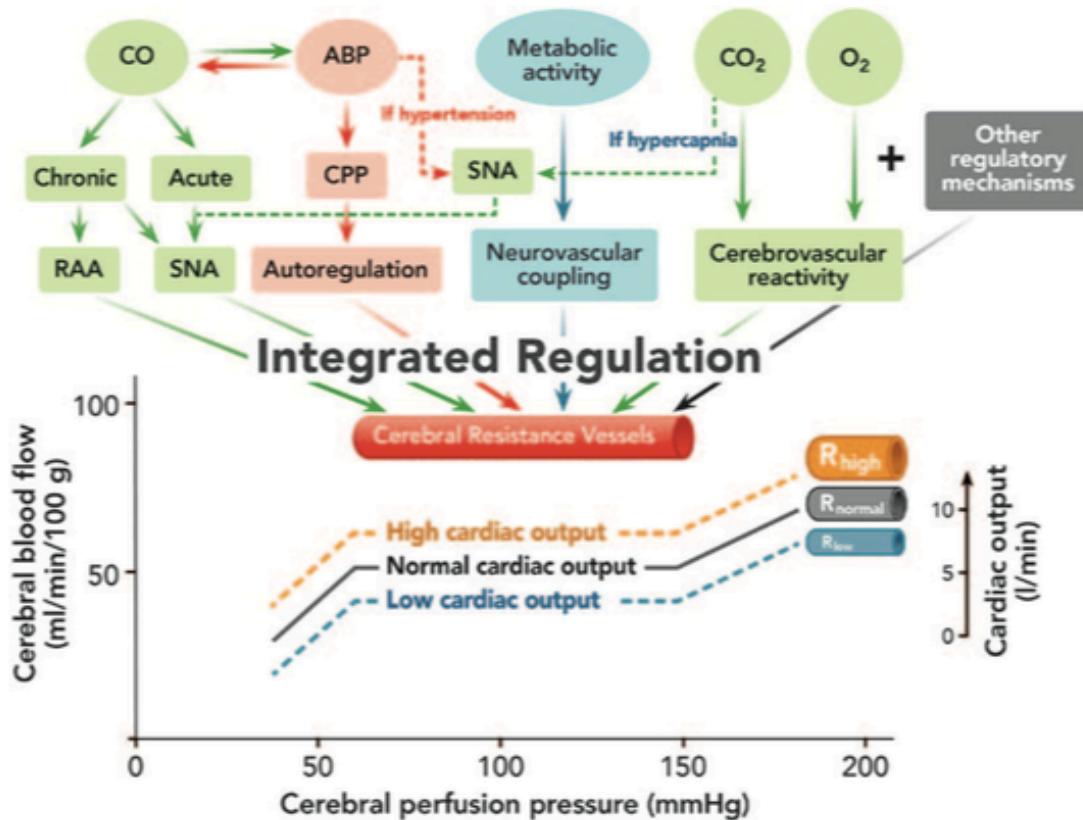
**Figure 1.5** Physiological factors influencing vascular tone of cerebral blood vessels. Figure from: (Sherwood, 2015)

### 1.8.2 Metabolic Mechanisms

CVR and thus, CA are highly sensitive to changes in  $P_{aCO_2}$  (Busija & Heistad, 1984).  $CO_2$  control mechanisms of CA are especially important in HF because this by-product is a powerful modulator of cerebral vasomotor tone (Kety & Schmidt, 1948), and changes in  $P_{aCO_2}$  as result of dyspnoea is often a consequence of this cardiac pathology. Hypercapnia, defined as elevations in  $P_{aCO_2}$ , leads to vasodilation of cerebral arterioles and a subsequent increase in CBF. Conversely, hypocapnia, a reduction in  $P_{aCO_2}$ , leads to vasoconstriction and a subsequent decrease in CBF. The changes in CBF distribution in response to changing  $P_{aCO_2}$  is a vital homeostatic function referred to as cerebrovascular  $CO_2$  reactivity (Ainslie & Duffin, 2009). Carbon dioxide diffuses readily and almost immediately across the blood-brain barrier, creating simultaneous changes in pH (Raichle & Plum, 1972). The physiological process of  $CO_2$  reactivity helps maintain central pH and thus, remove excess metabolic waste in conditions of hypercapnia, or attenuate the fall of brain tissue  $PCO_2$  in hypocapnia (Ainslie & Duffin, 2009). The profound vasodilating effect of  $CO_2$  is highlighted by previous work identifying that 5% and 7%  $CO_2$  inhalation in humans causes increases in CBF by 50% and 100%, respectively (Kety & Schmidt, 1948). It is important to note that a physiological threshold of maximal dilation and constriction does exist. For example, profound hypotension or hypercapnia can greatly diminish  $CO_2$  reactivity and impede autoregulation as the vessels are already maximally dilated from the respective challenge (Greene & Lee, 2012). While the proposed mechanisms behind the actions of  $CO_2$  has not been fully explained, some evidence suggests that the activation of  $K^+$  channels in vascular smooth muscle, in response to altered  $CO_2$  and concomitant change in pH, is responsible for the appropriate response of dilation or constriction (Ainslie & Duffin, 2009), typically ascribed to occur at the level of the arterioles (Atkinson, Anderson, & Sundt, 1990).

### *1.8.3 Neurogenic Mechanisms*

Autoregulation of the brain's circulation in response to changes in BP and CBF may also be controlled through the role of the autonomic nervous system, as the cerebral vasculature is well innervated by sympathetic and parasympathetic nerve fibers (Yang & Liu, 2017; Zhang et al., 2002). Noradrenaline is the principal neurotransmitter of sympathetic nerves, and its release from nerve fibers is a well-established means of assessing sympathetic nerve activity (Mitchell et al., 2009). Mitchell et al. (2009) reported the release rate of noradrenaline into the plasma is significantly reduced when postganglionic sympathetic nerve activity is reduced (via clonidine and trimethaphan). Similar results of altered dynamic CA upon ganglionic blockade at the level of the neck were reported by Zhang et al. (2002). These findings suggest that sympathetic nerves have a regulatory function of CBF outside the blood brain barrier (Mitchell et al., 2009). The parasympathetic nervous system acts through the release of vasodilators, namely acetylcholine, and does not appear to be a primary flow regulator in normal conditions, rather, its effects are predominately observed in disease or injury states (ischemia and migraines) (Hamel, 2006). Cerebral arteries lose their peripheral nerve supply upon entry to the brain parenchyma, and neural input of the brain microcirculation is then received by "intrinsic innervation" (Hamel, 2006). Therefore, neural modulation of cerebral blood flow is isolated to large cerebral arteries on the surface of the brain, and neural activation to regulate CBF is limited because vascular resistance is predominately mediated by the microcirculation (Hamel, 2006). While neurogenic control of CA is still controversial, TCD measures do in fact support a modest role of the autonomic nervous system in response to the regulation of CBF (Ainslie & Brassard, 2014). A conceptual framework of the integrated factors that regulate cerebral perfusion and influence CA are summarized in Figure 1.6.



**Figure 1.6** The conceptual framework of the integrated regulation of brain perfusion. The scale of CO on the right side is smaller than that of CBF on the left side to reflect the lesser extent of change in CBF induced by an alteration of CO.  
 Figure from: (Meng et al., 2015)

### 1.9 Impaired Cerebral Autoregulation in Heart Failure

The concept of CA stipulates that CBF remains relatively constant despite changes in BP or CPP. In many cardiovascular pathologic states, changes in CPP, arterial BP, CO, and CO<sub>2</sub> are common, due to either primary or secondary symptoms of the disease. The continual stress of shifting BP and CPP push the system enough to reveal the underlying disease process (Donnelly, Aries, & Czosnyka, 2015). Pilot work in our lab involving a walking protocol in HF has shown to produce a highly variable, oscillating signal of CBFV. While this may suggest the impairment of CA, the significance of this signal and the cerebral autoregulatory response mechanisms however, when compared to that of someone without HF, is unknown. The remainder of this

proposal will discuss proposed mechanisms in the literature that underlie dysfunctional CA in HF patients by discussing the link between reduced CO and CBF. Notably, both acute (Van Lieshout et al., 2001) and chronic (Loncar et al., 2011) reductions in CO have been shown to lower CBF, even when BP is within the autoregulatory range.

### *1.9.1 Direct Evidence*

While several studies have demonstrated an association between impaired CA and cerebrovascular disorders (Fontana et al., 2015; Salinet, Robinson, & Panerai, 2015), there is limited direct evidence that cerebral autoregulatory mechanisms are affected in patients with HF. The first study to investigate dynamic CA in HF was conducted in 52 ischemic HF patients with an average LVEF of 40% (20-45) (Caldas et al., 2017). Dynamic CA was modeled using transfer function analysis using spontaneous fluctuations of MAP and changes in CBFV as input and output, respectively (Claassen et al., 2015). ARI was estimated from the CBFV step response derived by transfer function analysis using standard template curves which can be described elsewhere (Tiecks et al., 1995). Caldas et al. reported that dynamic CA at rest was significantly reduced in patients with ischemic HF compared to healthy age-matched controls (Caldas et al., 2017). Ejection fraction in these patients ranged from 20-45%, which suggests reduced CBF and impaired autoregulatory mechanisms. This hypothesis of reductions in CO leading to limitations of CBF however, was not supported in healthy subjects where changes in CO were not correlated to the ARI index (Deegan et al., 2010). Notably, results from a number of studies do suggest that CO may play a role in determining CBF (Van Lieshout et al., 2003, 2001) but the relationship remains unclear. It is hypothesized that increased sympathetic activation could be a contributing factor in the reduced cerebrovascular regulation in these patients however, further investigation is required (Caldas et al., 2017). In 2018, research in the topic of CA in HF was advanced by

direct evidence of impaired CA in patients with HF in response to isometric exercise (Caldas et al., 2018). Similar methods were used to assess dynamic CA, along with obtaining a value of critical closing pressure and resistance area product. As a consequence of impaired CA in these patients, most of the variables considered including HR, CBF, and BP, did not return to their baseline values after the isometric handgrip exercise. These results suggest that blood pressure modulations are buffered less efficiently and metabolic demands may not be met during common daily activities (Caldas et al., 2018). This thesis will be the first to examine the cerebrovascular hemodynamic regulation of CBF in patients with HF in response to posture changes and walking.

### *1.9.2 Indirect Evidence*

In addition to the direct evidence of impaired CA in HF, there are several vascular adaptations that occur in these patients that suggest the reduced CBF seen in both the supine and upright posture (Fraser et al., 2015) may play an important role in the impairment of CA. While direct evidence in this topic is limited, there are numerous consequences of this cardiac pathology that give rise to the reduced CBF and therefore, several mechanisms that suggest CA impairment. Brain hypoperfusion is a common outcome of HF that can develop from low CO, reduced CPP, or hypotension, all described as characteristics of HF. Brain hypoperfusion is not adjusted by CA (Qiu, Von Strauss, Fastbom, Winblad, & Fratiglioni, 2003) and a result, has been shown to cause clinically relevant deficits in various cognitive domains, including increasing the risk of dementia (Duschek, Matthias, & Schandry, 2005). Further, cerebral hypoperfusion affects delivery and use of O<sub>2</sub> and glucose (De la Torre, 2000). Interruptions of these substrates within the cerebrovasculature can lead to cerebral ischemia and impair cerebrovascular CO<sub>2</sub> reactivity (Ogoh, Nakahara, Ainslie, & Miyamoto, 2010) due to the considerable sensitivity of CA to O<sub>2</sub>

deprivation, further complicating the already complex disease. The neuronal energy crisis that accompanies hypoperfusion is typically followed by neuronal dysfunction. Prolonged chronic ischemia in severe conditions may lead to the death of neurons in ischemic-sensitive zones such as the hippocampus (Ruitenbergh et al., 2005), clinically progressing to additional cognitive impairment and AD / dementia, resulting from reduced CBF and thus, impairment of cerebral autoregulatory mechanisms in these patients.

In contrast, hypertension is another major vascular risk factor that may be present, commonly seen in patients with HFpEF (Borlaug & Paulus, 2011). The brain is a low resistance, high flow organ and is therefore particularly susceptible to hemodynamic pulsatile flow patterns (Mitchell et al., 2011). Chronic hypertension results in high levels of pulsatile CBF, which can damage and impair endothelial and smooth muscle cell function within the cerebral microvasculature, predisposing the system to cerebral ischemia, and focal infarcts (Heffernan et al., 2015). Impaired endothelial function may be responsible for the increase in systemic vascular resistance and reduced nitric oxide release (White, Vallance, & Markus, 2000) that contribute to the reduced CBF and compromised CA seen in hypertensive HF patients.

Hyperventilation is a common symptom in the setting of HF that can lead to chronic hypocapnia (Fanfulla et al., 1998), and impair cerebrovascular CO<sub>2</sub> reactivity. Hyperventilation, leading to low PaCO<sub>2</sub>, is associated with increased pulmonary congestion (Tkacova, Hall, Liu, Fitzgerald, & Bradley, 1997) and dyspnoea that occurs upon exertion of these patients, typically at a level of activity that is usually well-tolerated in a healthy individual. Cheyne-Stokes respiration is the best-known disturbance of the breathing pattern (Tobin & Snyder, 1984), characterized by periodic irregularity of respiration in which movement gradually decreases to a period of apnea, then returns to normal (Lorenzi-Filho et al., 2005). This particular pattern of



breathing is present in 30-50% of patients with HF (Sin et al., 1998) and participates in a vicious cycle that further stresses the failing heart (Lorenzi-Filho et al., 2005), while promoting profound oscillations in BP and HR (Leung et al., 2003). Under the conditions of hypocapnia in HF, the reduction of CO<sub>2</sub> may lead to a chronic reduction of CBF and thus, promote cerebral ischemia due to the elevation of CVR. This effect could be exaggerated upon ADL or moderate exercise in hypocapnic HF patients where increased hyperventilation may occur as a compensatory mechanism to the physiological and physical demand of postural transitions and walking.

### *1.9.3 Consequences of Impaired Cerebral Autoregulation*

Compromised CA in some HF patients has several other physiological consequences. Reduced CBF will lead to hypoxia, the reduction of amyloid-beta (A $\beta$ ) clearance, and the increase of inflammatory responses within the microglia (Cermakova et al., 2015). The activated microglia are not able to phagocytose the excess A $\beta$ , resulting in neurotoxicity and further compromised cerebral perfusion (Shah et al., 2012), as well as the formation of A $\beta$  plaques and neurofibrillary tangles (Cermakova et al., 2015); defined as hallmark features of AD pathology (Glass, Saijo, Winner, Marchetto, & Gage, 2010). Many neuroimaging studies in patients with HF report total and regional brain atrophy (Vogels et al., 2007), reduced axonal integrity (Kumar et al., 2011), and structural abnormalities including the development of WMH (Prins et al., 2013) in regions of the brain involved in cognition (Prins et al., 2013; Serber et al., 2008); all possibly developed from reduced CBF and impaired autoregulatory mechanisms, secondary to cardiac pathology and reduced CO. When heart function is improved, such as with a transplant or cardiac resynchronization therapy, CO and CBF can be restored (Gruhn et al., 2001) and improvements in cognition have in fact been noted (Dixit et al., 2010).

