EXERCISE RESPONSE AND RECOVERY POST-STROKE

ARTERIAL STIFFNESS AND CENTRAL HEMODYNAMIC RESPONSE AND RECOVERY IN INDIVIDUALS POST-STROKE

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TITLE: ARTERIAL STIFFNESS AND CENTRAL HEMODYNAMIC RESPONSE AND RECOVERY IN INDIVIDUALS POST-STROKE

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LAY ABSTRACT:

Arterial stiffness has been recently identified as an important risk marker for stroke. Aerobic exercise reduces the risk of stroke by lowering arterial stiffness. But during exercise, there is an increase in arterial stiffness that usually subsides by 5 minutes. Lengthy exposure to arterial stiffness can cause damage to organs like the kidneys and liver. The purpose of this thesis was to measure the arterial stiffness and cardiovascular response to exercise in people with stroke. We also studied the relationship between the responses, fitness and walking ability. Ten people with stroke participated in this study. After aerobic exercise, arterial stiffness stayed high above resting levels and did not recover after 20 minutes. Also, heart rate recovery was related to fitness but not walking ability. This study tells us that people with stroke have an weakened ability to recover from aerobic exercise and that higher fitness levels can improve exercise recovery.

ABSTRACT:

Background. Stroke affects over 80 million individuals worldwide. Elevated arterial stiffness has emerged as a novel independent risk marker for stroke. While arterial stiffness is improved after chronic aerobic training, a single bout of aerobic exercise leads to transient increases that typically resolve within 5 minutes of recovery. Elevated arterial stiffness may persist for up to 30 minutes following exercise in populations with cardiovascular disease. However, no study has examined the effect of acute aerobic exercise on arterial stiffness and central hemodynamics in individuals with stroke. Moreover, no study has explored the clinical significance of these responses.

Objectives. The primary objective of this thesis was to characterize the response and recovery of arterial stiffness and central hemodynamics to peak aerobic exercise in individuals ≥ 6 months post-stroke. The secondary objective was to explore the relationships between the exercise response and recovery of arterial stiffness and central hemodynamics, with cardiorespiratory fitness and walking ability.

Results. This cross-sectional study recruited 10 adults with stroke (mean ± SD age=56.9 ± 11.8; median [IQR]= 2.9 [1.9] years post-stroke; n=4 females). After peak aerobic exercise, cfPWV increased from rest and remained elevated for 20 minutes (p<0.05). Heart rate increased and remained elevated for 10 minutes post-exercise (p<0.05), while systolic blood pressure decreased and remained reduced for 15 minutes (p<0.05). Positive associations were found between cardiorespiratory fitness and heart rate reserve (r=0.74, p=0.02), and with each phase of heart rate recovery (HR_{60s} r=0.80, p=0.005, HR_{120s} r=0.79, p=0.006; HR_{300s} r=0.72, p=0.02; and HR_{600s} r=0.75, p=0.01). There were no

relationships between response and recovery of hemodynamic variables with walking ability.

Conclusion. Individuals with chronic stroke may have impaired arterial stiffness and heart rate recovery following peak aerobic exercise. Moreover, heart rate reserve and all phases of heart rate recovery were related to cardiorespiratory fitness, but not walking ability.

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LIST OF ABBREVIATIONS

6MWT = 6-minute walk test

ANS = Autonomic nervous system

CAD = Coronary artery disease

cfPWV = Carotid-femoral pulse wave velocity

CPET = Cardiopulmonary exercise test

CVD = Cardiovascular disease

DBP = Diastolic blood pressure

DBPr = Diastolic blood pressure reserve

DBP_{rec} = Diastolic blood pressure recovery

HR_{120s} = Heart rate recovery at 120 seconds

HR_{180s} = Heart rate recovery at 180 seconds

HR_{300s} = Heart rate recovery at 300 seconds

HR_{600s} = Heart rate recovery at 600 seconds

HR_{60s} = Heart rate recovery at 60 seconds

HRR = Heart rate reserve

MAP = Mean arterial pressure

PNS = Parasympathetic nervous system

SBP = Systolic blood pressure

SBPr = Systolic blood pressure reserve

SBP_{rec} = Systolic blood pressure recovery

SNS = Sympathetic nervous system

VO_2peak = Peak oxygen uptake

CHAPTER 1: LITERATURE REVIEW

1.1 Brief overview and aims

Stroke is the second leading cause of death globally and affects over 80 million individuals worldwide (Johnson et al. 2019). Risk factors for primary stroke are well established and include current smoking, diabetes mellitus and hypertension (O'Donnell et al. 2010). In addition to these traditional risk factors, novel risk markers have also been identified to predict future stroke risk. In particular, arterial stiffness, or the hardening of the artery, has emerged as a novel independent risk marker for stroke and is a strong predictor of functional recovery post-stroke (Gasecki et al. 2012). The management of both traditional and novel risk factors is of utmost importance to improve cardiovascular health, reducing the risk of recurrent stroke or other cardiovascular event (Billinger et al. 2014).

Aerobic exercise training is well established as an effective method of managing traditional risk factors for cardiovascular disease and stroke in the general population (Lin et al. 2015). The effect of exercise training on novel risk markers is less well established, but has shown positive effects on arterial stiffness. For instance, endurance trained older adults demonstrate 35% less arterial stiffening in comparison to their sedentary counterparts (Tanaka et al. 2000).

Acute bouts of aerobic exercise may have opposite effects on arterial stiffness. Acute aerobic exercise typically transiently increases arterial stiffness and in the general population, rapidly returns towards and even below resting levels 5 minutes after exercise cessation (Mutter et al. 2017). In contrast, among those with altered cardiovascular profiles such as adults with hypertension (Gkaliagkousi et al. 2014), obesity (Bunsawat et

al. 2017) and those who smoke (Doonan et al. 2011), the increase in arterial stiffness following exercise may persist for up to 30 minutes. The prolonged exposure to increases in arterial stiffness following acute exercise has been associated with elevated cerebrovascular pulsatility, an important determinant of adverse cerebrovascular health (Lefferts et al. 2018a; Choi et al. 2018). Early studies suggest that individuals with cardiovascular disease (Miyahara et al. 1990) and stroke (Francica et al. 2015) may also have impaired central hemodynamics after acute aerobic exercise. These findings suggest that the effects of aerobic exercise on arterial stiffness and central hemodynamics may be important markers of cardiovascular health. Still, the effects of acute aerobic exercise on arterial stiffness are unknown in stroke. Additionally, the association between the changes in arterial stiffness and central hemodynamics, with functional outcomes are unclear in this population.

To explore these relationships, this literature review focuses on: 1) the pathogenesis, risk factors and effects of stroke and cerebrovascular disease, 2) the development of arterial stiffness across the adult life course, 3) the effect of acute aerobic exercise on arterial stiffness and central hemodynamics, and 4) the prognostic value of post-exercise changes in arterial stiffness and central hemodynamics.

1.2 Overview of stroke and cerebrovascular disease

1.2.1 Characteristics of stroke

The World Health Organization defines stroke as a “rapidly developed clinical sign of focal (or global) disturbance of cerebral function, lasting more than 24 hours or

leading to death, with no apparent cause other than of vascular origin" (Aho et al. 1980). In Canada, it was estimated that 405,000 Canadians experience the cognitive or physical effects of stroke, and this number is projected to reach 726,000 by the year 2038 (Krueger et al. 2015). Additionally, stroke and cerebrovascular disease accounts for nearly 14,000 deaths per year in Canada, making it the fourth leading cause of mortality in the nation (Government of Canada 2018).

Since the World Health Organization's first operational definition of stroke in the 1970s, a number of stroke subtypes and classifications have emerged over the years to reflect each distinct pathophysiological origin (Sacco et al. 2013). As there is no global consensus on the classification of stroke, a pragmatic classification was developed that included five distinct subtypes: cerebral infarctions, lacunar infarcts, total anterior circulation infarct, partial anterior circulation infarct, or posterior circulation infarcts (Amarenco et al. 2009). A more simplistic classification model adopted by both Heart and Stroke Canada and the American Stroke Association that primarily involve the distinction between ischemic and haemorrhagic stroke. *Ischemic stroke* accounts for over 80% of all stroke cases and is described as the loss of neurological function following a sudden decrease or loss of blood flow to part of the brain (Brouns and De Deyn 2009). Its pathogenesis is complex in nature, but is most typically associated with atherothrombosis or emboli deriving from local or peripheral vasculature (Brouns and De Deyn 2009; Benjamin et al. 2017). *Haemorrhagic stroke* is a rupture to a cerebral vessel and is most commonly attributed to high blood pressure and chronic degeneration of the vascular wall (Testai and Aiyagari 2008). While haemorrhagic stroke accounts for a lower proportion

of all stroke cases (10 to 20%), it is more severe and has a much higher mortality rate than ischemic stroke (Benjamin et al. 2017). In addition to these two subtypes of stroke, transient ischemic attacks (TIAs) have been identified as temporary neurological dysfunction due to focal ischemia, without the presence of acute infarction (Easton et al. 2009).

1.2.2 Risk factors for stroke

Cerebrovascular events are strongly associated with advancing age and are often attributed to aging although can still be prevalent in the younger population (Vermeer et al. 2007). The risk of stroke is also high among those with pre-existing cardiovascular disease (CVD). For instance, in a large study of 173,233 individuals with acute myocardial infarction, over 4% of individuals experience an ischemic stroke 1 year after the index event (Ulvenstam et al. 2014) of which over half of experienced a stroke within 30 days (Kajermo et al. 2014). Individuals with coronary artery disease are also at a 1.5-fold higher risk (RR=1.50, 95% CI 1.18, 1.90) for developing ischemic stroke (Olesen et al. 2017).