Heart failure is also associated with an increased risk of falls resulting in debilitating injuries (Van Diepen, Majumdar, Bakal, McAlister, & Ezekowitz, 2008), as the act of standing during ADL challenges cerebral autoregulatory mechanisms. As a consequence of impaired CA in HF, there is evidence to suggest reduced CO, CBF and concomitant cerebral hypoperfusion, as the mechanism behind this link. Cerebral hypoperfusion, secondary to cardiac pathology, may lead to syncope (Arthur & Kaye, 2000), an independent predictor of sudden death and mortality (Kapoor, 1990). 20-30% of syncope cases are due to OH (Allcock & O'Shea, 2000), previously described as a common vascular comorbidity in HF. Additionally, results from Middlekauff et al. (1993) found that patients with advanced HF and syncope have a one-year mortality of 45% compared to that of 12% in HF patients without syncope (Middlekauff, Stevenson, & Saxon, 1993). The following section of this proposal will describe the current study rationale.

## 2.0 Study Rationale

Individuals with HF are predisposed to cerebral ischemia, due to the inability to regulate CBF (Fraser et al., 2015), secondary to cardiac pathology and reduced CO. The inability of these individuals to maintain adequate blood flow to the brain suggests the impairment of CA, or the impairment in the capability of cerebral autoregulatory mechanisms to respond. Dynamic CA is impaired in patients with HF at rest (Caldas et al., 2017), and during isometric exercise (Caldas et al., 2018), however, the cerebrovascular hemodynamic alterations in response to orthostatic stress within the HF population is unknown.

Reduced CO and CBF in the setting of HF has been reported in both the supine and upright position (Fraser et al., 2015). Pilot work in our lab involving a walking protocol in HF has shown to produce a highly variable, oscillating signal of CBFV. The gap in the literature is the knowledge to determine the significance of this signal, compared to that of individuals without HF. Accordingly, the purpose of this thesis is to investigate the cardio- and cerebrovascular responses to postural changes and walking in individuals with HF. Ambulatory measurements of CBFV, in conjunction with beat-to-beat measurements of BP and continuous expired CO<sub>2</sub>, will provide critical information regarding the autoregulatory control of blood flow in HF, under conditions of real-life scenarios. The following section will outline the objectives and hypotheses of this thesis.

### **3.0 Study Objectives and Hypotheses**

#### *Objective 1:*

To assess the steady-state cerebrovascular responses to quiet standing and walking in individuals with HF, compared to healthy age-matched controls.

#### *Hypothesis 1:*

Assessed by within-subject linear regression, individuals with HF will have impaired static CA (unregulated changes in CBFV with fluctuating blood pressures), in response to standing and walking, compared to age-matched controls.

#### *Objective 2:*

To assess the transient cerebrovascular response of a transition to quiet standing in individuals with HF, compared to healthy age-matched controls.

#### *Hypothesis 2:*

Assessed by determining the absolute and percent changes in cerebrovascular resistance index ( $CVRi = MAP/CBFV$ ), individuals with HF will have impaired dynamic CA (smaller percent change in  $CVRi$ ) compared to controls, in response to a transition to quiet standing.

#### *Objective 3:*

To determine if arterial stiffness is related to cerebrovascular impairments in individuals with HF during ADL.

#### *Hypothesis 3:*

Increased arterial stiffness will be correlated with an increased MCA pulsatility index, obtained by transcranial Doppler ultrasound, in individuals with HF during standing and walking.

## 4.0 Methods

### 4.1 Ethics (also described in Murray, see Declaration)

The experimental procedure for this study was approved by the Office of Research Ethics at the University of Waterloo (ORE #21025). The project was approved with Kevin Murray and Jessica Poirier as student investigators. All participants volunteered for the study after reading and signing the information-consent form. All participants were aware of their right to withdraw from the study at any time without reason or penalty.

### 4.2 Recruitment (also described in Murray, see Declaration)

**Table 4.1 Participant inclusion/exclusion criteria** (Table also presented in Murray, see Declaration)

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"><li>Men and women greater or equal to 65 years old</li></ul>	<ul style="list-style-type: none"><li>NYHA functional class IV</li><li>Transplant recipient</li><li>Major hospitalization for a cerebrovascular event/procedure less than 4 weeks to 6 months ago</li><li>Hospital admission that required an overnight stay within the past 3 months (risk of delirium)</li><li>History of myocardial infarction in the past 3 months</li><li>History of drug/alcohol abuse</li><li>Known stenosis of carotid artery &gt;50%</li><li>Atrial fibrillation requiring Warfarin or Coumadin</li><li>Taking alpha adrenergic blocking agents</li><li>Uncontrolled hypertension (greater or equal to 140/90) and/or resting HR &gt;110</li><li>Severe arthritis or arthralgia limiting mobility</li><li>Diagnosed sleep apnea</li><li>Psychiatric illness or use of psychoactive drugs</li><li>Neurological disorders</li><li>Diagnosed with vasovagal syncope, vasodepressor syncope, and postural hypotension/syncope</li><li>Prior diagnosis of dementia or MoCA score &lt;21</li><li>Recent change to medication regime</li></ul>

#### *4.2.2 Recruitment of Heart Failure Participants*

Ten stable heart failure participants were recruited for this study. Recruitment occurred at two family practices in the Kitchener-Waterloo region (New Vision family health care team and Northfield Medical at The Boardwalk). Participants were first approached about the study by a health care professional within the circle of care from the respective clinic. They were provided with a short description of the study and upon interest, potential participants received a phone call from a research associate to obtain more information. This phone call went over the exclusion criteria and those eligible to participate were scheduled for testing. A list of current medications was provided by the patient on the day of testing.

#### *4.2.3 Recruitment of Controls*

Thirteen age-matched controls were recruited in our sample. In general, these participants were high-functioning and healthy older adults from both the Kitchener-Waterloo community and retirement homes (Schlegel Villages). Data collection techniques for all participants were the same as described below.

### **4.3 Experimental Protocol Overview** *(also described in Murray, see Declaration)*

Data collection took place at the Schlegel-University of Waterloo Research Institute for Aging. The study was completed in one 2-hour visit. Prior to the test day, participants were instructed to avoid eating 90 minutes before arriving to the lab, to wear comfortable shoes, a loose-fitting t-shirt, and bring a list of any/all current medications. Upon arrival for testing, each participant read and signed the information-consent form. The experimental protocol was described, and any questions or concerns were addressed.

Following the initial orientation, participants completed a general health questionnaire to give researchers a profile of their individual health status (Appendix A). Height and weight measurements were obtained and body mass index (BMI) was later calculated (*equation also presented in Murray, see Declaration*).

$$\text{BMI (kg/m}^2\text{)} = \text{mass (kg)} / \text{weight (m}^2\text{)} \quad [\text{Eq1}]$$

Following these anthropometric measurements, participants were asked to lie supine on a bed, where they were instrumented with a single-lead electrocardiogram (ECG; Powerlab, AD Instruments, Colorado Springs, CO, USA) and continuous beat-to-beat monitoring of HR and BP (Finometer NOVA, Finapres Medical Systems, Amsterdam, the Netherlands). Upon 10 minutes of supine rest and optimization of all signals, a standard ultrasound (US) examination was performed. The US imaging was divided into 2 sections; vascular imaging of the right common carotid artery (CCA) and standard echocardiogram to assess cardiovascular health.

Once the supine US images were taken, the participants were prepared for ambulatory monitoring. Several pieces of non-invasive equipment were placed on the participant to measure continuous beat-to-beat responses of BP, CBFV, and breath-by-breath expired CO<sub>2</sub>. Once all signals were optimized and stable, participants then completed 3 postural transitions.

1. Supine rest (*5 minutes*) – Sit (*2-5 seconds*) – Quiet Stand (*3 minutes*)
2. Sit (*5 minutes*) – Walk<sub>Normal</sub> pace (*3 minutes*)
3. Sit (*5 minutes*) – Walk<sub>Slow</sub> pace (*3 minutes*)

The transitions were block randomized between participants. The two walking trials, in a random order, were always completed one after the other, and the supine to stand transition randomly occurred before, or after, the walking transitions. Changes in BP, CBFV, and expired CO<sub>2</sub> were

recorded and saved for post-hoc analysis. All equipment was then be removed from the participant, cleaned, and stored.

#### **4.4 Data Collection** *(also described in Murray, see Declaration)*

##### *4.4.1 Resting Cardiovascular Assessment*

Resting vascular and cardiac US measures were recorded using a standard clinical ultrasound system (iE33, xMatrix, Koninklijke Philips Electronics, NV USA); a 10-17 MHz linear array transducer (L9-3, Koninklijke Philips Electronics NV USA) was used for the duration of the vascular imaging.

##### *Resting Heart Rate and Blood Pressure:*

Measures of BP and HR 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. Beat-to-beat BP throughout the supine US measurements was measured using finger-cuff photoplethysmography (Finometer NOVA, Finapres Medical Systems, Amsterdam, the Netherlands). The finger was wrapped with an inflatable cuff that uses infrared light transmitted through the skin to assess the unloading of the vessel wall and thus, non-invasively measure arterial pressure during each heartbeat. Finger arterial pressure can accurately estimate brachial artery pressure in participants after the waveform has been level corrected using a fluid filled tube attached to the finger cuff and a pressure transducer secured at heart level, and, accurately calibrated using a supine return-to-flow calibration (Helschien, Chao, & Ulbricht, 2009).

Notably, use of the Finometer device for measurement of blood pressure satisfied the validation



criteria of the Association for the Advancement of Medical Instrumentation and can be recommended in the clinical set-up and for research purposes (Schutte, Huisman, Rooyen, Malan, & Schutte, 2004). ECG was recorded beat-to-beat and the R-R intervals were later used to determine HR.

*Pulse Wave Velocity:*

Carotid-femoral pulse wave velocity is considered the gold standard for arterial stiffness assessment (Van Bortel et al., 2012). With reference to standardized guidelines (Van Bortel et al., 2012), applanation tonometry (SPT-301, Millar Instruments, Houston, TX USA) was used to record pulse arrival times of both the right CCA and femoral artery ( $PP_{car}$  and  $PP_{fem}$ ) simultaneously, for 30-40 cardiac cycles, in order to obtain a measure of carotid PWV. PWV was determined by the difference in the arrival pulse wave to each site, divided by 80% of the total distance between pulse sites [Eq2] (*equation also presented in Murray, see Declaration*). Signals were bandpass filtered at 5-30 Hz to identify the foot of the waveform, and pathlength was estimated using a rigid measuring stick.

$$cfPWV \text{ (cm/s)} = \frac{0.8 \times \text{cf distance (cm)}}{\text{cf pulse wave transit time (s)}} \quad [\text{Eq2}]$$

*Echocardiography:*

With reference to standardized guidelines (Lang et al., 2005), standard echocardiography was performed using a phased array probe (x5-1, Koninklijke Philips Electronics NV United States) by an experienced sonographer. LV volumes were estimated using Simpson's Biplane method from apical 4-chamber and 2-chamber views. Diastolic function was assessed from trans-mitral velocities and tissue-Doppler imaging of the lateral and septal mitral annulus to

calculate E/A and E/e' ratios. The E/A ratio represents the ratio of peak velocity blood flow from gravity in early diastole (E wave) to peak flow velocity flow in late diastole caused by atrial contraction (A wave). The E/e' represents the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'). Cardiac output was estimated from time-integration of the trans-aortic velocity wave in the apical 5-chamber view and the aortic root diameter was determined from the parasternal long axis view.

#### *4.4.2 Ambulatory Monitoring (also described in Murray, see Declaration)*

*Hemodynamics:* Following the US imaging, all participants were outfitted with ambulatory devices to measure cardio- and cerebrovascular responses during, and after the postural change and transition to walking; all devices were time synced post-collection. Continuous, beat-to-beat measurements of arterial BP and cardiac index measurements were obtained by finger-cuff plethysmography using the Portapres (Portapres Model-2, Finapres Medical Systems, Amsterdam the Netherlands). The Portapres is described as the ambulatory Finapres however, throughout the duration of the test, this device was placed on a walker used comfortably by each participant. The Portapres provides estimated brachial BP values, CO and SV by using the Modelflow algorithm (Kenfack et al., 2004). Data collected by the Portapres were later imported into BeatScope software to obtain a beat-to-beat BP trend throughout the recorded transitions.

*Cerebral Blood Flow Velocity:* Blood flow velocity of the MCA was measured using a portable transcranial Doppler (TCD) device (TCD-X, Atys Medical, Soucieu-en-Jarrest France). A 2MHz transducer was placed over the right temporal window with a slight forward orientation to track the M1 segment of the MCA; the probe was held in place by the use of a lightweight spectacle frame to ensure stable probe positioning throughout the recorded transitions. The

temporal window is a small, thin area of the temporal bone that allows for the vessels of the Circle of Willis to be exposed to US. Should the signal become weak, the orientation of the robotically controlled probe is adjusted automatically to search for the signal with maximal intensity, ensuring the stability of the recording over time. Insonation of the MCA was confirmed by the auditory pitch, velocity profile, strength of signal, signal depth, and probe angle. The outer envelope of the MCA velocity Doppler spectrum was exported for later analysis. Due to the technology utilized for this study, occasional temporary signal loss of CBFV data was encountered and thus, the signal was cleaned using a spline interpolation function in R 3.6.0 (R Core Team, Vienna, Austria; see Appendix B).

*Expired CO<sub>2</sub>*: End tidal CO<sub>2</sub> (ETCO<sub>2</sub>) was continuously measured with a portable respiratory monitor (Capnostream 35, Medtronic, United States) via a close fitting nasal canula. Prior to the testing session, the capnograph was calibrated using 5.05% CO<sub>2</sub>. Data were stored on an external storage device to be later analyzed.