Risk factors for CVD and stroke can be modifiable or non-modifiable. Age and the presence of pre-existing conditions may not be modifiable, but a vast proportion of risk factors can be attributed to behaviour and thus can be modified by behaviour. The American Heart Association campaign "Life's Simple 7" outlined seven risk factors for CVD and stroke that can be modified by healthy behaviour: smoking abstinence, engaging in daily physical activity (≥150 minutes at a moderate to vigorous intensity), eating healthy (quantified as the 40_{th} percentile for higher consumption of fiber and

polyunsaturated fat, and lower consumption of trans fat and higher glycemic index foods), maintaining a healthy weight (BMI <25 kg/m2), and maintaining optimal cholesterol (<200mg/dL), blood pressure (<120/80 mmHg) and glucose (<100mg/dL) levels (Lloyd-Jones et al. 2010). In a meta-analysis of four large prospective cohort studies (pooled n=127,536), collectively adhering to the seven modifiable behaviours reduced the risk of stroke by 69% (RR=0.31, 95% CI 0.25, 0.38) (Fang et al. 2016).

1.2.3 Effects of stroke

Immediately following a stroke, a cascade of secondary biological processes are involved. Specifically, early mechanistic studies elucidated the connection between acute cerebrovascular events and subsequent systemic cardiovascular damage. Autonomic nervous system (ANS) dysfunction immediately following a stroke have shown to induce injury to cardiac tissues (Hawkins and Clower 1971). Increased sympathetic nervous system (SNS) activity produces catecholamines, which damage myocardium (Hawkins and Clower 1971) and hypothalamus activation have also shown to create electrocardiographic abnormalities through similar mechanisms (Melville et al. 1963; Fassbender et al. 1994). Stroke is often a consequence of cardiovascular damage and aging, however it is clear that the cerebrovascular event may cause secondary effects on the cardiovascular system. The effect of stroke on secondary cardiovascular damage is key to understanding the well-documented high prevalence of myocardial infarction (17%,) and recurrent stroke (43%,) 10 years after first ischemic stroke (Boulanger et al. 2018).

Stroke is a complex condition that is associated with a broader range of disability compared to other conditions (Adamson et al. 2004). A number of impairments to physical, cognitive, communication and psychosocial functioning may occur. It is estimated that 50% of individuals with ischemic stroke have reduced mobility, with over half of those individuals unable to walk without assistance (Ma et al. 2014). Additionally, over 30% experience depression (Hackett and Pickles 2014) and up to 74% experience cognitive impairment (Nys et al. 2007). Together, these effects of stroke often create barriers to participation in physical activity (Saunders et al. 2014), which in turn, it creates a vicious cycle of disability, physical inactivity, accumulation of additional CVD risk factors (e.g. damage to arterial structures) and an increased risk for recurrent events (Saunders et al. 2014).

1.3 Arterial stiffness

Arterial damage does not only occur after stroke, but also accumulates over time depending on an array of factors prior to a stroke. One of the processes that occur involves the hardening of the artery, termed arterial stiffness. Arterial stiffness is a process that occurs with age and is associated with an increased risk of stroke (van Sloten et al. 2015).

1.3.1 Mechanisms for the development of arterial stiffness

The arterial wall is comprised of three major components: the tunica intima (innermost layer), media and adventitia (outermost layer) (Figure 1). Each layer has its

own structural composition and functions, and therefore host different mechanisms for the development of arterial stiffness.

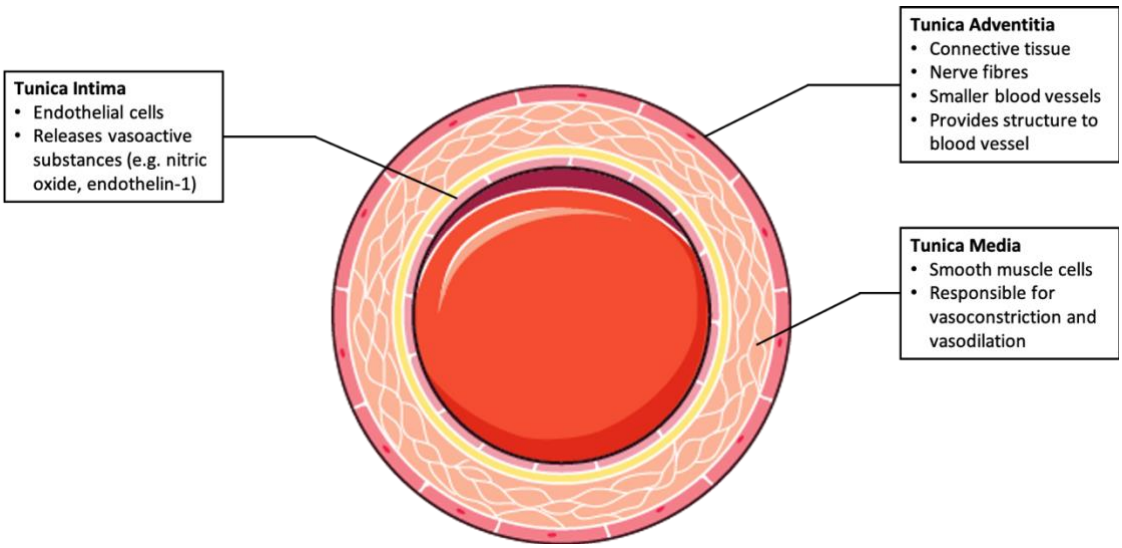

Figure 1. Anatomical cross-section of an artery, with annotated layers. Image adapted from *Servier Medical Art* (https://smart.servier.com/).

The *tunica intima* is the innermost layer of the artery made up of endothelial cells primarily responsible for secreting vasoactive substances that modulate the function of the artery (Touyz and Delles 2019). With advancing age, increased inflammation and damage to endothelial cells increases the amount of collagen found in the arterial wall, making them more stiff (Xu et al. 2000; Johnson et al. 2001). Increased intimal collagen reduces the ability of the artery to stretch followed by decreased production of nitric oxide. Finally, this leads to impaired vasodilation, reducing the body's ability to accommodate blood to target tissues (Peng et al. 2003). The *tunica media* contains cyclical layers of smooth muscle cells which constrict or dilate in response to vasoactive substances released by endothelial cells (Touyz and Delles 2019). In the tunica media,

hypertrophy and cohesion of the vascular smooth muscle cells occur due to age, creating stiffer arteries and contributing to the development of hypertension and other CVDs (Sehgel et al. 2015). Lastly, the *tunica adventitia* is the most external layer of connective tissue also containing nerve fibres and smaller blood vessels that supply the tunica media (Touyz and Delles 2019). Increased collagen is created by the dysfunctional degradation of the extracellular matrix of the tunica adventitia (Jacob 2003). This creates a hardened encasement of the artery, further reducing its ability to distend.

There is not one single mechanism for the development of arterial stiffness. However, it is important to consider that the overall process of arterial stiffening is primarily characterized by changes to various structural components at each layer of the artery and likely works in tandem with mechanisms of aging and CVD development (Townsend et al. 2015).

1.3.2 Measurement of arterial stiffness

There are a number of invasive and non-invasive approaches to measuring arterial stiffness, each with their distinct methodologies and arterial segments being studied. Interestingly, invasive methods using biological samples of the artery are not the criterion standard for assessing arterial stiffness as using ex-vivo approaches only provide information regarding the structural composition of arteries rather than a comprehensive overview of their functioning (Touyz and Delles 2019). Instead, non-invasive approaches are more commonly used in hopes to provide direct clinical application to the measurements.

Frequently used measures of arterial stiffness include augmentation index, arterial distensibility and compliance (Laurent et al. 2006), but carotid-femoral pulse wave velocity (cfPWV) is currently recommended by the American Heart Association as the criterion standard to assess the stiffness of the aorta (Townsend et al. 2015). The calculation for cfPWV is as follows:

$$cfPWV = \frac{distance}{time}$$

cfPWV is measured by placing a pressure transducer at the carotid artery and another at the femoral artery to capture the pulse wave forms at each arterial site (Figure 2). In the above equation, *time* represents the delay between the foot of the carotid waveform and the foot of the femoral waveform (*t* in Figure 2). *Distance* refers to the distance between the two pressure transducers, measured directly above the subject (d in Figure 2). To obtain a valid estimate of aortic stiffness, it is recommended to use 80% of the distance measured on the subject to represent the position of the aorta relative to the placement of the tonometer on the carotid artery (The Reference Values for Arterial Stiffness' Collaboration 2010). Greater velocity indicates greater arterial stiffening.

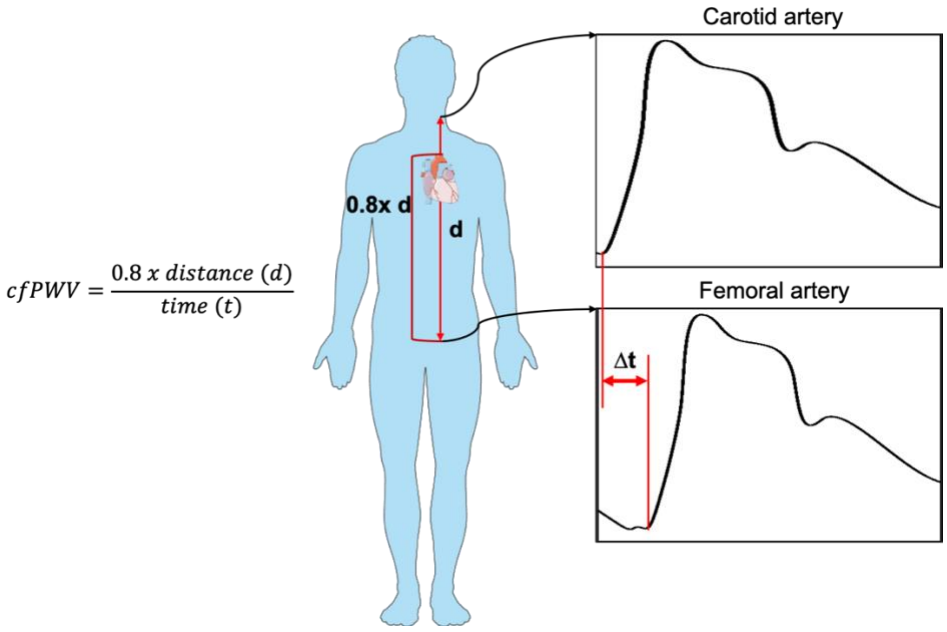

Figure 2. Components of the equation for cfPWV in a human subject.