#### **4.5 Outcome Analysis**

Continuous hemodynamics, CBFV, and expired CO<sub>2</sub> were time synced post-collection using MATLAB (MATLAB 9.4, The Mathworks, Inc., Natick, Massachusetts, United States). Data alignment is also explained in Murray, see Declaration. The outer envelope of the TCD Doppler spectrum was averaged over each cardiac cycle to determine mean CBFV, also referred to as MFV; MFV will be used throughout the remainder of this thesis. Similarly, arterial blood pressure tracings were averaged over a cardiac cycle to provide an indication of mean arterial pressure, as well as pressure at the level of the MCA (BP<sub>MCA</sub>).

$$\text{BP MCA (mmHg)} = \text{MAP(mmHg)} - (\text{heart to head distance (cm)} \times 0.78) \quad [\text{Eq3}]$$

MFV and BP<sub>MCA</sub> were then used to calculate an index of cerebrovascular resistance index.

$$\text{CVRi} = \text{BP MCA (mmHg)} / \text{MFV(cm/s)} \quad [\text{Eq4}]$$

Pulsatility index was calculated as:

$$\text{PI} = (\text{SFV} - \text{DFV}) / \text{MFV (cm/s)} \quad [\text{Eq5}]$$

Critical closing pressure was calculated as:

$$\text{CrCP (mmHg)} = \text{BP MCA (mmHg)} - \left[ \frac{\text{MFV} - \text{DFV (cm/s)}}{\text{BP MCA} - \text{MCA DBP (mmHg)}} \right] \quad [\text{Eq6}]$$

With reference to (Weyland et al., 2000), perfusion pressure was calculated as:

$$\text{Perfusion pressure (mmHg)} = \text{BP MCA (mmHg)} - \text{CrCP (mmHg)} \quad [\text{Eq7}]$$

Adjusted MFV was calculated as:

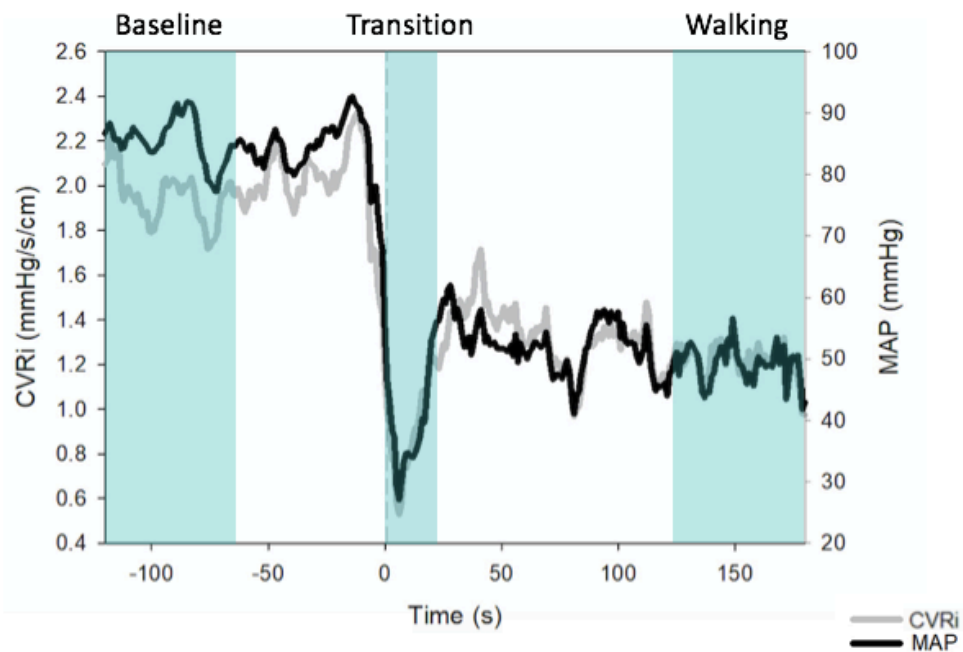
$$\text{Adjusted MFV (cm/s/mmHg)} = \text{MFV (cm/s)} / \text{ETCO}_2 \text{ (mmHg)} \quad [\text{Eq8}]$$

Adjusted CVRi was calculated as:

$$\text{Adjusted CVRi (cm/s)} = \text{BP MCA (mmHg)} / [\text{MFV (cm/s)} / \text{ETCO}_2 \text{ (mmHg)}] \quad [\text{Eq9}]$$

Baseline values were defined as a 1-minute average of stable signal between minutes 3-4 (-120 to -60 seconds) of seated, or supine rest. The classic pressor response to orthostatic stress (transition-nadir and nadir-overshoot) was exported for each transition, as well as the respective slope values where transition was equal to the value at time 0. The nadir was marked as a 3-point average, centered around the single lowest value, 0-30 seconds post transition. Mean values were calculated for each parameter between minute 2-3 (120-180 seconds) of standing, or walking. An average of the baseline values from the walking trials (SitWalk<sub>Normal</sub> pace and SitWalk<sub>Slow</sub> pace) was used as the seated baseline for each variable. An example demonstrating the regions of interest can be seen in Figure 4.1. Delta values and percent change from baseline were calculated by subtracting the nadir and post value from the baseline, and dividing that value by the baseline, respectively. MFV was plotted against BP<sub>MCA</sub> to assess CA by linear regression analysis. In this

analysis, a slope closer to 0 indicated intact autoregulation (maintained MFV with fluctuating blood pressure), whereas a slope closer to 1 indicated impaired autoregulation (unregulated changes in MFV with fluctuating blood pressure). Notably, participants were excluded in the analysis of various variables in the case of data dropout or equipment malfunctions during ambulation.



**Figure 4.1** Representative beat-to-beat data from a control participant during a postural transition. CVRi – cerebrovascular resistance index; MAP – mean arterial pressure.

#### 4.6 Statistical Analysis *(also described in Murray, see Declaration)*

It would be difficult to calculate a proposed sample size to observe differences in CA as no previous studies have assessed CA through ambulation. Hypothesis 2 of the current study is looking at the change in CVRi in response to a supine-to-stand transition (upright posture), based on the calculation  $CVRi = BP_{MCA} / MFV$ . As a result, the proposed sample size for this study was based off CBF data from Fraser et al., 2015, with the assumption that a change in CBF will also

reflect a change in CVR<sub>i</sub>. A plot digitizer (Rohatgi, 2015) was used to extract estimated mean and standard deviation values from Fraser et al., 2015. Specially, the proposed sample size for this project was calculated utilizing the change values from supine to upright posture in CBF of the right internal carotid artery, as well as CBF values of the same artery in the seated posture independently, compared to healthy controls.

Extracted from the plot digitizer, CBF  $\Delta_{\text{mean}}$  in control participants was - 3.78, and - 38.07 in the HF group. Pooled  $\sigma = 36.3$ ,  $\alpha=0.05$ , and  $\beta=0.8$ , which yielded a sample size of 18 participants per group. Similarly, CBF<sub>mean</sub> measured in upright posture and extracted for the plot digitizer in control and HF participants were 274.6 mL/min and 221 mL/min respectively, with a pooled  $\sigma = 59.4$ , which yielded a sample size of 20 participants in each group.

Participant characteristics including age, BMI, height, weight, and resting vascular measurements were summarized as mean  $\pm$  standard deviation. Comparisons between HF and control participants were made using independent Student's t-tests for normally distributed data, and Mann-Whitney U Rank Sums tests for non-normally distributed data. For categorical variables, comparisons between HF and control participants were made using Fisher's exact test. Repeated-measures correlation analysis were used to assess the relationship between cardio- and cerebrovascular variables during steady-state baseline and post transition. This analysis was conducted on the combined group (all participants), as well as the control and HF groups independently. Pearson's r correlations were used to assess the relationship between PI and cfPWV. Statistical significance was set at  $\alpha = 0.05$ . Repeated-measures correlation analyses were run in R 3.6.0 (R Core Team, Vienna, Austria). All other statistical analyses were completed using SigmaPlot 14.0 (Systat Software Inc., San Jose, CA, United States).

## 5.0 Results

### 5.1 Resting Characteristics in HF and Control Groups

The 13 matched control and 10 HF participants were common between the current thesis and Kevin Murray's thesis, with Table 5.1 and 5.2 containing the same characteristic information. Of particular relevance to this thesis is that no differences were detected in resting brachial SBP and DBP. Additionally, the HF group had lower systolic cardiac function, represented by lower LVEF, compared to control participants ( $P < 0.001$ ), with a LVEF range of 20-61%. This large range of LVEF can be attributed to this cohort including participants with HFrEF, HFmEF, and HFpEF. Table 5.3 contains supine and seated baseline characteristics for control and heart failure participants.

**Table 5.1 Participant characteristics**

	Control (n=13)	Heart Failure (n=10)	<i>P</i> -value
Sex (Male/Female)	4/9	7/3	N.S.
Age (years)	78.8±7.8	78.4±8.4	N.S.
BMI (kg/m <sup>2</sup> )	24.2±4.2	28.8±3.6	0.012
Height (cm)	163±12	173±11	0.040
Weight (kg)	64.8±15.3	87.3±18.1	0.004
Smoking history (n (%))	1 (8%)	8 (80%)	<0.001
Brachial SBP (mmHg)	137±14	133±11	N.S.
Brachial DBP (mmHg)	71±7	69±13	N.S.
<i>Vascular Measures</i>			
cfPWV (m/s)	10.6±2.8	9.4±2.0	N.S.
<i>Systolic Cardiac Function</i>			
LVEF (%)	61±6	45±12	<0.001
<i>Diastolic Cardiac Function</i>			
E/A ratio	1.2±0.4	1.2±0.4	N.S.
E/e' ratio	6.7±1.8	7.2±1.2	N.S.

All values are mean±standard deviation. All blood pressure, vascular, and cardiac measurements were taken during supine rest. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; cfPWV – carotid-femoral pulse wave velocity; LVEF – left ventricle ejection fraction; E – early diastolic peak mitral inflow velocity; A – late diastolic peak mitral inflow velocity; e' – early diastolic peak mitral annular velocity.

**Table 5.2 Medical characteristics**

	Control	Heart Failure	<i>P</i> -value
β-blocker	0 (0)	8 (80)	<0.001
ACE-inhibitor	1 (8)	6 (60)	0.020
Anticoagulants	0 (0)	5 (50)	0.007
ARB	1 (8)	1 (10)	N.S.
ARNi	0 (0)	1 (10)	N.S.
Calcium channel blocker	1 (8)	3 (30)	N.S.
Diuretics	1 (8)	7 (70)	0.006
Nitroglycerin spray	0 (0)	3 (30)	N.S.
Statins	3 (23)	6 (60)	N.S.

All values are n (%). ACE – angiotensin converting enzyme; ARB – angiotensin II receptor blocker; ARNi angiotensin receptor-neprilysin inhibitor.

**Table 5.3 Baseline characteristics**

	Supine Rest		Seated Rest	
	Control	Heart Failure	Control	Heart Failure
HR (bpm)	60±11	62±6	66±11	63±7
BP <sub>MCA</sub> (mmHg)	95±17	88±32	63±23	50±14
MFV (cm/s)	49.2±10.5	40.1±6.6	45.8±5.3	38.0±4.5
PI	1.04±0.21	1.05±0.30	1.23±0.19	1.23±0.30
CVRi (mmHg/cm/s)	2.0±0.5	2.2±0.8	1.4±0.5	1.3±0.4
ETCO <sub>2</sub> (mmHg)	37.7±3.3	33.8±5.0	36.7±3.2	31.2±5.8

All values are mean±standard deviation. HR – heart rate; BP – blood pressure; MCA – middle cerebral artery; MFV – middle cerebral artery; PI – pulsatility index; CVRi – cerebrovascular resistance index; ETCO<sub>2</sub> – end-tidal carbon dioxide.

The following sections of this thesis describe data that are unique to the testing of hypotheses in the current study.

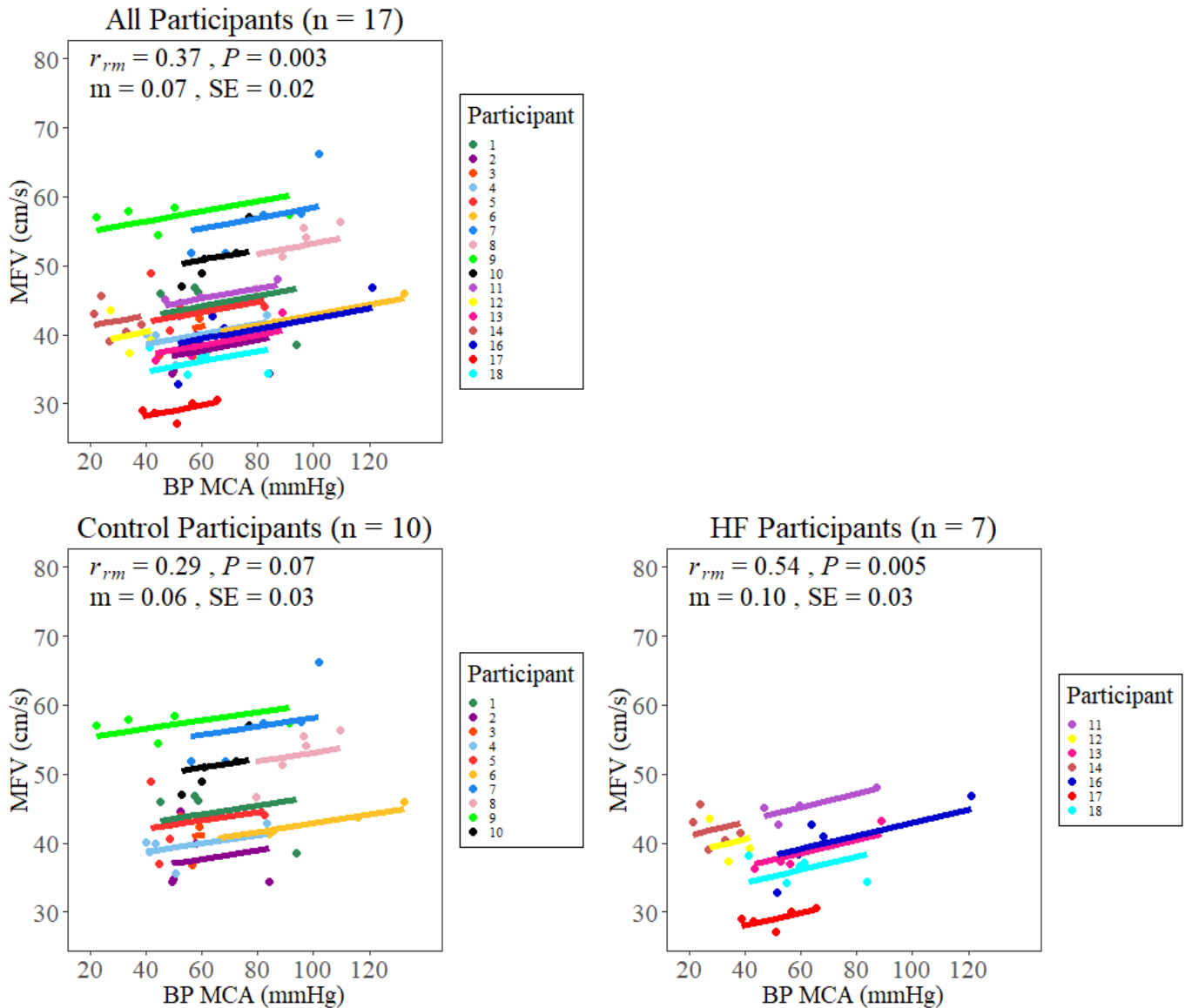
## 5.2 Static Cerebral Autoregulatory Response to Ambulation

The steady-state cerebrovascular responses to quiet standing and walking are presented in Figure 5.1 and 5.2. Absolute values between groups and transitions are presented in Supplementary Table 5.5 (see Appendix C). As CA reflects the properties of cerebral vessels to maintain relatively constant flow during changes in arterial blood pressure, the relationship between absolute values of MFV and BP<sub>MCA</sub> was explored across conditions by repeated-

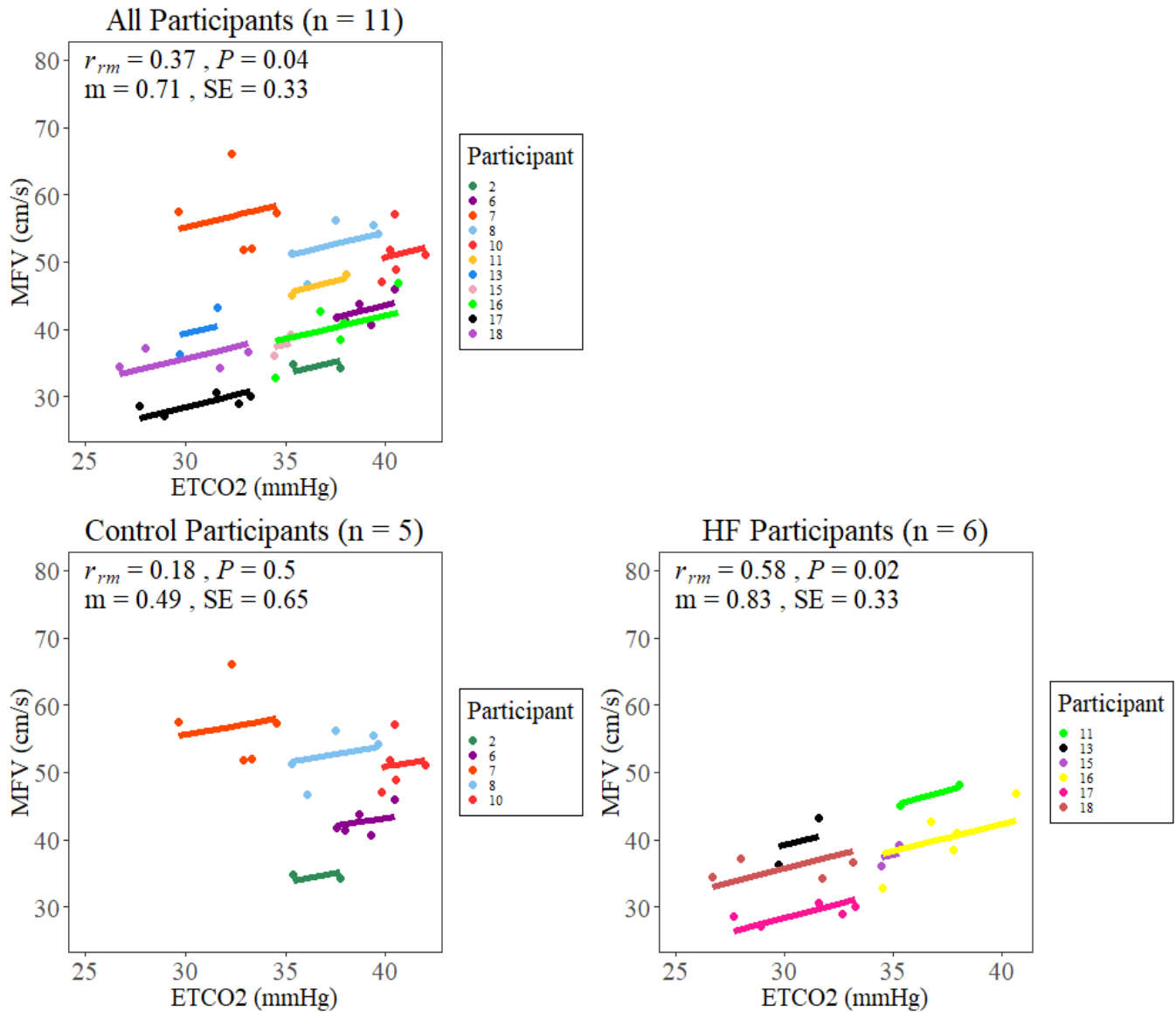


measures correlation analysis (Figure 5.1). There was a positive correlation observed between MFV and  $BP_{MCA}$  in the combined group of both control and HF participants ( $r_{rm}=0.37$ ,  $P=0.003$ ). Within the control group, there was a trend for a small positive correlation ( $r_{rm}=0.29$ ,  $P=0.07$ ), whereas a moderate positive correlation was observed in the HF group ( $r_{rm}=0.54$ ,  $P=0.005$ ).

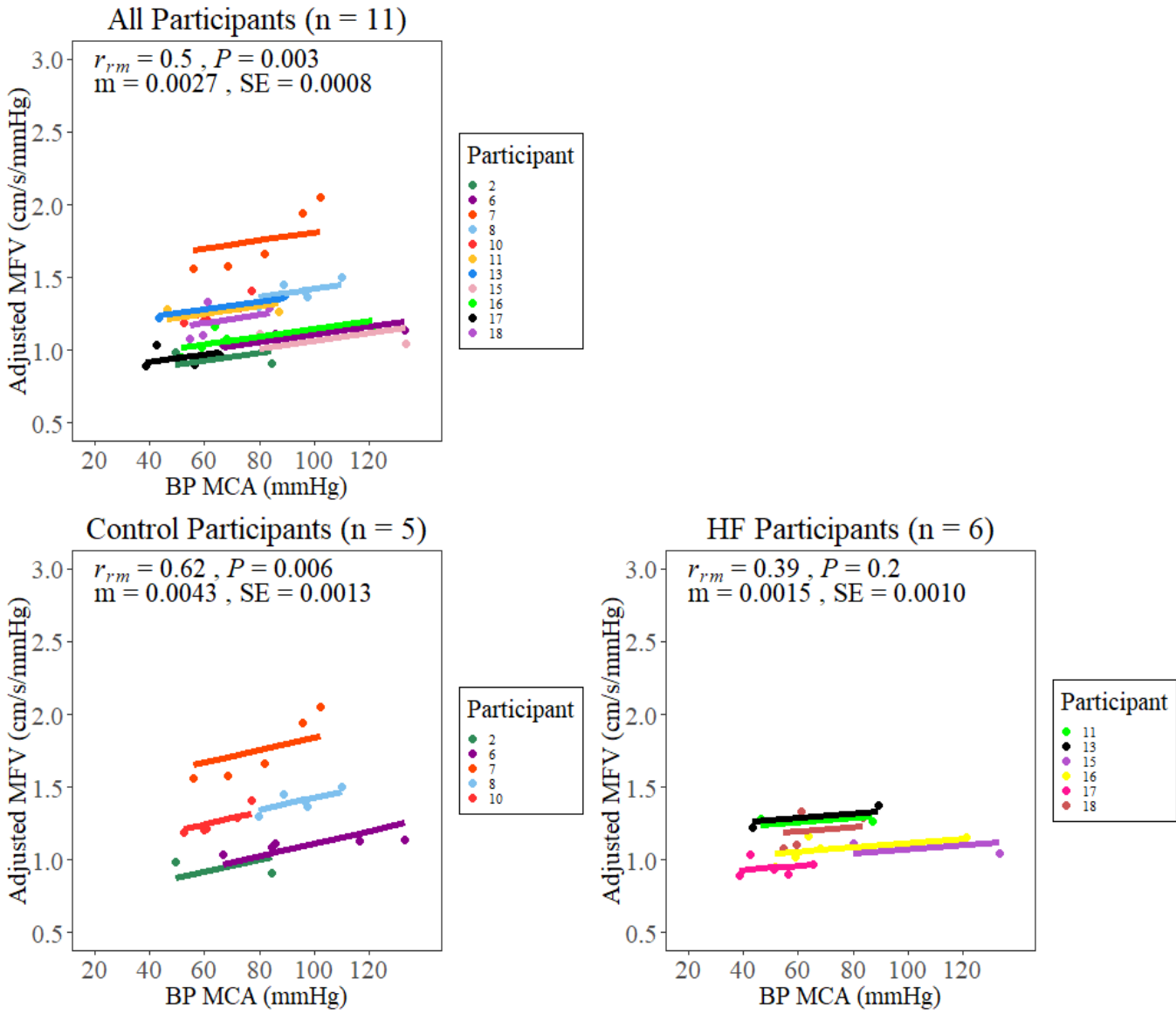
$ETCO_2$  is also known to impact CBF (Busija & Heistad, 1984). Figure 5.2 shows the repeated-measures correlation analysis between absolute MFV and  $ETCO_2$ . There were no significant correlations in either the combined, or the control group. Within the HF group, there was a moderate positive correlation ( $r_{rm}=0.58$ ,  $P=0.02$ ). Figure 5.3 shows the repeated-measures correlation analysis between adjusted MFV ( $MFV/ETCO_2$ ) and  $BP_{MCA}$  to adjust for the changes in  $ETCO_2$ . There were moderate positive correlations observed in both the combined and control group ( $r_{rm}>0.5$ ,  $P<0.01$ ). There were no correlations observed in the HF group. Repeated-measures correlations between  $CVR_i$ , adjusted  $CVR_i$ , CrCP, and perfusion pressure against  $BP_{MCA}$  are presented in Appendix E. There was a strong positive relationship between  $CVR_i$  and  $BP_{MCA}$  in the combined, control, and HF group ( $r_{rm}>0.9$ ,  $P<0.001$ ) (Figure 5.6). Similar to adjusted MFV,  $CVR_i$  was adjusted to correct for the changes in  $ETCO_2$  as  $[BP_{MCA} / (MFV / ETCO_2)]$ . A strong positive relationship was observed between adjusted  $CVR_i$  and  $BP_{MCA}$  in the combined, control, and HF group ( $r_{rm}\geq 0.9$ ,  $P<0.001$ ) (Figure 5.7). Further, there was a strong positive relationship between CrCP (Figure 5.8) and perfusion pressure (Figure 5.9) against  $BP_{MCA}$  in the combined, control, and HF group ( $r_{rm}>0.7$ ,  $P<0.001$ ) and ( $r_{rm}>0.7$ ,  $P<0.001$ ), respectively. Repeated-measures correlations between  $BP_{MCA}$  and  $ETCO_2$  are presented in Appendix F. There were no significant correlations observed in the combined, control, or HF group.



**Figure 5.1** Repeated-measures correlations between absolute values of MFV and  $BP_{MCA}$ . Individual data are represented by unique coloured circles for each participant with approximately 5 data points per person. Data points are: supine and seated baseline (-120 to -60 sec average of beat-to-beat data), standing, walk normal and walk slow (120 to 180 sec average of beat-to-beat data). Solid lines represent repeated-measures correlations for each participant, with the colours matching the individual data points. For each graph  $r_{rm}$ ,  $P$ , slope ( $m$ ), and standard error (SE) values are shown in the top left corner. MFV – mean flow velocity; BP – blood pressure; MCA – middle cerebral artery.



**Figure 5.2** Repeated-measures correlations between absolute values of MFV and ETCO<sub>2</sub>. Graph format is the same as described in Figure 5.1. MFV – mean flow velocity; ETCO<sub>2</sub> – end-tidal carbon dioxide.



**Figure 5.3** Repeated-measures correlations between adjusted MFV and BP<sub>MCA</sub>. Graph format is the same as described in Figure 5.1. Adjusted MFV – MFV / ETCO<sub>2</sub>; BP - blood pressure; MCA – middle cerebral artery.

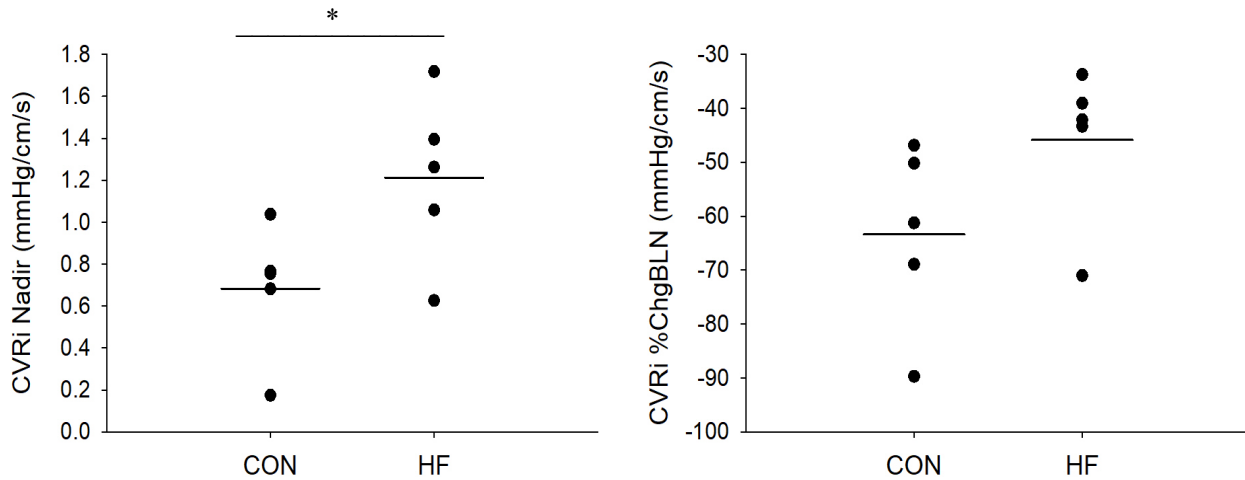
### 5.3 Dynamic Cerebral Autoregulatory Response to Supine to Stand Transition

A summary of the dynamic cardio- and cerebrovascular responses following a supine to stand transition (see “Transition” in Figure 4.1) are presented in Table 5.4. Dynamic changes in the remaining variables are presented in Supplementary Table 5.7 (see Appendix D). For HF and control participants, CVRi nadir values, and percent change from baseline to nadir, are shown in Figure 5.4. Absolute nadirs were lower in control participants compared to HF participants ( $P=0.050$ ). There was no between group difference in percent change from baseline to nadir.

**Table 5.4 Immediate cardio- and cerebrovascular response following a supine to stand transition between groups.**

	Supine-Stand		<i>P</i> -value
	Control	Heart Failure	
<b><i>Nadir: (average of 3 values taken between 0 to 30 sec post transition)</i></b>			
BP <sub>MCA</sub> (mmHg)	32±13	45±25	0.227
MFV (cm/s)	39.0±10.2	34.0±7.5	0.624
CVRi (mmHg/cm/s)	0.7±0.3	1.2±0.4	0.050
<b><i>Δ BL-Nadir</i></b>			
BP <sub>MCA</sub> (mmHg)	-63±16	-51±13	0.163
MFV (cm/s)	-10.1±3.5	-5.6±3.1	0.180
CVRi (mmHg/cm/s)	-1.2±0.4	-1.0±0.3	0.434
<b><i>% Change BL-Nadir</i></b>			
BP <sub>MCA</sub> (mmHg)	-66±12	-56±16	0.173
MFV (cm/s)	-21.3±7.9	-14.4±8.4	0.175
CVRi (mmHg/cm/s)	-63.4±17.1	-45.8±14.5	0.119

Values are mean±standard deviation. Transition is equal to the value at time 0. Nadir (BP<sub>MCA</sub> n: HF=6 CON=8, MFV n: HF=6 CON=5, CVRi n: HF=5 CON=5); Δ BL-N (BP<sub>MCA</sub> n: HF=6 CON=8, MFV n: HF=6 CON=6, CVRi n: HF=5 CON=5); % Change BL-N (BP<sub>MCA</sub> n: HF=6 CON=8, MFV n: HF=6 CON=6, CVRi n: HF=5 CON=5). BP – blood pressure; MCA – middle cerebral artery; MFV – mean flow velocity; CVRi – cerebrovascular resistance index.