1.3.3 Psychometric properties of carotid-femoral pulse wave velocity

Non-invasive, tonometry-derived arterial waveforms and invasive measurements of arterial stiffening were first compared in 1989, yielding identical pulse pressure waveforms and confirming the validity of non-invasive measurements in individuals without CVD (Kelly et al. 1989). Since, cfPWV via applanation tonometry is considered to be the gold-standard measure of arterial stiffness (Townsend et al. 2015). A number of studies examining test-retest reliability and reproducibility of cfPWV via applanation tonometry have emerged since the technique's inception.

The reliability of a measurement tool refers to the magnitude of measurement error between measurements made on the same subject (Bartlett and Frost 2008). It encompasses distinct concepts of both repeatability and reproducibility. Repeatability refers to the variation of the same measurement under identical conditions, and is meant

to represent errors due to measurement only (Bartlett and Frost 2008). A common measure of repeatability is test-retest reliability, determined by performing multiple measurements on the same individual with the same rater. cfPWV has demonstrated moderate to good (ICC=0.50 to 0.90) (Koo and Li 2016) test-retest reliability in individuals without CVD using applanation tonometry (ICC=0.87, $p<0.001$) (Keith et al. 2013) and Doppler ultrasound (ICC=0.62, $p<0.05$) (Sutton-Tyrrell et al. 2001).

Reproducibility refers to the variation between measurements under changing conditions such as different raters or different times of day (Bartlett and Frost 2008). A commonly used measure of reproducibility includes inter-rater reliability. Only one study reported good inter-rater reliability (ICC=0.90) for cfPWV in the general population (Clark et al. 2011). Other studies of young adults and pregnant women report ICCs of 0.84 and 0.96 within their own respective research labs (Perdomo et al. 2016; Murray et al. 2018).

Test-retest and inter-rater reliability for applanation tonometry have also been examined in other populations such as hypertension (test retest: Reliability Coefficient (RC)=0.935; inter-rater: RC=0.890) (Asmar et al. 1995), spinal cord injury (test-retest: ICC=0.91; inter-rater: ICC=0.98) (Currie et al. 2014), and also among subjects with a wide range of cardiovascular risk factors (test-retest mean difference ± SEM: 0.07 ± 0.24 m/s; inter-rater mean difference ± SEM: -0.30 ± 0.26 m/s) (Wilkinson et al. 1998). The high-level of validity and reliability applanation tonometry-derived cfPWV reinforce recommendations for its use to estimate arterial stiffness (Townsend et al. 2015).

1.3.4 Aging, arterial stiffness and cardiovascular disease

Central arterial stiffness, when measured using cfPWV, has strong prognostic value for a variety of conditions. A landmark systematic review and meta-analysis of 17 longitudinal studies (n=15,877) reported that a 1 standard deviation increase in cfPWV is associated with ~50% increased risk of cardiovascular events, cardiovascular and all-cause mortality (Vlachopoulos et al. 2010). These findings were supported by a more recent review (10 studies, 22,472 participants) which outlines the importance of the measure, demonstrating that cfPWV is associated with stroke, CVD events, all-cause and cardiovascular mortality in large epidemiological studies (van Sloten et al. 2015).

Given the prognostic significance of cfPWV, there has been great interest in establishing reference values across different age groups and conditions for its use in clinical settings. A study across 13 centres (n=1,455) demonstrated a gradient of arterial stiffness development, wherein cfPWV increases substantially with age, especially in those with pre-existing hypertension (The Reference Values for Arterial Stiffness' Collaboration 2010). Values of cfPWV increase from 6 m/s to 10 m/s among normotensive young adults through older adulthood. However, among age-matched individuals with hypertension, cfPWV values increase at a higher rate with age, progressing from nearly 8 m/s to over 14 m/s.

1.3.5 Arterial stiffness and stroke

A number of studies have examined the association between elevated cfPWV and risk of stroke. Most prominently, a meta-analysis of 10 population-based studies (n=17,662, 208,301 person-years of follow-up) found that a 1-SD increase in cfPWV

increases the risk of stroke by 18% (HR=1.18, 95% CI 1.05, 1.33) (van Sloten et al. 2015). Moreover, increases in cfPWV are predictive of stroke severity, with a 1-SD increase leading to an increased risk of stroke mortality by 39% after adjusting for age, blood pressure and other cardiovascular risk factors (RR=1.39, 95% CI 1.08, 1.72) (Laurent et al. 2003). Additionally, individuals with a cfPWV of >9.0m/s following acute ischemic stroke have a much lower chance of achieving early functional recovery, measured by the National Institutes of Health Stroke Scale (NIH) (OR=0.15; 95% CI 0.05-0.42) (Gąsecki et al. 2012).

The first study to define reference values of cfPWV in individuals with acute stroke (n=198, median age=62 years old) found that cfPWV was on average nearly 12 m/s (De Silva et al. 2008). Since then, there has been exponential growth in the number of studies assessing cfPWV in individuals with stroke. Some heterogeneity still exists among these values in this population, as they are dependent on age, number of comorbidities, type and acuity of stroke (Tuttolomondo et al. 2010). However, it appears that cfPWV is elevated in the acute phase of stroke (Tuttolomondo et al. 2010) and remains higher than the values reported for adults of a similar age without CVD or stroke in the chronic phase of recovery (Tang et al. 2014; Lee et al. 2014), with cfPWV ranging between 10 and 12 m/s.

1.4 Acute effects of exercise on arterial stiffness and central hemodynamics

1.4.1 Post-exercise response and recovery of arterial stiffness

The literature regarding the effect of acute exercise on central arterial stiffness in the general population is vast owing to the breadth of existing exercise modalities, intensities of exercise and measures of arterial stiffness. Two recent systematic reviews have been fundamental in attempting to quantify the arterial stiffness response to acute exercise (Mutter et al. 2017; Pierce et al. 2018). Pierce and colleagues (2018) found, in a systematic review of 41 studies and 1,211 participants between 18-45 years old, that an acute bout of aerobic exercise did not increase cfPWV (Pierce et al. 2018). However, the authors acknowledged that there were several methodological limitations to their conclusions including the absence of control groups in a number of included studies, differences in acute exercise protocols, and perhaps most importantly, heterogeneity in timing of post-exercise arterial stiffness assessments (Pierce et al. 2018). Indeed, the latter limitation was outlined in a previous systematic review (43 studies, n=1,089 adults >20 years old) by Mutter et al. (2017), finding that acute changes may be time-sensitive and be affected differently depending on the arterial segment being studied. Specifically, they found that central arterial stiffness was elevated within the first 5 minutes post-exercise, and returned to baseline levels thereafter whereas peripheral arterial stiffness decreased within the first 5 minutes post-exercise, and remained low beyond then (Mutter et al. 2017). While Pierce and colleagues (2018) did not find a change in cfPWV following aerobic exercise, Mutter and colleagues (2017) suggest a time-dependent course of arterial stiffening immediately following aerobic exercise.

The vast majority of studies exploring the acute changes in arterial stiffness following exercise were not consistent in the timepoints of measurement, the duration of measurement, exercise intensity or duration, nor in the definitions of timing to capture the "immediate" post-exercise response. Of the studies that have examined the longitudinal timecourse of arterial stiffening following acute aerobic exercise, most measured cfPWV at discrete timepoints after exercise cessation. For instance, Doonan et al. (2011) measured cfPWV at 2, 5, 10 and 15 minutes after exercise cessation and found cfPWV to be elevated only up to 5 minutes post-exercise (Doonan et al. 2011). The method of measuring cfPWV at discrete timepoints has excellent test-retest reliability in both young (ICC=0.94) and older adults (ICC=0.94) without apparent CVD (Keith et al. 2013; Perissiou et al. 2019). However, it is possible that taking measurements only at discrete timepoints loses sensitivity in detecting changes post-exercise. To our knowledge, only one study (Rakobowchuk et al. 2009) successfully collected continuous measurements of cfPWV after intense aerobic exercise but selected discrete timepoints for analysis (rest, 2, 15, 30, 45 and 60 minutes post-exercise). Changes to cfPWV following peak exercise are highly sensitive to physiological processes in recovery, particularly in the immediate timecourse following exercise termination. Changes may be non-linear, underscoring the need for continuous collection and subsequent analysis of cfPWV following exercise to capture all transient time-dependent changes that may occur.

The transient increases in arterial stiffness (cfPWV) with exercise is thought to occur due to both increased heart rate and blood pressure in the central system (Spronck et al. 2015; Tan et al. 2016). As exercise intensity increases, there is an increase in

circulating levels of epinephrine and norepinephrine (Greiwe et al. 1999). The effects of both catecholamines are twofold and act to 1) increase heart rate and 2) increase smooth muscle tone in the central arteries (Greiwe et al. 1999). An increased heart rate reduces the available time for elastic recoil in the arteries, which creates a more distended and stiff artery (Tan et al. 2016). Additional increases in arterial stiffening are caused by increases in smooth muscle tone (Spronck et al. 2015). During exercise recovery, there is a rapid reduction in circulating levels of catecholamines, which reduce heart rate and smooth muscle tone, which may then help revert exercise-induced transient increases in arterial stiffness (Perini et al. 1989).

Several studies have extended the analysis of acute arterial stiffness responses following exercise to populations whom may possess altered vascular structure and function, such as those with or at risk for CVD. Among individuals with hypertension, two studies reported that cfPWV was increased immediately following maximal exercise, which persisted 10 to 30 minutes afterwards (Gkaliagkousi et al. 2014; Lefferts et al. 2018b). Similar findings have been reported among individuals with obesity (Bunsawat et al. 2017) and metabolic syndrome (Radhakrishnan et al. 2017), where acute high intensity exercise increased cfPWV immediately following exercise cessation, which persisted 10 to 15 minutes thereafter. Among individuals who smoke (Doonan et al. 2011) and those who are overweight (BMI of 25 – 29.9 km/m$_2$) (Moore et al. 2016), these dynamics remain consistent where cfPWV increased immediately following exercise termination and persisted well into exercise recovery rather than returning towards baseline values. Increased SNS activity is characteristic of populations such as hypertension (Mancia and

Grassi 2014), obesity and metabolic syndrome (Lambert et al. 2010). It is possible that SNS overactivation may influence the persistent elevations in cfPWV after exercise. Persisting elevations in cfPWV may be of clinical importance for individuals at risk for CVD, but only one study has explored its subsequent effects on cardiovascular health. In individuals with and without hypertension, persistently increased cfPWV following exercise was positively associated with carotid pulsatility index, indicating large changes in blood flow through the cerebral arteries that is detrimental to the cerebrovascular health (Lefferts et al. 2018a). Taken together, in populations at risk for CVD, the increases in cfPWV that persist for up to 30 minutes following acute exercise can present with a deleterious effect on vascular health.

1.4.2 Exercise response and recovery of central hemodynamics

Exercise responses and recovery of central hemodynamics has been well studied among individuals with CVD and those at risk for CVD typically using heart rate and blood pressure reserve and recovery. Changes in central hemodynamics are monitored following a cardiopulmonary exercise test (CPET), where individuals typically exercise on a treadmill or cycle ergometer until volitional fatigue (Riebe et al. 2018). Researchers examine different phases of change throughout the exercise protocol from resting and exercise values, as well as fast (60-second) and slow phases (>60 seconds) of recovery. The changes that occur during each phase represent distinct systems functions in response to a disturbance in homeostasis. While exercise dynamics of heart rate and blood pressure may be related, it is important to recognize the subtle differences between the two. The

subsequent sections will summarize the literature related to heart rate and blood pressure responses to exercise in the general population and in individuals with stroke.

1.4.2.1 Heart rate reserve and recovery

During exercise, the SNS is activated and the parasympathetic nervous system (PNS) is suppressed causing an increase in heart rate. The difference between resting heart rate and peak heart rate achieved during exercise is heart rate reserve (HRR). It represents the degree to which an individual is able to supply their body with adequate blood flow during exercise, and thus is strongly related to cardiorespiratory fitness in the general population ($r=0.99$, $p<0.001$) (Dalleck and Kravitz 2006; Riebe et al. 2018). HRR decreases with age (Christou and Seals 2008) and is negatively associated with the risk of type 2 diabetes (Jae et al. 2016), cardiovascular (Cheng et al. 2002) and all-cause mortality (Cheng et al. 2002). While also considered paramount for exercise prescription, HRR is easy to measure, requires minimal training and has strong prognostic value.

Following peak exercise, the heart enters two phases of recovery: the fast-phase and slow-phase (Figure 3).

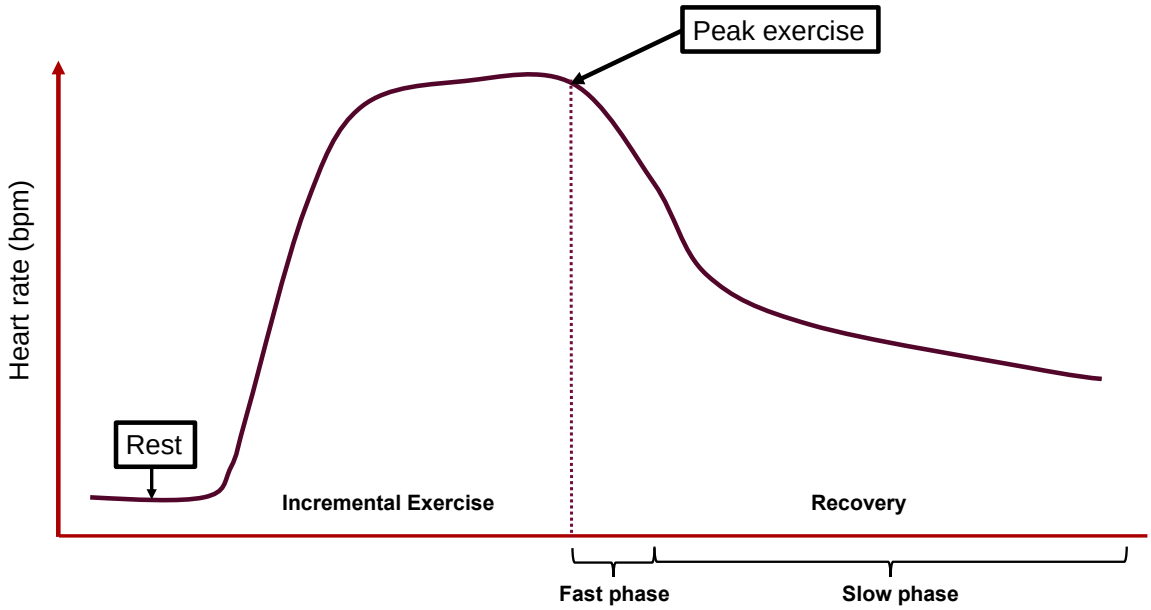

Figure 3. Phases of heart rate response and recovery before, during and after an incremental exercise test. To the left of the dashed line, red represents response during the test. To the right, in recovery, yellow represents the fast phase of recovery and green represents the slow phase of recovery following test termination.

The fast phase of heart rate recovery occurs within the first 60 seconds following exercise termination and embodies the immediate short-term recovery representing PNS reactivation and partial SNS withdrawal (Coote 2010). It is usually expressed as HR_{60s} and calculated as the difference between peak heart rate and heart rate at 60 seconds post-exercise. In the general population, there is typically a large reduction in heart rate in the first 60 seconds of exercise recovery (i.e. higher HR_{60s} value). Lower HR_{60s} values suggest impaired fast phase of heart rate recovery, which may be indicative of cardiovascular pathology. A recent meta-analysis found that for every 10-beats per minute (bpm) reduction in HR_{60s}, there is an associated 13% increased risk of

cardiovascular events and 9% increased risk of all-cause mortality (Qiu et al. 2017). One of the first studies to examine HR_{60s} suggested that values <12 bpm was an abnormal response and indicative of autonomic nervous system impairment (Cole et al. 1999). Subsequent studies have supported this cut-point to hold prognostic value across a number of populations. Among individuals with acute myocardial infarction (Nissinen et al. 2003), coronary artery disease (Vivekananthan et al. 2003) and heart failure (Nanas et al. 2006), HR_{60s} of <12 bpm has been reported to be highly predictive of all-cause mortality. In contrast however, other studies involving individuals with heart failure (Tang et al. 2009), chronic obstructive pulmonary disease (Lacasse et al. 2005) and in populations without chronic conditions (Jouven et al. 2005), HR_{60s} up to 30 bpm were still be predictive of mortality.

The slow-phase of heart rate recovery quantifies the recovery response beyond the first minute of post-exercise recovery (Figure 3). This phase of recovery primarily represents SNS withdrawal and return to homeostasis (Coote 2010). Studies examining the slow-phase of recovery have used varying methodologies of measurement, capturing the response after 2 (Cole et al. 2000a), 3 (Gayda et al. 2012), 5 (Perini et al. 1989), or 30 minutes (Javorka et al. 2002) post-exercise, or HR_{120s}, HR_{180s}, HR_{300s} and HR_{1800s}, respectively. In contrast to established cut-off values of <12 bpm associated with autonomic dysfunction for HR_{60s} (Cole et al. 1999), analogous values for slow-phase timepoints are not as well-established. For example, a cohort study of 2,193 individuals with angina found that HR_{120s} <22 bpm is associated with an increased risk of mortality (HR=2.6, 95% CI 2.4, 2.8) (Shetler et al. 2001) but another study found that HR_{120s} ≤42

bpm predicted mortality among the general population (HR=1.55, 95% CI 1.22, 1.98) (Cole et al. 2000b). With differences in measurement and cut-off values presented across an array of populations, the prognostic significance of the slow-phase of heart rate recovery has yet to be established.

1.4.2.2 Blood pressure response and recovery

With exercise, systolic blood pressure follows a similar response pattern to heart rate, characterized by a rise with increasing exercise intensities and a gradual return to baseline levels after exercise termination. Also similar to heart rate, the autonomic nervous system is the key driver for exercise and post-exercise changes, with SNS activation and PNS withdrawal leading to increased blood pressure during exercise, and PNS activation and SNS withdrawal during recovery. However, in contrast to the timecourse of heart rate recovery which seems to return towards baseline levels rather rapidly in individuals without pathologies (i.e. within 5 min), systolic blood pressure may take several minutes to a few hours to return to resting levels (Le et al. 2008). Moreover, due to the limited research in SBP_{rec}, there has been no distinction made yet between fast and slow phases of blood pressure recovery.