**Figure 5.4** Immediate cerebrovascular resistance index response following a supine to stand transition. Individual data are displayed as single points. The solid line indicates the mean. \* $P=0.05$  between groups. CVRi – cerebrovascular resistance index.

#### 5.4 Relationship between PI and cfPWV

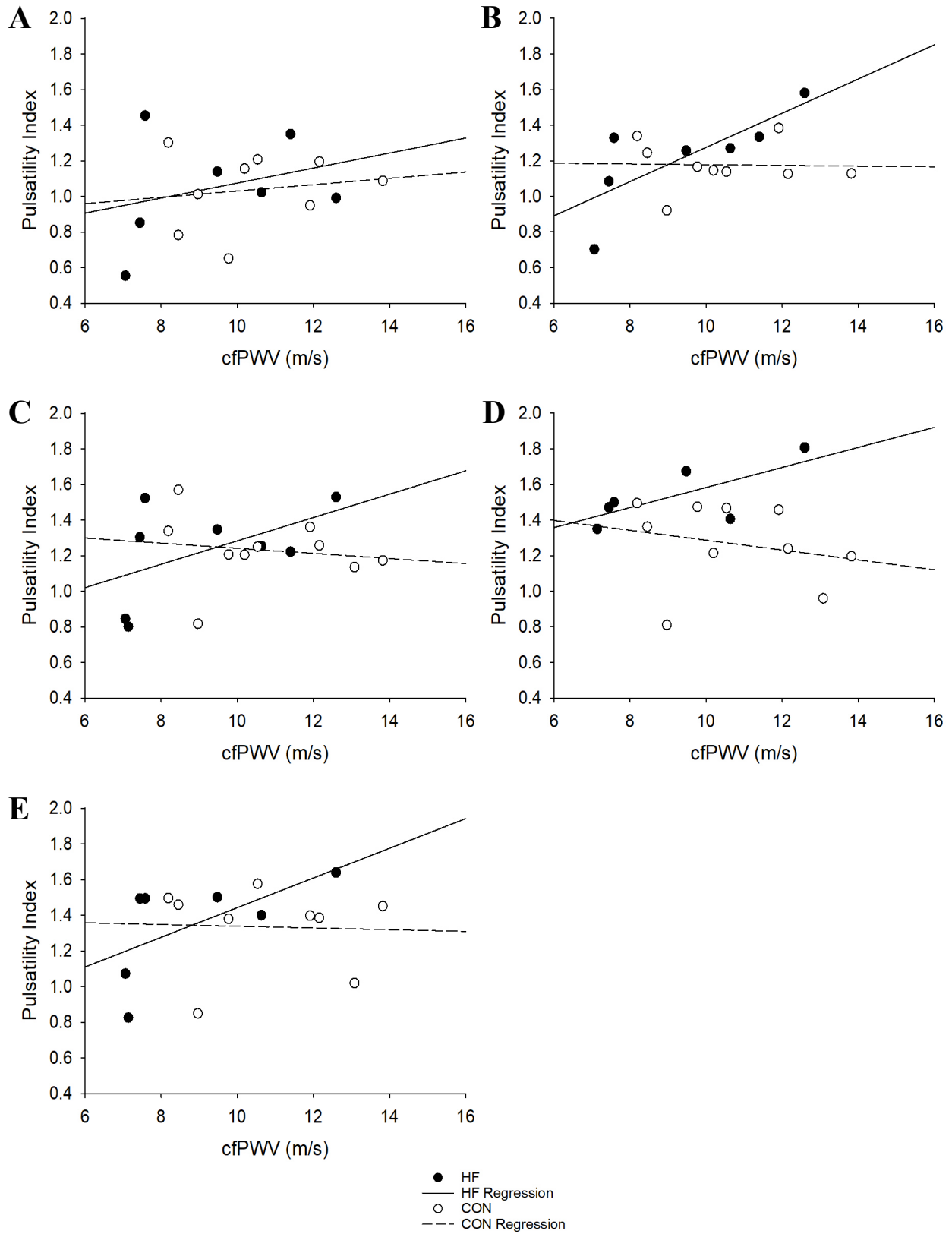
The supine, seated, and walking values of PI for each control and HF participant are presented in Table 5.5. Figure 5.5 shows scatterplots with group-specific correlations between PI and cfPWV for each transition. There were no significant correlations for the control or HF group during supine baseline, however, there was a moderate positive correlation for the HF group during the quiet stand ( $r=0.767$ ,  $P=0.044$ ). There were no significant correlations during the seated rest, walk normal, or walk slow transitions.

**Table 5.5 cfPWV and Pulsatility Index during transitions.**

	Control	Heart Failure	<i>P</i> -value
<b><i>cfPWV (m/s)</i></b>			
Supine	9.4±2.0	10.6±2.8	N.S.
<b><i>Pulsatility Index</i></b>			
Supine BL	1.04±0.21	1.05±0.30	N.S.
Standing	1.18±0.14	1.22±0.27	N.S.
Sit BL	1.23±0.19	1.23±0.30	N.S.
Walk Normal	1.35±0.24	1.35±0.29	N.S.

Walk Slow	1.29±0.26	1.53±0.17	0.05
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Baseline values are -120 to -60 sec average beat-beat data. Post values are 120 to 180 sec averaged beat-beat data. cfPWV – carotid-femoral pulse wave velocity; PI – pulsatility index.



**Figure 5.5** Relationship of PI and cfPWV between groups and transitions. Black circles



represent HF participants and white circles represent control participants. The solid black line indicates the linear regression for HF participants. The dashed black line indicates the linear regression for the control participants. A – supine rest (CON n=9  $r=0.016$   $P=0.69$ , HF n=7  $r=0.31$   $P=0.51$ ); B – standing (CON n=9  $r=0.029$   $P=0.94$ , HF n=7  $r=0.77$   $P=0.04$ ); C – seated rest (CON n=10  $r=0.15$   $P=0.67$ , HF n=8  $r=0.52$   $P=0.19$ ); D – walk normal (CON n=9  $r=0.42$   $P=0.92$ , HF n=7  $r=0.61$   $P=0.14$ ); E – walk slow (CON n=10  $r=0.23$   $P=0.52$ , HF n=7  $r=0.67$   $P=0.10$ ). PI – pulsatility index; cfPWV – carotid-femoral pulse wave velocity.

## **6.0 Discussion**

In this study, we challenged and measured cerebral autoregulatory mechanisms using both supine-to-stand and sit-to-walk transitions. We first sought to determine whether static CA was impaired in individuals with HF; this hypothesis was supported by unregulated changes in MFV with fluctuating blood pressure in individuals with HF, in response to both standing and walking. Second, we sought to determine whether dynamic CA was impaired in individuals with HF; this hypothesis was supported by a higher CVRi nadir (average of 3 lowest values taken 0 to 30 seconds post transition) in the HF group compared to controls. Lastly, we sought to determine the relationship between increased arterial stiffness and increased PI in individuals with HF; this hypothesis was supported during standing and disproved during walking.

### **6.1 The Effect of Standing and Walking on Static CA (Objective 1)**

In general, static measurements of CA evaluate the overall efficiency of the autoregulatory action and can therefore provide critical information on the regulation of brain blood flow. Previous studies have assessed CA in cerebrovascular disorders as rest (Fontana et al., 2015; Salinet et al., 2015) however, no studies have investigated CA in a clinical population through transitions to standing and walking. Of note, previous studies have assessed CA through a sit-to-stand transition (Lipsitz et al., 2000; Sorond et al., 2009), but not through a sit-to-walk transition. The novelty of CA being assessed from ambulatory transitions may be more realistic to scenarios experienced by older adults on a regular basis.

The origin of the autoregulation curve (see Figure 6.1), usually attributed to Lassen (Lassen, 1959) has become the accepted model for static CA. From this model, impaired static CA is defined as the loss of the plateau (zero slope) in the CBF versus MAP relationship. To the

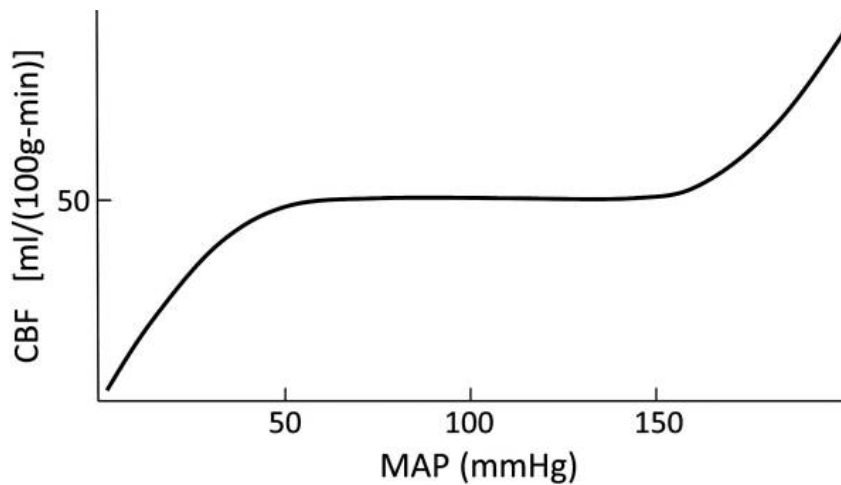
best of our knowledge, the current study is the first to measure the cardio- and cerebrovascular responses to a transition to walking in individuals with HF, and therefore, the first to assess CA from ambulatory transitions in this clinical population. There was a trend between MFV and  $BP_{MCA}$  in the control group ( $r_{rm}=0.29$ ,  $P=0.07$ ) whereas, this relationship was positively correlated in the HF group ( $r_{rm}=0.54$ ,  $P=0.005$ ), suggesting the impairment of static CA.

The concept of the plateau region (zero slope) in the CA curve has had considerable influence on the assessment of static CA in clinical studies. It is important to note however, that there may be a positive slope of the CBF-MAP relationship (as opposed to a plateau) that does not necessarily imply impaired autoregulation (Panerai, 1998). Consistent with this theory are the results from the current study that show that both control and HF participants to have a small slope in the MFV- $BP_{MCA}$  relationship however; the slope in the HF group was greater than that of the controls ( $m=0.01$  vs  $m=0.06$ ). These results suggest the maintenance of CBF in our HF sample was not as tightly regulated during variations in blood pressure throughout ambulation.

There are many factors that could have influenced the correlation observed between MFV and  $BP_{MCA}$  in the HF group (Figure 5.1) including the potential of neurovascular coupling, skeletal muscle pump activation, the reduction in cardiac output, changes in carbon dioxide, as well as the use of common HF medication.

The relative contributions of neurovascular coupling and skeletal muscle pump activation during walking have not been fully isolated within the setting of our study and therefore, may have contributed to the correlation observed in the HF group. In normal physiological function, the act of walking increases CBF however, in the setting of our study, walking did not seem to have an effect on MFV in the HF group (Murray, see Declaration). Another explanation could be ascribed to the cause-and-effect mechanism of reduced cardiac output leading to limitations in

CBF (reviewed in Meng et al, 2015), and perhaps the regulation of CBF over fluctuations in BP (discussed below).



**Figure 6.1** Illustration of the traditionally viewed concept of cerebral autoregulation. Typically CBF is thought to be maintained constant (the autoregulatory plateau) via changes in cerebrovascular resistance, over a wide range of blood pressure. Once the limits of autoregulation are reached, cerebrovascular resistance cannot correct for further changes in pressure, and the brain becomes “pressure passive”, as represented by the linear portion of the curve <50 mmHg (lower limit) or >150 mmHg (upper limit).

Figure from: (Fantini et al., 2016)

In the setting of HF, the classic autoregulatory plateau shifts downward when CO is reduced, resulting in lower CBF over a wide range of pressure. This proposition is corroborated by previous work reporting lower CBF in supine posture (Loncar et al., 2011), as well as lower CBF in the supine and seated posture (Fraser et al., 2015) in individuals with HF compared to healthy controls. Additional studies report lower supine MFV in individuals with HF compared to controls (Vogels et al., 2008). It is unknown however, how this downward shift in the plateau may influence the upper and lower boundary of CA. If the boundaries of CA shift closer together (smaller plateau), the maintenance of CBF over a range of pressure will decrease and vice versa. The ability to detect differences between HF and control participants throughout activities such as an active stand and walking suggest that perhaps the limits of CA are negatively influenced by

lower CO (Murray, see Declaration), and the relatively constant/plateau of CBF in HF is over a more restricted range of pressure.

Carbon dioxide is a known modifier of CBF; specifically, a 1 millimetre of mercury increase in arterial PCO<sub>2</sub> induces a 2% - 3% increase in CBF and vice versa (Peebles et al., 2007). In this study, there was a moderate positive relationship between MFV and ETCO<sub>2</sub> in the HF group ( $r_{rm}=0.58$ ,  $P=0.02$ ), a relationship that was not present in control participants (Figure 5.2). Upon adjusting MFV for changes in ETCO<sub>2</sub> (MFV/ETCO<sub>2</sub>), we found a moderate positive relationship in both the combined and control group whereas, no significant correlations in the HF group (Figure 5.3). These results suggest ETCO<sub>2</sub> was likely the main contributor underlying the positive correlation in the HF group between MFV and BP<sub>MCA</sub> (Figure 5.1).

A correlation was not observed between MFV and ETCO<sub>2</sub> in the control group (Figure 5.2) however, a moderate positive relationship was observed between adjusted MFV and BP<sub>MCA</sub>. This finding suggests that ETCO<sub>2</sub> was not a main contributor to the MFV-BP<sub>MCA</sub> relationship in control participants. These results may also suggest that even through small changes in carbon dioxide induced by ambulation, control participants have a greater ability to regulate CBF via the mechanisms of cerebrovascular reactivity; an ability that may be reduced in the setting of HF. Periodic breathing patterns are common in the setting of HF; perhaps the constant fluctuations in CO<sub>2</sub> that occur as a result of these breathing patterns “desensitize” HF individuals to changes in CBF thus, explaining why a correlation was not present between adjusted MFV and BP<sub>MCA</sub> in the HF group. Further exploration into cerebrovascular reactivity in response to ambulation in the setting of HF may help explain the results presented in the current thesis.