Nonetheless, delayed SBP_{rec} is known to be associated with adverse events. For instance, delayed SBP_{rec} among individuals without CVD is associated with a 1.69-fold increased risk of myocardial infarction (Laukkanen et al. 2004) and a 4.6-fold increased risk of stroke (Kurl et al. 2001). Its prognostic value may be explained by its association with a history of pre-existing CVD or stroke (Yosefy et al. 2006), endothelial dysfunction (Nishiyama et al. 2014) and carotid intima-media thickness (Steptoe et al. 2006).

A systematic review of 5 longitudinal studies (n=8,321) found that cut-off values for exaggerated SBP responses to symptom-limited CPETs ranged between >190mmHg to >230mmHg (Le et al. 2008), suggesting no widely accepted cut-off point for an exaggerated response to exercise. In spite of the lack of consensus, the exaggerated response is positively correlated with a number of adverse events. For instance, men with a SBP response of >19.7 mmHg per minute of incremental exercise are at a 2.3-fold increased risk of stroke (Kurl et al. 2001). Moreover, SBP ≥210, ≥214 mmHg, ≥230mmHg also were associated with an increased risk of hypertension (Manolio et al. 1994; Allison et al. 1999) and myocardial infarction (Laukkanen et al. 2004) in the general population.

Immediately following peak exercise, there is a decrease in blood pressure owing to increased PNS activity, which acts to slow heart rate and increase vasodilation of the arteries. There have been a number of methods employed to quantify SBP_{rec} following a peak exercise test, however it is most common to examine the ratio of SBP recovery at a given time post-exercise (Le et al. 2008). SBP_{rec} is typically calculated by dividing SBP measured at 1 minute post-exercise by peak SBP from the exercise test. One of the first studies to examine SBP_{rec} reported higher 1-minute recovery ratios among individuals with CAD compared to matched controls without CAD (Acanfora et al. 1988). Miyahara et al (1990) subsequently validated the use of brachial blood pressure against invasive catheterization and defined a 1-minute SBP recovery ratio of >0.94 to be an abnormal recovery response in individuals with and without CAD. Still, despite compelling evidence for the use of 1-minute SBP_{rec}, there is still a great degree of heterogeneity and

no consensus with regards to timepoints post-exercise to examine, which range from 1 (McHam et al. 1999), 3 (Taylor and Beller 1995) or 5 (Yosefy et al. 2006) minutes into recovery.

1.4.2.3 Post-exercise response and recovery of central hemodynamics in stroke

To date, a number of studies have examined response and recovery of heart rate in individuals with stroke or cerebrovascular disease, but far less for blood pressure response and recovery.

With respect to the heart rate response during peak exercise, a scoping review (112 studies, n=5,008 participants) reported that CPETs elicited heart rate responses of only 78% of predicted age-predicted maximal heart rate in individuals with stroke and TIA (Gäverth et al. 2015). In another review of 60 studies, only 20% (n=12/60) studies examining results of CPETs in people with stroke reported peak blood pressure, and none reported blood pressure recovery response (van de Port et al. 2015). Individuals with stroke were shown to have lower blood pressure responses to exercise, with no study reporting mean peak SBP >200mmHg (range: 139 to 180 mmHg) (van de Port et al. 2015). It is possible that participants were unable to achieve high heart rates or blood pressures due to cardiovascular pathologies in addition to physical limitations such as fatigue and motor control. However, no study reported controlling for the use of medication that may affect the response. Additionally, inadequate reporting of peak exercise parameters such as participants' respiratory exchange ratio and ventilatory threshold may limit the conclusions drawn in this study (van de Port et al. 2015).

Heart rate and blood pressure recovery from exercise in individuals with stroke is not yet fully understood. To our knowledge, only 3 studies (Jin et al. 2013; Francica et al. 2015; Li et al. 2019) have reported heart rate recovery following exercise post-stroke (Table 1), and no study to date has examined blood pressure recovery in this population. The first study examining heart rate recovery of individuals in the chronic stage of stroke recovery (n=128, mean age=57.6, time post-stroke=18.7 months) found that HR_{60s} was ~13 bpm in this population, which is higher than the 12bpm threshold value for HR_{60s} (Jin et al. 2013).

A study by Fancica and colleagues (2015) found that individuals in the chronic stage of stroke recovery (n=14, mean age=57.0, time post-stroke=60.0 months) had lower HR_{60s}, HR_{120s} and HR_{180s} after a submaximal CPET, compared to sex- and age-matched older adults (Francica et al. 2015). Similarly, individuals with TIA (n=120, mean age=37.8, time post-TIA=not reported) had impaired HR_{60s}, HR_{120s}, HR_{180s}, HR_{240s} and HR_{300s} compared to controls (Li et al. 2019). Together, the studies by Francica et al. (2015) and Li et al. (2019) indicate that individuals with stroke may have impaired hemodynamic recovery from exercise compared to adults without CVD although interestingly, fast-phase HR_{60s} recovery values in both studies are >12bpm (20bpm; Francica et al, 2015 and 17bpm; Li et al, 2019 (Table 1)), suggesting that this population may have preserved PNS reactivation after exercise. In contrast, HR_{120s} values are <42bpm (29bpm; Francica et al, 2015 and 32bpm; Li et al, 2019 (Table 1)) suggesting impaired slow-phases of recovery due to impaired SNS withdrawal following exercise. These three studies provide evidence towards autonomic nervous system imbalances in

individuals with stroke and TIA when indexed to heart rate recovery, however further work is required to confirm these findings.

Table 1. Comparison of heart rate recovery across studies in individuals with stroke.

Study	**HR_{60s}**	**HR_{120s}**	**HR_{180s}**	**HR_{240s}**	**HR_{300s}**
Jin (2013)	13 ± 3	NR	NR	NR	NR
Francica (2015)	20 ± 5	29 ± 6	46 ± 9	NR	NR
Li (2019)	17 ± 7	32 ± 11	43 ± 13	NR	54 ± 16

HR_{60s} = heart rate recovery at 60 seconds; HR_{120s} = heart rate recovery at 120 seconds; HR_{180s} = heart rate recovery at 180 seconds; HR_{240s} = heart rate recovery at 240 seconds; HR_{300s} = heart rate recovery at 300 seconds; NR = not reported; bpm = beats per minute.

1.4.2.4 Relationships of hemodynamics to cardiorespiratory fitness and walking ability

Despite the well-understood degree of motor limitations that occur post-stroke, only two studies have examined the relationship between cardiorespiratory fitness and walking ability in individuals with stroke. Contrary to evidence in populations without stroke, it appears that correlations between cardiorespiratory fitness and walking ability may only be low (Pang et al. 2005) to moderate (Tang et al. 2006a) ($r=0.40$, $p<0.005$; $r=0.56$, $p<0.001$, respectively). The strength of the relationship may strongly be influenced by balance, strength (Pang et al. 2005) and walking speed (Tang et al. 2006a), suggesting that walking ability may not be fully reflective of cardiovascular health in people with stroke. However, these studies used seated or semi-recumbent cycle ergometer or protocols which may underestimate cardiorespiratory fitness as these protocols engage less muscle groups. Seated or semi-recumbent cycle ergometers may be problematic for individuals with more impairment in lower- compared to upper-limb motor function, which may have influenced the observed relationship between walking ability and cardiorespiratory fitness. Protocols using exercise modalities that

accommodate all levels of ability such as recumbent steppers may offer a more valid assessment of this relationship.

It is possible that other measures that are less dependent on exercise modality are more related to walking ability in individuals with stroke, such as cardiovascular response and recovery from exercise. To date, only one study has examined cardiovascular recovery from peak exercise and walking ability in individuals with stroke. They found that both the fast-phase of heart rate recovery (HR_{60s}) and walking ability improved after a 12-week aerobic exercise intervention (Jin et al. 2013). They did not examine the relationships between these improvements, but found positive correlations between HR_{60s} and cardiorespiratory fitness ($r=0.69$, $p<0.001$). With moderate evidence of relationships between cardiorespiratory fitness and walking ability (Pang et al. 2005; Tang et al. 2006a), and cardiorespiratory fitness and cardiovascular recovery in stroke (Jin et al. 2013), it is possible that there may be a relationship between cardiovascular recovery and walking ability in individuals with stroke.

1.5 Content of thesis

Despite the breadth of studies in the general population and among those with CVD, diabetes and metabolic syndrome, no previous study has quantified the immediate, post-exercise response and recovery of arterial stiffness in individuals with stroke. Moreover, there is little evidence surrounding the response and recovery of heart rate and blood pressure to high-intensity exercise in individuals with stroke, and their association with walking ability and cardiorespiratory fitness is not well understood in this

population. Thus, this thesis examined the acute arterial stiffness and central hemodynamic response to peak aerobic exercise in individuals with stroke and explores their association to functional outcomes.

1.5.1 Study objectives and hypotheses

Primary objective: To characterize the response and recovery of arterial stiffness, heart rate and blood pressure to high-intensity aerobic exercise in community-dwelling adults with chronic stroke.

Hypothesis: Since hypertension is highly prevalent in the stroke population, and TIA is very similar to stroke, we based our hypothesis on findings by Gkaliagkousi et al (2014) and Li et al. (2019). We hypothesized that arterial stiffness, heart rate and blood pressure will remain elevated for ≥ 15 minutes after peak aerobic exercise in individuals post-stroke.

Secondary objective: To explore the relationship between the response and recovery of arterial stiffness, heart rate and blood pressure, and cardiorespiratory fitness and walking ability in individuals post-stroke.

Hypotheses: Based on previous literature by Dalleck and Kravitz (2006) and Jin et al (2013) we hypothesized that 1) there will be a positive correlation between immediate post-exercise changes in arterial stiffness, heart rate and blood pressure, and cardiorespiratory fitness and walking ability, and 2) there will be a negative correlation between post-exercise recovery of arterial stiffness, heart rate and blood pressure, and cardiorespiratory fitness and walking ability.

POST-EXERCISE CHANGES IN ARTERIAL STIFFNESS AND CENTRAL HEMODYNAMICS IN ADULTS WITH STROKE

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CHAPTER 2: MATERIALS AND METHODOLOGY

2.1 Study Design & Setting

This study was a cross-sectional analysis examining changes in arterial stiffness following peak aerobic exercise in individuals post-stroke. The analysis used baseline data from two larger clinical trials. One study was a randomised controlled trial comparing the effects of high-intensity interval training compared to moderate intensity continuous training on cardiovascular and functional outcomes. The other study was a prospective, single group study comparing the cardiovascular response to acute maximal exercise, high intensity interval exercise and moderate intensity continuous exercise. Both studies were approved by the Hamilton Integrated Research Ethics Board (HiREB #3113, #4713). Data collection for this analysis took place from June 2019 to February 2020. All data was collected in the Ivor Wynne Centre at McMaster University in Hamilton, Ontario, Canada.

2.2 Participants

2.2.1 Participant recruitment

Participants were recruited from local community stroke groups from Hamilton, Burlington and Halton regions and from a database of community-dwelling individuals with stroke who have previously participated in studies from our lab and consented to be contacted for future research. All potentially eligible participants were screened for eligibility via telephone phone call prior to their first visit.

2.2.2 Participant eligibility

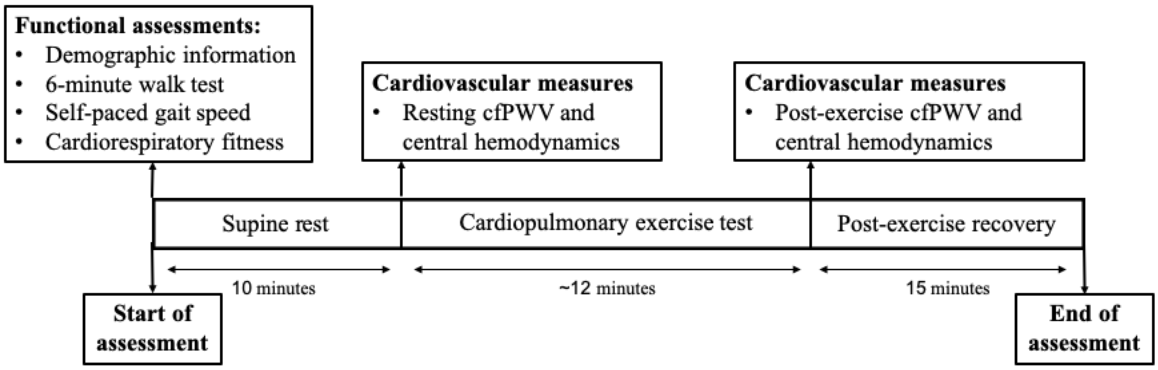
Participants were eligible for either study (HiREB #3113, or #4713) if they were 1) 40 to 80 years old, 2) ≥6 months following their first-ever, single stroke confirmed by

MRI or CT scan, 3) living in the community, and 4) able to walk at least 10 metres. Participants were excluded from the study if they 1) experienced a stroke was of non-cardiogenic origin/tumor, 2) had a modified Rankin scale score of >2, 3) were actively engaged in stroke rehabilitation services, 4) were class C or D American Heart Association Risk Score, 5) had any neurological or musculoskeletal condition precluding safe exercise, 6) experienced pain that worsened with exercise, and 7) had any contraindications to exercise testing or training as outlined by the American College for Sports Medicine (Riebe et al. 2018).

2.3 Study Assessments

A detailed schematic overview of the experimental procedure is shown Figure 4.

Figure 4. Schematic overview of the experimental procedure.



In brief, participants first completed functional assessments, followed by resting cardiovascular measurements (dependent variables: cfPWV, HR, MAP, SBP and DBP) after 10 minutes of supine rest. Participants then completed a cardiopulmonary exercise test (CPET), followed by post-exercise cardiovascular measurements for 15 consecutive minutes. The length of time post-exercise (independent variable) was recorded from the

end of the CPET protocol to the acquisition of the first pulse pressure waveform. Participant demographics including age, biological sex, details of stroke (i.e. type, location and date of stroke) and other relevant medical history (i.e. comorbidities and medication use) were recorded. Participants were also assessed for stroke severity, cognitive function and upper limb motor impairment. Stroke severity was measured by the National Institutes of Health Stroke Scale (Brott et al. 1989) and the modified Rankin Scale (van Swieten et al. 1988), where higher scores in both tests indicate greater severity (maximum scores: 42 and 6, respectively). Cognitive function was measured by the Montreal Cognitive Assessment (MoCA) (Hobson 2015), where higher scores indicate higher cognitive functioning (maximum score: 30). Upper limb motor impairment was measured by the arm and hand impairment inventories of the Chedoke-McMaster Stroke Assessment (Gowland et al. 1993), where higher scores indicate greater motor recovery (maximum score: 14, 7 for both arm and hand).

2.3.1 Functional measures

2.3.1.1 Cardiorespiratory fitness

Cardiorespiratory fitness, measured by a CPET reflects the body's ability to perform dynamic, moderate- to vigorous-intensity exercise for an extended period of time and is an important determinant of overall health (Riebe et al. 2018). Individuals with stroke present with reduced cardiorespiratory fitness, and in some cases are as low as 60% of age-matched counterparts (Mackay-Lyons and Makrides 2002). These reductions may be due to poor cardiovascular health that contributed to the development of stroke, or because of secondary conditions that impair their ability to perform exercise post-stroke

(Billinger et al. 2012). Typically measured using a cycle ergometer (van de Port et al. 2015), the assessment of cardiorespiratory fitness is feasible in the stroke population, but presents some significant limitations (Tang et al. 2006b). For instance, measuring cardiorespiratory fitness using a cycle ergometer protocol has only moderate test-retest reliability (ICC=0.50, 95% CI 0.10, 0.77) and may be susceptible to differences of up to 21% between repeated assessments (Tang et al. 2006b). Furthermore, reduced lower-limb motor ability may reduce an individuals' ability to perform high-intensity exercise. A recumbent stepper protocol has been validated to address these challenges, eliciting greater cardiorespiratory fitness than a cycle ergometer protocol (16.6 ± 4.5 mL/kg/min vs. 15.4 ± 4.5 mL/kg/min) (Billinger et al. 2008). Therefore, to accommodate a wider range of stroke severity in cardiorespiratory fitness assessments, it is currently recommended to use a recumbent stepper protocol (van de Port et al. 2015).

As such, participants completed a modified CPET on a recumbent stepper (model NuStep T4r, NuStep LLC, Ann Arbor, MI, USA) validated for individuals with stroke (Billinger et al. 2008). Peak oxygen consumption (VO_2peak, mL/kg/min) was the primary outcome of test, collected using a metabolic mixing chamber system (model Quark CPET, COSMED SrI, Rome, Italy) to assess cardiorespiratory fitness. The CPET was also used as the exercise stimulus upon which we examined exercise response and recovery of cardiovascular variables. Subjects performed a 4-minute warm-up at approximately 20 watts, followed by a graded exercise test which increased in resistance every two minutes for a maximum of 7 stages at a minimum cadence of 80 steps per minute. The test was terminated if subjects reached volitional fatigue, could not

consistently sustain the appropriate cadence and/or achieved any of the ACSM test termination criteria for exercise testing (Riebe et al. 2018). Immediately after peak aerobic exercise was achieved, participants engaged in passive recovery for 1 minute. To accommodate the variability in participants' functional abilities, individuals were then permitted to cool down at a self-selected cadence which lasted up to 5 minutes after peak aerobic exercise. During the CPET, heart rate data was obtained using a wireless heart rate monitor (Polar H10 Heart Rate Sensor, Polar Electro, Kempele, Finland). Blood pressure (Dinamap V100, General Electric Healthcare, Chicago, IL, USA) and a ratings of perceived exertion (RPE) scale (Borg 1982) were monitored in each stage of the exercise test.

2.3.1.2 Self-paced gait-speed test

Walking ability was quantified using the 10-meter self-paced gait-speed test (m/s, primary outcome of the test). Among individuals with stroke, gait speed is reflective of lower-limb muscle function (Nasciutti-Prudente et al. 2009), strength (Severinsen et al. 2011), and walking activity at home and in the community (Fulk et al. 2010). Impaired gait speed (< 0.82 m/s) is an important marker of health and is predictive of all-cause mortality among older adults (Stanaway et al. 2011). Depending on the severity of stroke, individuals have marked limitations in walking speed, ranging broadly from 0.23 m/s to 0.95 m/s, however a vast proportion of individuals fall below 0.73 m/s (Beyaert et al. 2015). While there are large differences in gait speeds between individuals, only methodological differences exist in the distance walked between tests. Studies have used variable distances of 8 (Eng et al. 2002), 9 (Fulk and Echternach 2008) and 10 meters

(Severinsen et al. 2011) to assess gait-speed. Despite differences in test distances, gait-speed tests have repeatedly demonstrated good to excellent test-retest reliability across individuals with a range of abilities (Fulk and Echternach 2008).

Participants in this study were instructed to walk at their self-selected walking pace along a 10-meter hallway. To account for acceleration and deceleration, only the walking time of the middle 6 meters were recorded. Participants underwent two trials, and the average of the trials were taken. Gait aids (e.g. walkers, canes) were permitted for this test if needed. Safety supervision, but not physical assistance, was provided if needed.