The researchers were presented with many challenges when collecting and analyzing the carbon dioxide signal. Participants were instructed to breathe through their nose during data

collection periods however, that was not possible for all study participants. This inconsistency, combined with occasional equipment malfunction during ambulation, resulted in a large amount of data dropout (ex:  $n=5$  vs.  $n=10$  in the control group). Perhaps an increased sample size would have allowed for a greater number of participants to be included in the analysis between adjusted MFV and  $BP_{MCA}$  and would better reflect the regulation of brain blood flow during transitions to standing and walking.

Our sample of HF participants were relatively “healthy” HF patients. Typical characteristics of HF include a wide spectrum of disease severity in adults over the age of 65, primarily female, and well medicated. The average age of our HF study sample was 78 and the wide spectrum of disease severity is reflected by the large range of LVEF (20-61%), attributed to the inclusion of HFrEF, HFmEF, and HFpEF patients. The male/female ratio in the HF group was 7/3. Of note, an increased number of female participants with HF may be a better reflection of HF on a larger scale. The HF participants included in our study were on various medications for HF therapy (Table 5.2), also reflecting the greater population of HF.

Interpretation of these findings should consider the use of various common medications prescribed in this clinical population, and how they may affect the limits of the cerebral autoregulatory curve. A standard component of HF therapy is the inhibition of the sympathetic drive to the heart (Florea & Cohn, 2014); as a result, many of the individuals with HF included in this cohort were on similar ‘anti-SNS’ medication regimes. There is a chance that medication use in this HF cohort may have affected the results of this hypothesis by shifting the limits of the autoregulatory curve however, no previous studies in individuals with HF have reported the effects of common HF medications on the CA curve. As recommended by Caldas et al., 2017, future investigations of patient subgroups under different pharmacological medication regimes,

such as the use of  $\beta$ -blockers (which directly affect cerebral perfusion), might help explain the role of sympathetic overactivity on static CA.

The relationship between CVRi and adjusted CVRi against  $BP_{MCA}$  are presented in Appendix E (Figures 5.6 and 5.7). These indices provide a representation of how cerebrovascular resistance index changes in response to changes in blood pressure and is a major determinant of flow [Eq4]. Results from these graphs strongly support intact autoregulation in the combined, control, and HF group in the steady-state response to ambulation. A slope closer to 1 in this analysis is indicative of maintained CBF and thus, intact CA. Also presented in Appendix E is the relationship between CrCP and perfusion pressure against  $BP_{MCA}$  (Figures 5.8 and 5.9). CrCP is defined as the theoretical value of blood pressure at which CBF approaches zero (Panerai, 2003) [Eq6], while cerebral perfusion pressure is calculated from the difference of MAP and downstream pressure of the cerebral circulation [Eq7]. While not directly related to the hypotheses of this thesis, these measures of resistance are considered to be physiologically relevant in understanding cerebral autoregulation (Weyland et al., 2000)

Potential implications of an impaired autoregulatory system may include prolonged cerebral hypoperfusion by way of reduced CBF, exacerbated in the presence of vascular risk factors- with already diminished perfusion by advancing age (De la Torre & Mussivand, 1993). This two-fold burden on CBF may contribute to both exercise intolerance, and to the declining cognitive state of the clinical HF population by causing intermittent hypoperfusion, potentially through the impairment of CA, during daily activities such as standing and walking. Understanding the mechanisms behind impaired static CA in HF can help develop treatment or therapies to ultimately increase longevity and quality of life in patients suffering from a failing heart.

## 6.2 The Effect of a Supine to Stand Transition on Dynamic CA (Objective 2)

In the clinical setting of HF, assessment of CA may identify patients at risk for cerebral hypoperfusion and syncope (Arthur & Kaye, 2000) as a consequence of impaired autoregulation. While there are a number of ways to assess and measure dynamic CA, differences in methods used to provoke changes in MAP, along with various analysis techniques, make it difficult to compare results. In healthy populations, some studies report differences in dynamic CA between postures (Deegan et al., 2010; Sato et al., 2012), while others do not (Gelinas et al., 2012; Romero et al., 2011). In these studies, dynamic CA was assessed using the autoregulation index in response to thigh-cuff deflation, rate of regulation in cerebrovascular conductance in response to 60 degree head-up-tilt, transfer function analysis in response to 90 degree head-up and head-down tilts, and transfer function analysis in response to 70 degree upright tilt with dehydration, respectively.

This study is the first to incorporate the assessment of dynamic CA through a simple supine-to-stand postural transition in individuals with HF, compared to healthy age-matched controls. In the acute response upon transition, there were no significant differences between HF and control, but HF had a higher absolute CVRi and smaller percent change at nadir compared to control participants, which might suggest impaired dynamic CA. However, no group-differences were observed in  $BP_{MCA}$  or MFV nadirs. Taken together, these data suggest preservation of dynamic CA in HF compared to control participants.

These findings contradict previous work in individuals with HF that report impaired dynamic CA during supine rest (Caldas et al., 2017), and during submaximal isometric handgrip contraction (Caldas et al., 2018). Caldas and colleagues modeled dynamic CA by transfer function analysis using spontaneous fluctuations of MAP and changes in CBFV as input and



output respectively. In the current study, the lack of difference between individuals with HF and controls could be attributed to the method of dynamic CA assessment. While posture transitions have been used previously to assess dynamic CA (Lipsitz et al., 2000; Sorond et al., 2009), other common approaches include leg cuff deflations and transfer function analysis. The lack of a ‘gold-standard’, together with the absence of well-established protocols for data measurement create major difficulties for introducing this assessment into clinical practice (Panerai, 2008).

Additionally, interpretation of these findings should also consider the well-known limitations of cardiac output and baroreceptor sensitivity in patients with HF, exacerbated by the use of  $\beta$ -blockers in 80% of the participants in the HF group. As suggested by Ogoh et al (2010), cardiac baroreflex dysfunction could attenuate dynamic CBF regulation (Shigehiko Ogoh, Tzeng, Lucas, Galvin, & Ainslie, 2010). Therefore, the lack of difference observed in this study is likely due to other factors including variability in the acute response of ambulatory transitions and small sample size. Further investigations are required to assess the prognostic value of dynamic CA parameters for the medium- and long-term outcomes of patients with HF.

### **6.3 Relationship between cfPWV and PI (Objective 3)**

Increased arterial stiffness with aging is associated with greater arterial pulse pressure (Hirata, Yaginuma, Rourke, & Kawakami, 2006). The transmission of elevated pressures into the microcirculation is detrimental, especially in low resistance organs such as the brain. Consistent with our hypothesis, we found that increased cfPWV was moderately related to an increase in PI during quiet standing in our HF group; a response that was not apparent during walking, or in either condition in control participants. The relationship of between increased PI and cfPWV may also help explain the impairment in CA observed in this HF cohort (discussed below).

The correlation observed in the current study during standing in the HF group may be partly explained by the trend toward lower  $DFV_{MCA}$  in the HF group compared to the controls (Murray, see Declaration). Elevations in pulsatility have previously been explained as a compensatory mechanism to maintain CBF, despite falling perfusion pressure (Lewis, Wong, Bannan, Piper, & Reilly, 1999). Lower  $DFV$  observed during standing in this HF cohort would imply downstream vasoconstriction leading to higher cerebrovascular resistance; this response is consistent with changes that occur during induced hypotension at the point of syncope (Thomas et al., 2009).

Of note, the index of PI is independent of pressure [Eq5] so caution must be taken when making conclusions on resistance indices (Richards, Czosnyka, Whitehouse, & Pickard, 1998). The finding of higher PI could also be attributed to smaller cross-sectional area of the vessel; however, we were unable to measure vessel diameter with the technology used this study. Results from this hypothesis are further supported by previous research in individuals with HF that report a greater increase in PI in the seated position, compared to supine posture and healthy controls (Fraser et al., 2015).

A possible group-difference in the relationship between increased PI and increased  $cfPWV$  may also reflect differences in vascular health. Hypertension and endothelial dysfunction, commonly seen in HFpEF (Borlaug & Paulus, 2011; Lam & Lund, 2016) can lead to elevated pulsatile flow patterns (Heffernan et al., 2015). Increased pulsatility in the brain has been recognized to promote various structural and functional changes to the brain, previously confirmed in individuals with HF (Alosco et al., 2013; Prins et al., 2013). A consequence of these changes, secondary to increased brain pulsatility, may result in the impairment of CA observed in this HF cohort.

As this hypothesis was only exploratory, the findings presented need to be viewed with caution. While we cannot conclude definitive statements regarding cause-and-effect, we can suggest associations between increased PI, structural and functional changes in the cerebrum, and compromised CA seen in this HF cohort. Further work to track changes in arterial stiffness, PI, and cerebral autoregulation seems warranted.

## **7.0 Limitations**

### **7.1 Participant Limitations**

Increases in sample size and better age- and sex-matching of controls is essential in all aspects of this study. While this lack of matching is a limitation, many studies do not detect any sex-related effect in cerebral hemodynamics (Deegan et al., 2010; Katsogridakis, Dineen, Brodie, Robinson, & Panerai., 2011). Of note, (Deegan et al., 2011) reported better regulation in women >70 years old compared to men. Therefore, it is possible that the higher ratio of female participants in the HF group may have influenced the results of this study. Increased sample size may have decreased the between-subject variability of the cardio- and cerebrovascular responses observed in this study presented in Appendix G, as well as increased the number of individuals included in the assessment of dynamic CA. It is a considerable challenge to collect data during the acute phase of a transition, especially in chronically ill patients, as the equipment used for ambulation is very sensitive to movement and outside noise. In this case, an increased sample size would have potentially allowed for differences in dynamic CA to be detected.

Both HF and control participants were on medications that may have affected the regulation of CBF, and since we were unable to take participants off their medications for this study it should be considered as a potential limitation. Specifically in the HF sample, obtaining information such as duration of HF diagnosis may have allowed for exploration of changes in cerebral autoregulation that may correlate with disease progression.

### **7.2 Methodological Limitations**

TCD ultrasound cannot provide absolute measurements of CBF. Since it is not possible to estimate vessel diameter, CBFV 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 MCA diameter however, results are equivocal. Previous research report an unchanging MCA diameter (Serrador et al., 2000), while other reports show MCA diameter to change during hypo- and hypercapnia (Coverdale et al., 2014). While no previous studies have directly assessed changing MCA diameter in the setting of HF, various factors such as genetic differences, and atherosclerotic plaque development will likely influence individual CBF values; a direct interpretation of CBFV as CBF should be cautioned.

This study was limited to the assessment of dynamic CA though a supine-to-stand postural transition. As this technique includes the manual selection of nadir, the small sample size after data dropout may have contributed to the lack of difference observed. The most common approach to assess dynamic CA is by transfer function analysis (Panerai, 2008). Perhaps this technique of assessing dynamic CA, as opposed to a supine-to-stand postural transition, would reveal cerebrovascular impairments in this HF cohort that we were not able to identify. Further, investigations of myogenic, metabolic, and neurogenic mechanisms in the same clinical population could provide additional information on the regulation of brain blood flow in this population.

## **8.0 Future Directions**

Results from this study show a potential impairment of static CA in individuals with HF compared to control participants, however, further work is warranted to replicate these findings and build upon the results presented here. Increases in sample size of HF participants, and a healthy age- and sex-matched control group is necessary to further assess static and dynamic CA in response to ambulatory stressors in future studies.

Future considerations should help characterize the validity of CA measures in individuals with HF during postural transitions and walking as representative real-world situations. In general, as we move toward more individualized medicine, decision-making on BP management should consider the effects on cerebral autoregulation. Additionally, as recommended by Caldas et al., 2018, an important future direction could be the longitudinal assessment of how cerebral autoregulation is affected over the course of aging and HF progression. Potentially, changes in HF severity in response to lifestyle changes or clinical intervention may affect CA. Therefore, incorporating techniques for the assessment of CA into standard clinical practice should be seen as a priority for both clinicians and researchers.

## 9.0 Conclusion

This thesis sought to determine if cerebral autoregulation was impaired in a sample of HF participants during ambulatory transitions, reflective of real-world scenarios of standing and walking. Overall, we found individuals with HF have potentially impaired static CA compared to healthy controls in response to ambulation. We speculate this impairment is a result of reduced CO (Murray, see Declaration) in the HF group, potentially coupled with a greater difference in the CBF response to fluctuations in carbon dioxide throughout standing and walking. Results from this thesis may help explain previously reported exercise intolerance and cognitive impairment in the clinical population.

These results provide novel insights about cerebral hemodynamics in heart failure populations. While multimodal recordings in participants with HF represents a challenge from a methodological standpoint, we present evidence for attention to be brought on cerebral hemodynamics outside a laboratory setting in this clinical population. Future work should continue to characterize hemodynamic responses that represent the stress of daily activities by utilizing advanced ambulatory monitoring technology in order to answer clinically relevant questions. This research provides the foundation for the assessment of cerebral autoregulation through ambulation in older adults.

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## Appendix

### Appendix A: Health Status Questionnaire

#### Health Status Form

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

Researchers and Contact Information:

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Participant ID: \_\_\_\_\_

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

#### Current Health (within the past 3 months)

List current health issues:

- 1.
- 2.
- 3.
- 4.

List current medications:

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.

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

#### Recent Nutritional Intake

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

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

#### Physical Activity

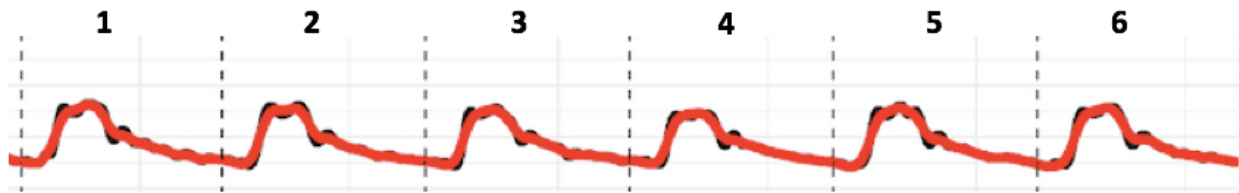
How many days per week do you participate in at least 30 minutes of continuous physical activity?  
Circle one.

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

List the activities you have performed in the last 3 months and the frequency.

- 1.
- 2.
- 3.
- 4.
- 5.

## Appendix B: Spline Interpolation of CBFV Signal



The black line is the raw CBFV signal. The red line is the CBFV signal exported from the spline interpolation script. The centered numbers represent each cardiac cycle. There is very little difference between the two tracings when the CBFV signal is strong.

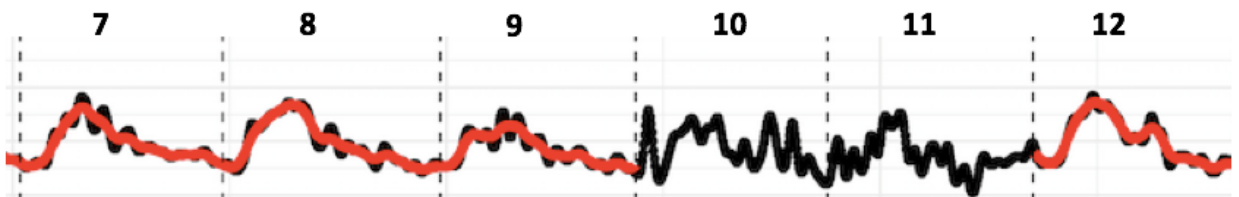


Figure format is the same as described above. The spline interpolation is able to smooth out the raw CBFV signal in cardiac cycles 7-9 however, data dropout was encountered in cardiac cycles 10 and 11 that was not able to be salvaged through the spline interpolation.

## Appendix C

**Supplementary Table 5.6 Cardio- and cerebrovascular hemodynamics between groups and transitions.**

	Supine-Stand		Sit-Walk <sub>Normal</sub>		Sit-Walk <sub>Slow</sub>	
	Control	HF	Control	HF	Control	HF
<b><i>Baseline: supine or seated (-120 to -60 sec average of beat-beat data)</i></b>						
HR (bpm)	60±11	62±6	65±11	64±7	66±11	63±7
BP <sub>MCA</sub> (mmHg)	95±17	88±32	62±25	51±17	63±26	48±13
MCA SBP (mmHg)	143±33	133±53	104±40	87±22	105±47	81±15
MCA DBP (mmHg)	70±13	65±23	41±18	33±15	42±18	32±14
PP (mmHg)	73±27	69±40	63±31	54±13	64±35	49±10
MFV (cm/s)	49.2±10.5	40.1±6.6	46.9±5.5	38.8±5.0	45.0±5.4	37.2±4.2
SFV (cm/s)	77.3±13.0	64.9±8.8	81.5±10.9	68.2±7.0	78.1±11.0	66.0±6.6
DFV (cm/s)	28.1±7.4	23.8±7.0	24.1±3.5	21.7±5.4	23.2±3.5	20.4±4.8
MCA RI	0.64±0.08	0.63±0.12	0.71±0.06	0.68±0.10	0.70±0.06	0.68±0.10
MCA PI	1.04±0.21	1.05±0.30	1.23±0.18	1.22±0.29	1.23±0.21	1.24±0.30
CVRi (mmHg/cm/s)	2.0±0.5	2.2±0.8	1.3±0.5	1.3±0.4	1.4±0.6	1.3±0.3
ETCO <sub>2</sub> (mmHg)	37.7±3.3	33.8±5.0	37.3±2.2	30.8±6.3	36.4±4.0	31.6±5.4
CrCP (mmHg)	38.3±16.4	30.7±20.3	18.7±17.0	9.9±16.1	18.8±13.1	10.9±16.5
Perfusion Pressure (mmHg)	56.8±17.4	57.4±18.2	48.1±18.4	41.4±9.2	44.2±20.4	38.1±4.8
<b><i>Post: standing or walking (120 to 180 sec average of beat-beat data)</i></b>						
HR (bpm)	69±14	68±5	86±11	83±10	79±12	77±6
BP <sub>MCA</sub> (mmHg)	60±14	50±17	60±21	46±17	62±24	47±12
MCA SBP (mmHg)	101±29	89±34	99±31	75±24	102±35	77±20
MCA DBP (mmHg)	40±11	32±12	36±17	29±14	40±19	29±11
PP (mmHg)	62±26	57±30	60±25	47±11	62±24	49±17
MFV (cm/s)	44.8±8.2	37.2±6.7	47.1±9.2	40.0±5.3	47.5±6.7	36.3±3.6
SFV (cm/s)	76.0±12.3	65.1±6.0	82.5±15.3	72.8±7.9	82.1±9.8	69.6±9.1
DFV (cm/s)	24.0±4.0	20.9±6.1	20.4±5.3	20.3±6.2	23.1±4.5	17.4±2.8
RI	0.68±0.04	0.68±0.09	0.75±0.08	0.72±0.09	0.71±0.07	0.73±0.07
PI	1.18±0.14	1.22±0.27	1.33±0.24	1.35±0.29	1.27±0.23	1.44±0.29
CVRi (mmHg/cm/s)	1.4±0.4	1.4±0.5	1.3±0.4	1.2±0.5	1.3±0.5	1.3±0.3
ETCO <sub>2</sub> (mmHg)	36.9±3.2	32.6±2.9	38.4±2.6	35.0±2.4	37.0±5.0	34.5±2.8
CrCP (mmHg)	17.1±11.1	10.6±14.4	18.0±13.6	7.7±11.1	18.8±13.1	10.9±16.5
Perfusion Pressure (mmHg)	42.4±14.9	39.5±15.1	41.9±12.1	38.8±9.1	43.8±13.9	35.3±8.3

All values are mean±standard deviation. Inferential statistics were not run on this data set as it was beyond the scope of the research question. HR – heart rate; BP – blood pressure; MCA – middle cerebral artery; SBP – systolic blood pressure; DBP – diastolic blood pressure; PP – pulse pressure; MFV – mean flow velocity; SFV – systolic flow velocity; DFV – diastolic flow

velocity; RI – resistance index; PI – pulsatility index; CVRi – cerebrovascular resistance index; ET $\text{CO}_2$  – end-tidal carbon dioxide; CrCP – critical closing pressure.



## Appendix D

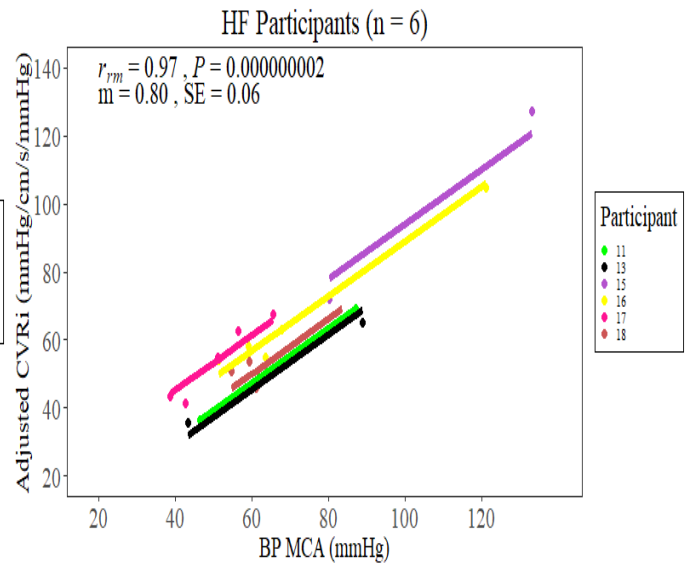
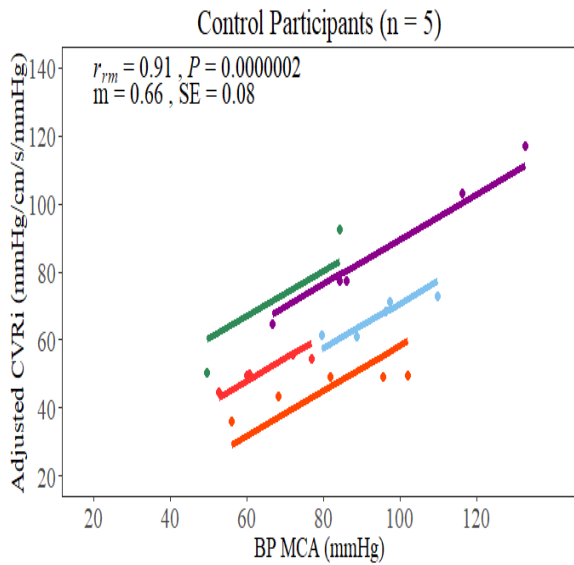
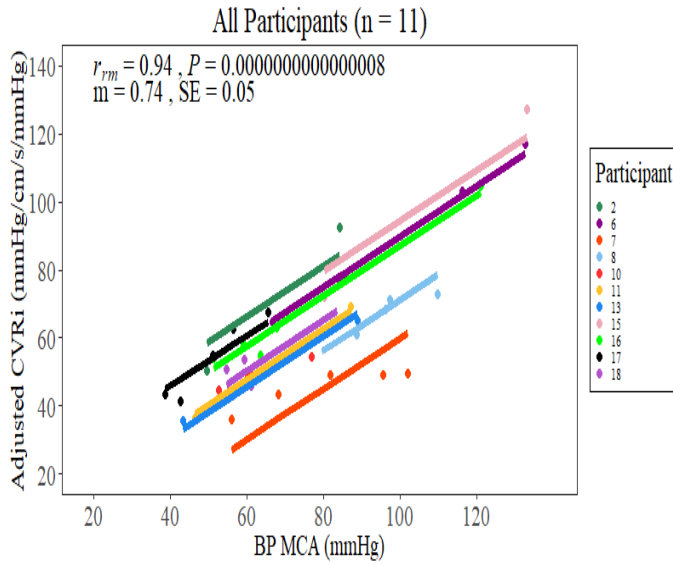
**Table 5.7 Immediate cardio- and cerebrovascular response following a supine to stand transition between groups.**

	Supine-Stand	
	Control	Heart Failure
<i>Nadir: (average of 3 values taken between 0 to 15 sec post transition)</i>		
HR (bpm)	78±12	84±11
BP <sub>MCA</sub> (mmHg)	32±13	45±25
MCA SBP (mmHg)	54±23	76±45
MCA DBP (mmHg)	20±13	23±16
MFV (cm/s)	39.0±10.2	34.0±7.5
SFV (cm/s)	67.5±16.8	58.4±8.1
DFV (cm/s)	20.1±6.2	18.2±5.7
CVRi (mmHg/cm/s)	0.7±0.3	1.2±0.4
CrCP (mmHg)	8.8±20.1	-9.3±13.9
<i>Transition-Nadir Slope</i>		
HR (bpm)	0.05±0.01	0.09±0.08
BP <sub>MCA</sub> (mmHg)	-0.17±0.05	-0.15±0.05
MCA SBP (mmHg)	-0.24±0.06	-0.20±0.11
MCA DBP (mmHg)	-0.11±0.02	-0.13±0.04
MFV (cm/s)	-0.03±0.02	-0.03±0.02
SFV (cm/s)	-0.03±0.02	-0.03±0.02
DFV (cm/s)	-0.02±0.03	-0.02±0.02
CVRi (mmHg/cm/s)	-0.003±0.0008	-0.002±0.0002
CrCP (mmHg)	-0.004±0.05	-0.17±0.09
<i>Δ BL-Nadir</i>		
HR (bpm)	17±7	22±14
BP <sub>MCA</sub> (mmHg)	-63±16	-51±13
MCA SBP (mmHg)	-91±26	-67±25
MCA DBP (mmHg)	-49±12	-49±9
MFV (cm/s)	-10.1±3.5	-5.6±3.1
SFV (cm/s)	-10.5±11.4	-5.9±7.0
DFV (cm/s)	-8.5±6.2	-5.4±4.6
CVRi (mmHg/cm/s)	-1.2±0.4	-1.0±0.3
CrCP (mmHg)	-29.3±13.6	-43.3±18.9
<i>% Change BL-Nadir</i>		
HR (bpm)	28±13	38±26
BP <sub>MCA</sub> (mmHg)	-66±12	-56±16
MCA SBP (mmHg)	-63±12	-49±17
MCA DBP (mmHg)	-72±14	-70±19
MFV (cm/s)	-21.3±7.9	-14.4±8.4

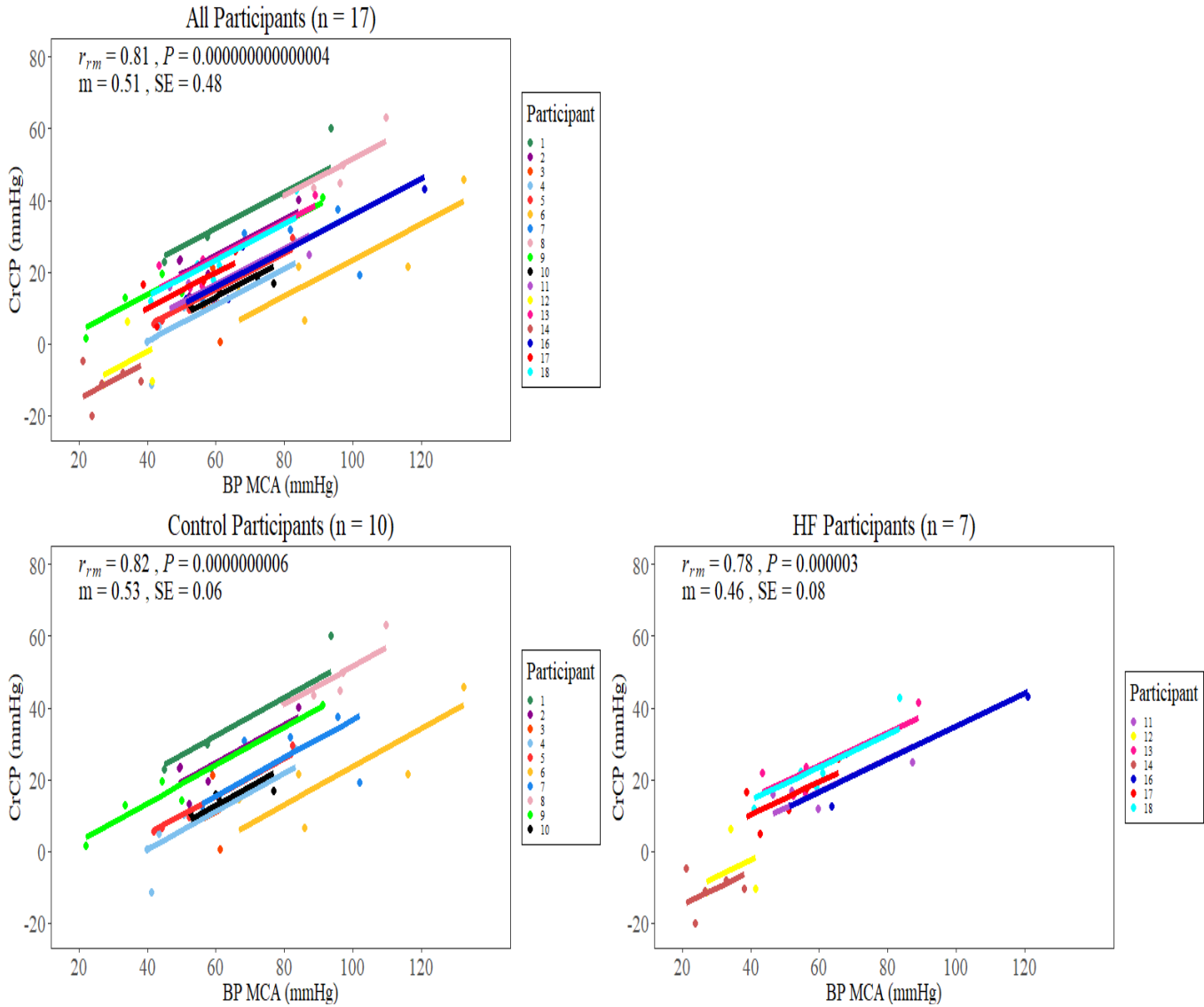
SFV (cm/s)	-13.5±14.7	-8.4±11.5
DFV (cm/s)	-29.2±15.6	-21.7±15.3
CVRi (mmHg/cm/s)	-63.4±17.1	-45.8±14.5
CrCP (mmHg)	-85.3±46.3	-127.0±53.7

All values are mean±standard deviation. HR is a maxima. Transition is equal to the value at time 0. Inferential statistics were run on BP<sub>MCA</sub>, MFV, and CVRi. HR – heart rate; BP – blood pressure; MCA – middle cerebral artery; SBP – systolic blood pressure; DBP – diastolic blood pressure; MFV – mean flow velocity; SFV – systolic flow velocity; DFV – diastolic flow velocity; CVRi – cerebrovascular resistance index; CrCP – critical closing pressure.