2.3.1.3 6-minute walk test

Walking ability was also quantified using the 6-minute walk test (6MWT). The 6MWT is a comprehensive submaximal exercise test that evaluates the global functioning of many bodily systems (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002). The use of this test in people with stroke embodies the comprehensive nature of the test, wherein the 6MWT may reflect both cardiovascular and neuromuscular health due to the downstream effects of stroke on a number of body systems (Eng et al. 2004). A systematic review and meta-analysis (127 studies, n=6,012) found that 6MWT distances in individuals with stroke are much lower than older adults without stroke or cardiovascular disease (284 m vs 499 m) (Dunn et al. 2015). Dunn and colleagues (2015) identified large variations in disability post-stroke, which has significant effects on distance covered. Despite the large heterogeneity of distance covered in individuals with stroke, the test still boasts excellent within-subject

(test-retest) reliability (ICC=0.97-0.99) and is moderately correlated with cardiorespiratory fitness ($r=0.66$, $p<0.05$) (Eng et al. 2004; Fulk et al. 2008).

The 6MWT was conducted according to the American Thoracic Society guidelines using a straight 20-meter hallway (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002). Participants were instructed to walk as many lengths between the two points as they could for 6 minutes. Gait aids (e.g. walkers, canes) and seated rest were permitted for this test if needed. To ensure participant safety, heart rate, blood pressure and ratings of perceived exertion (RPE) were recorded before and after the exercise test. The primary outcome of this test was distance walked in meters.

2.3.2 Cardiovascular measures

2.3.2.1 Central arterial stiffness

Central arterial stiffness was determined using the criterion standard carotid-femoral pulse wave velocity (cfPWV, m/s). For resting cfPWV measurements (pre-exercise), participants were instructed to lay supine for at least 10 minutes before the collection of cfPWV. The post-exercise measurement was taken after a maximum of 5 minutes of active recovery following the CPET. Participants were again instructed to lay supine, and pulse pressure waveforms were collected continuously for 15 minutes following the acquisition of the first clear signal (time between end of active recovery and first clear signal = 5.9 ± 1.7 minutes). Both resting and post-exercise cfPWV were measured via applanation tonometry using a pressure transducer (tonometer model SPT-301, Millar Instruments Inc., Houston, TX, USA). The probe was placed over the skin on

the non-paretic side at the carotid and femoral arteries of the participant. Pulse pressure waveforms were collected simultaneously by two experienced testers (KN & KM) The sampling rate was 2 kHz, and band-pass filtered at 5-30 Hz to identify the foot of each waveform (LabChart7 Pro, ADInstruments, Colorado Springs, CO, USA). The distance between the two sites was measured 5-6 inches above the participant to account for individual variation in body size and type.

In accordance with the ARTERY Society guidelines (Wilkinson et al. 2010), a minimum of 10 consecutive and consistent waveforms were collected after at least 10 minutes of supine rest to obtain a measure of resting cfPWV. In order to calculate cfPWV, the time delay between the foot of the carotid and the femoral waveform was averaged for at least 10 consecutive heart cycles and subsequently divided by 80% of the distance between both sampling sites (0.80 x measured distance between sites).

2.3.2.2 Central hemodynamics

Resting heart rate (bpm) and brachial blood pressure (mmHg) were determined using an automated blood pressure monitor (Dinamap V100, General Electric Healthcare, Chicago, IL, USA) following at least 10 minutes of supine rest. To address our primary objective, resting values and changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) a were continuously measured using a three-lead electrocardiograph system (Dual Bio Amp FE232, ADInstruments) and a beat-to-beat finger blood pressure monitoring system (Finometer MIDI, Finapress Medical Systems, Amsterdam, Netherlands). To address our secondary objective, heart rate calculations were derived from data of a wireless heart rate sensor

(Polar H10 Heart Rate Sensor, Polar Electro, Kempele, Finland) and a three-lead electrocardiograph system (Dual Bio Amp FE232, ADInstruments).

2.4 Statistical Analysis

Descriptive statistics using means and standard deviations, medians and interquartile ranges, were used to describe demographic information and sample characteristics for continuous, normally and non-normally distributed data, respectively. Frequencies and percentages were used to describe categorical data. All statistical analyses were performed using commercially available software (Stata 16.1, College Station, TX, USA).

2.4.1 Primary objective: Characterizing the response and recovery of cfPWV and central hemodynamics

Mixed-model analyses were applied to characterizing the response of cfPWV and central hemodynamics following acute, high-intensity aerobic exercise of individuals post-stroke. Dependent variables were cfPWV, HR, SBP, DBP and MAP, and the independent variable of interest was time post-exercise. We first visually assessed the relationship between the dependent and independent variables using lowess plots. If the relationship appeared to be non-linear, polynomial terms were considered in the analysis.

Age was included as a covariate in all models due to its relationship with arterial stiffness (The Reference Values for Arterial Stiffness' Collaboration 2010). MAP was included as a covariate in the model as it is known to influence changes in cfPWV (Spronck et al. 2015). Models were tested for both fixed and random intercepts and slopes, and the most appropriate residual covariance structures were applied. The

Bayesian Information Criteria and log likelihood ratio tests were used to determine the best fitting mixed model. Pairwise comparisons using a Sidak correction were used on all models to determine when statistically significant differences from rest were present (Kowalchuk and Keselman 2001). The accepted two-tailed significance level was set *a priori* to $p < 0.05$.

2.4.2 Secondary objective: Association between response and recovery of cardiovascular outcomes with functional outcomes

Calculations for exercise response and recovery of cfPWV, heart rate and blood pressure were defined as follows:

1. Arterial stiffness reserve (cfPWVr) was defined as the peak recovery cfPWV value following the CPET minus resting cfPWV.
2. In the absence of previous literature on the subject, arterial stiffness recovery (β cfPWV) was defined as the slope of recovery (m/s per minute) between the peak recovery cfPWV value following the CPET and cfPWV at 15 minutes post-exercise.
3. Heart rate reserve (HRR) was defined as peak heart rate achieved during the CPET minus resting heart rate.
4. Fast-phase heart rate recovery (HR_{60s}) was defined as the difference between heart rate at 60 seconds post-exercise at the end of passive recovery and peak heart rate.
5. Slow-phases of heart rate recovery (HR_{120s}, HR_{300s} & HR_{600s}) were defined as the difference between the difference between heart rate at 2, 5 and 10 minutes post-exercise, and peak heart rate.

6. Systolic and diastolic blood pressure reserve (SBPr/DBPr) were defined as peak blood pressures achieved during the CPET minus resting blood pressures.
7. Fast-phase systolic and diastolic blood pressure recovery (SBP_{rec}/DBP_{rec}) were defined as the ratio of blood pressure at 1-minute post-exercise during passive recovery divided by peak blood pressure.

Pearson's product moment correlation analyses were conducted to examine the associations between exercise response and post-exercise recovery of cfPWV and central hemodynamics (independent variables), and measures of cardiorespiratory fitness and functional ability (dependent variables). The accepted two-tailed significance level was set *a priori* to $p < 0.05$.

2.5 Sample Size Calculation

An estimate of the required sample size was derived for mixed models examining the effect of acute exercise on arterial stiffness in people with stroke (primary objective) (Stata 16.1, College Station, TX, USA). We considered cfPWV (dependant variable) and time post-exercise (independent variable) as fixed effects, and also included a random intercept in the calculation. Additionally, the preliminary model included age and mean arterial pressure as covariates, as they were also used in the current study. We calculated Cohen's f^2 effect size with a previously reported formula (Selya et al. 2012). We found an effect size of $f^2 = 0.21$, a moderate to large effect which is consistent with a priori estimates made from another modelling changes in cfPWV after acute exercise (Way et al. 2020). Using this f^2, a sample size of 36 individuals would be sufficient to detect a

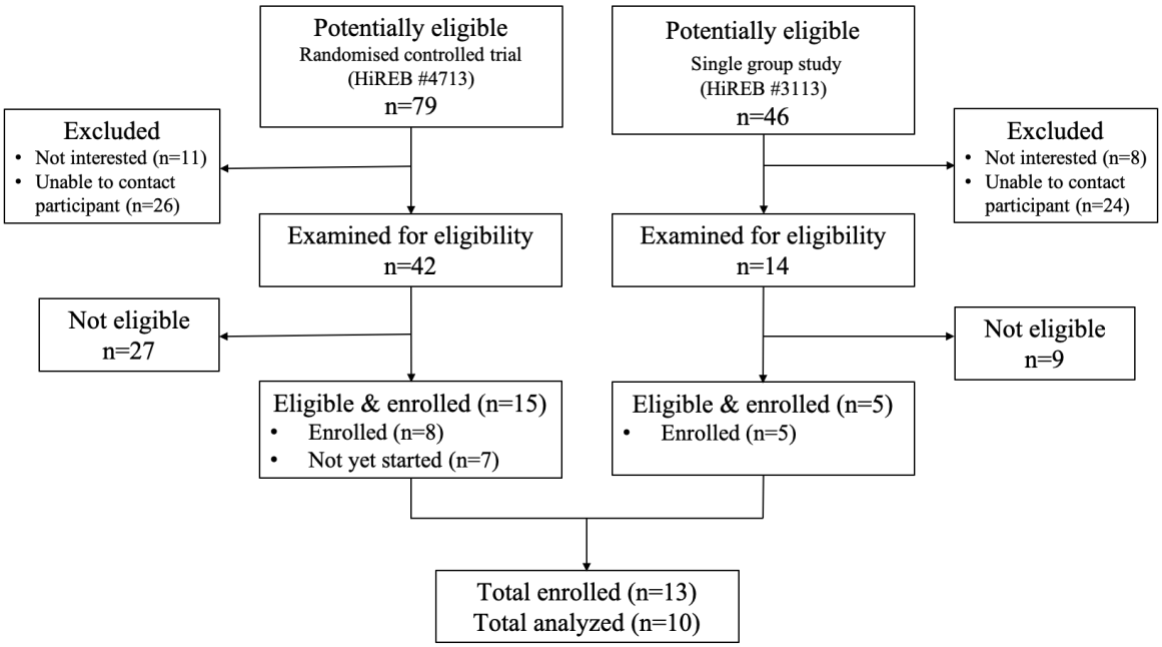
moderate to large effect (Cohen 1992) of acute exercise on cfPWV with 80% power and an alpha of 0.05.