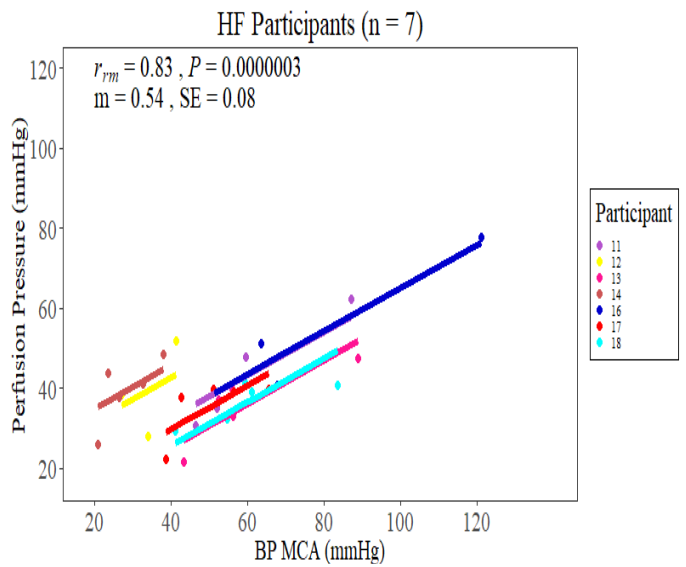
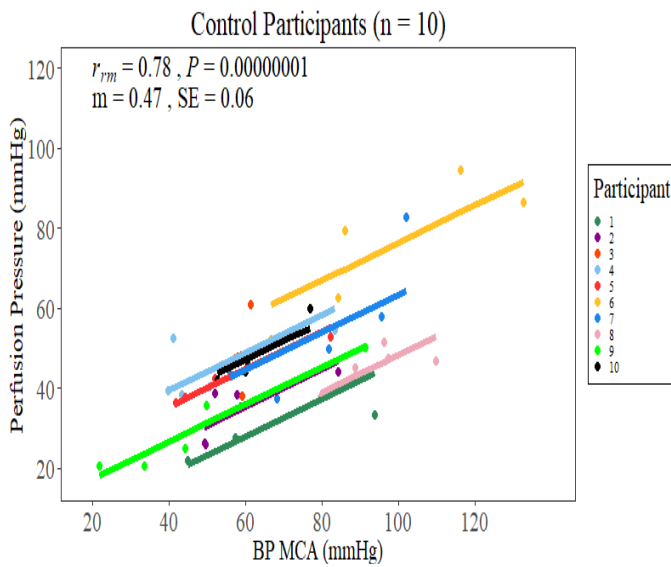
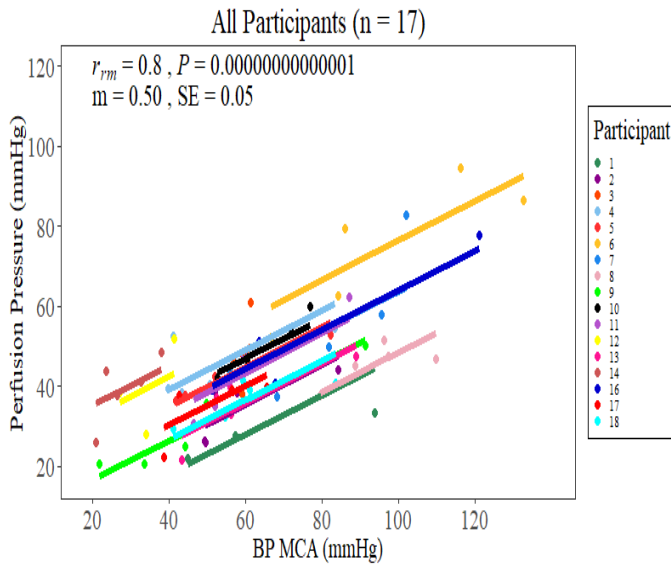




**Supplementary Figure 5.7** Repeated-measures correlations between Adjusted CVRi and  $BP_{MCA}$ . Graph format is the same as described in Figure 5.1. Adjusted CVRi –  $BP_{MCA} / (MFV / ET_{CO_2})$ ; BP – blood pressure; MCA – middle cerebral artery.

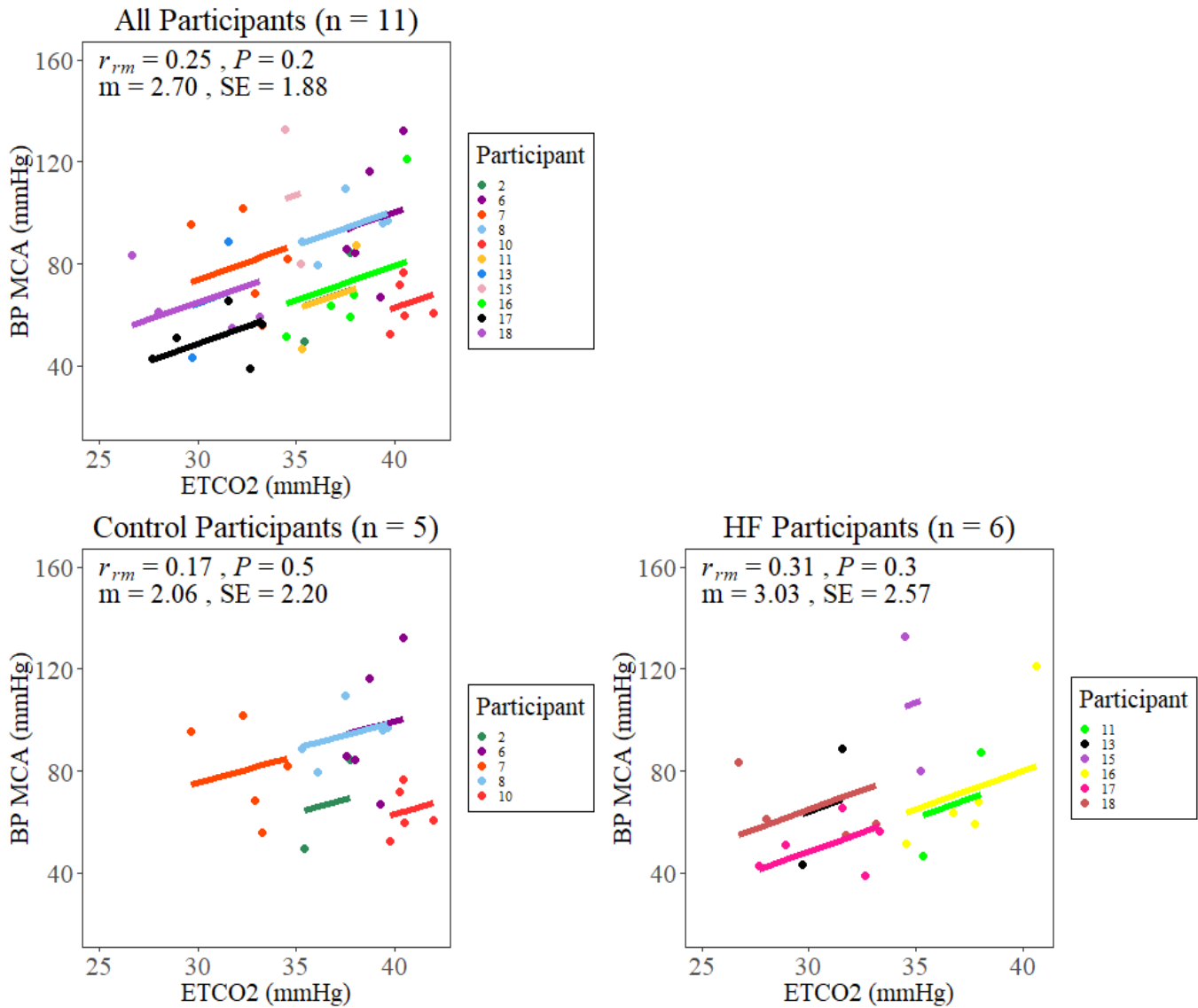


**Supplementary Figure 5.8** Repeated-measures correlations between CrCP and BP<sub>MCA</sub>. Graph format is the same as described in Figure 5.1. CrCP – critical closing pressure; BP – blood pressure; MCA – middle cerebral artery.



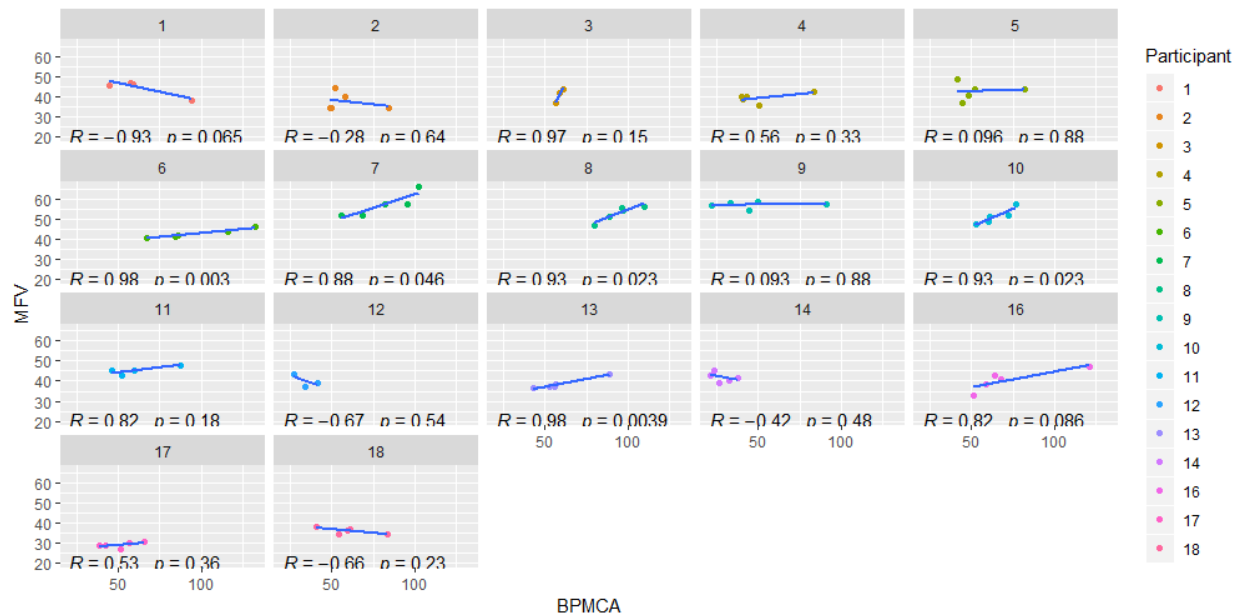
**Supplementary Figure 5.9** Repeated-measures correlations between perfusion pressure and  $BP_{MCA}$ . Graph format is the same as described in Figure 5.1. BP – blood pressure; MCA – middle cerebral artery.

**Appendix F: Repeated-measures correlations between  $BP_{MCA}$  and  $ETCO_2$ .**

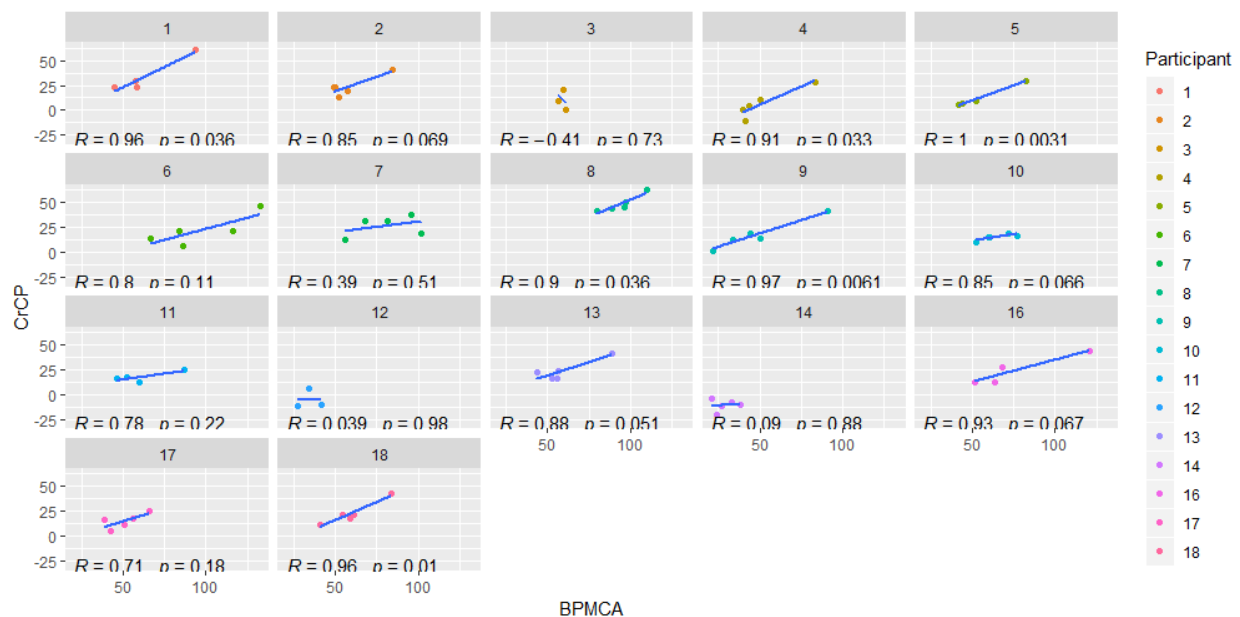


**Supplementary Figure 5.10** Repeated-measures correlations between  $BP_{MCA}$  and  $ETCO_2$ . Graph format is the same as described in Figure 5.1. BP – blood pressure; MCA – middle cerebral artery;  $ETCO_2$  – end tidal carbon dioxide.

## Appendix G: Individual Regressions for MFV and CrCP vs BP<sub>MCA</sub>



Graphs 1-10 are control participants. Graphs 11-18 are HF participants. *R* and *p* values are shown on the bottom of each graph. MFV – mean flow velocity; BP – blood pressure; MCA – middle cerebral artery.



Graph format is the same as described above. CrCP – critical closing pressure; BP – blood pressure; MCA – middle cerebral artery.