CHAPTER 3: RESULTS

3.1 Participant characteristics

A detailed flow of participants is described in Figure 5. Of 79 individuals with stroke approached for participation, 56 were assessed for eligibility and 13 were enrolled across both studies. As of March 18 2020, we were able to obtain baseline data on a total of 10 participants (n=6 male, n=4 female) before data collection was halted due to directives from McMaster University in response to the COVID-19 pandemic.

Figure 5. Participant recruitment flow chart.



Participant characteristics are presented in Table 2, disaggregated by sex. There were no differences between males and females across all variables. Although National Institutes of Health stroke scale and Montreal Cognitive Assessment scores suggest mild stroke severity and mild cognitive impairment, 6MWT distances were 66.4% ± 10.0% (males) and 100% ± 6% (females) of reference values (Enright and Sherrill 1998).

Table 2. Participant characteristics for entire sample (n=10) and disaggregated by sex.

Variable	Total n=10	Females n=4	Males n=6
Age (years)	56.9 ± 11.8	55.5 ± 13.3	57.8 ± 11.9
Type of stroke, n (%)			
Ischemic	6 (60.0%)	2 (50.0%)	4 (66.6%)
Haemorrhagic	0 (0%)	0 (0%)	0 (0%)
Unknown	4 (40.0%)	2 (50.0%)	2 (33.3%)
Time post-stroke (years), median (IQR)	2.9 (1.9)	2.8 (7.9)	3.1 (2.3)
Comorbidities, n (%)			
Hypertension	7 (70.0%)	2 (50.0%)	5 (83.3%)
Type 2 Diabetes	3 (30.0%)	0 (0.0%)	3 (50.0%)
Body mass index (kg/m$_2$), median (IQR)	28.2 (4.6)	27.9 (3.2)	29.2 (4.8)
Montreal Cognitive Assessment	24.8 ± 4.1	24.0 ± 5.7	25.3 ± 3.2
NIH Stroke Scale	2.9 ± 1.1	3.0 ± 1.4	2.8 ± 0.8
Chedoke-McMaster Stroke Assessment			
Arm inventory	5.9 ± 1.5	7.0 ± 0.0	5.0 ± 1.4
Hand inventory	5.4 ± 0.9	6.0 ± 0.8	5.0 ± 0.7
Self-paced gait speed (m/s)	1.2 ± 0.2	1.3 ± 0.2	1.1 ± 0.2
6-minute walk distance (m)	410.8 ± 119.3	459.3 ± 62.9	381.6 ± 141.8
Resting heart rate (bpm)	69.9 ± 10.6	72.2 ± 8.1	68.3 ± 12.5
Resting systolic blood pressure (mmHg)	125.8 ± 12.6	126.8 ± 15.1	125.2 ± 12.2
Resting diastolic blood pressure (mmHg)	73.3 ± 5.6	70.0 ± 2.2	75.4 ± 6.3
Peak heart rate (bpm)	135.9 ± 26.9	153.8 ± 23.0	124.0 ± 23.7
Peak systolic blood pressure (mmHg)	183.8 ± 26.6	186.2 ± 22.3	182 ± 31.2
Peak diastolic blood pressure (mmHg)	84.5 ± 7.4	86.5 ± 6.7	83.2 ± 8.1
VO_2peak (mL/kg/min)	19.0 ± 5.5	18.3 ± 5.2	19.5 ± 6.2
Resting carotid-femoral pulse wave velocity (m/s)	9.0 ± 2.1	9.6 ± 2.4	8.6 ± 1.9

Values are mean ± SD unless otherwise stated. SD = standard deviation; IQR = interquartile range; NIH = National Institutes of Health

3.2 Primary Objective: Characterizing the response and recovery of cfPWV and central hemodynamics

3.2.1 Post-exercise changes in cfPWV

Upon visual inspection of lowess plots (Appendix 1), the relationship between cfPWV and time post-exercise appeared to be non-linear. Thus, time$_2$ and time$_3$ terms were included in the model to capture the polynomial relationship. The best fitting model

included age (β=0.14 (SE= 0.04), 95% CI 0.05, 0.23, p=0.008) and MAP (β=0.02 (SE= 5), 95% CI 0.007, 0.03, p=0.005) as covariates, a random slope (variance estimate = 0.001 (SE= 0.0009), 95% CI 0.0003, 0.005) and intercept (variance estimate = 2.59 (SE= 1.20), 95% CI 1.04, 6.42), and an independent covariance structure. Results of the mixed model are presented in Table 3. There was a non-linear association between time post-exercise and cfPWV (β=0.0006 (SE= 0.0001), 95% CI 0.0004, 0.009, p<0.001). Post-exercise cfPWV was increased from resting levels, and remained elevated for up to 20 minutes post-exercise (Table 5, Figure 6).

Table 3. Mixed model analysis describing the changes in carotid-femoral pulse wave velocity after peak aerobic exercise (n=10, 245 observations)

Fixed Effects Variables	***β (SE)***	***95% CI***	***p***
Time post-exercise	0.30 (0.05)	0.18, 0.40	**< 0.001**
Time post-exercise^2	–0.03 (0.005)	–0.03, –0.02	**< 0.00**
Time post-exercise^3	0.0006 (0.0001)	0.0004, 0.009	**< 0.001***
Covariate: Age	0.14 (0.04)	0.05, 0.23	**0.008**
Covariate: Mean arterial pressure	0.02 (0.007)	0.007, 0.03	**0.005**
Constant	–0.52 (2.70)	–4.78, 5.81	0.848
Random Effects Parameters	***Estimate (SE)***	***95% CI***	
Slope	0.001 (0.0009)	0.0003, 0.005	
Intercept	2.59 (1.20)	1.04, 6.42	
Residual	0.21 (0.02)	0.17, 0.25	
Model Fit Statistics	***Statistic***		
Log Likelihood	-212.8		
Bayesian Information Criteria	475.2		

CI = Confidence Interval, SE = Standard Error, bold numbers indicate P<0.05

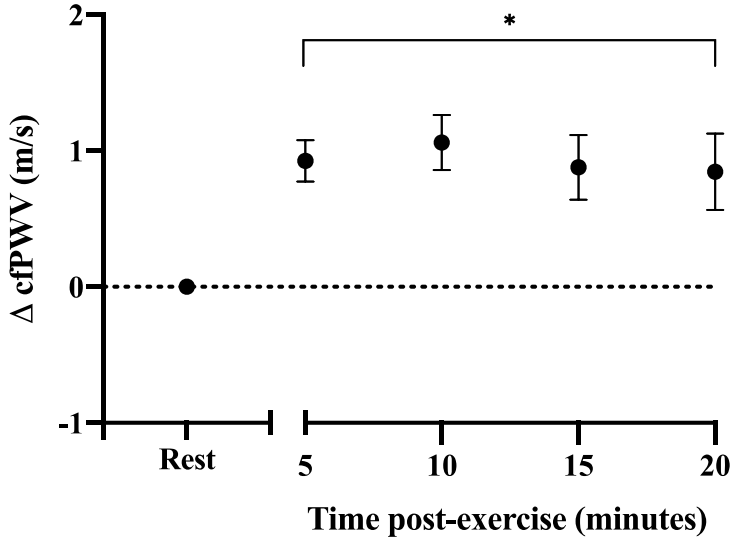


Figure 6. Changes in carotid-femoral pulse wave velocity at rest and after peak aerobic exercise. Data points are presented as predicted margins with standard error. Significantly different from resting values *P<0.05.

3.2.2 Post-exercise changes in central hemodynamics

With the exception of DBP, all relationships between central hemodynamic variables (HR, SBP and MAP) and time post-exercise appeared to be non-linear (Appendix II). Thus, when applicable, polynomial terms (time$_2$, time$_3$) were included in the model. Results from the mixed model analyses for all hemodynamic variables are found in Table 4.

3.2.2.1 Heart rate

The best fitting age-adjusted model included a random slope (variance estimate = 0.03 (SE= 0.02), 95% CI 0.01, 0.09) and intercept (variance estimate = 95.8 (SE= 43.4), 95% CI 39.4, 233.0), and an independent covariance structure. There was a non-linear association between heart rate and time post-exercise (β= 0.005 (SE=0.006), 95% CI

0.004, 0.006, p<0.001) (Table 4). Heart rate remained elevated at 5- and 10-minutes post-exercise, but was not different from baseline by 15 minutes post-exercise (Figure 7, panel A).

3.2.2.2 Systolic blood pressure

The best fitting age-adjusted model included a random intercept (variance estimate = 204.7 (SE= 51.5), 95% CI 83.9, 499.0), and an independent covariance structure. There was a non-linear relationship between SBP and time post-exercise (β= 0.06 (SE= 0.01), 95% CI 0.05, 0.08, p<0.001). SBP was reduced post-exercise and remained lower than baseline levels for up to 15 minutes, returning to baseline levels by 20 minutes (Figure 7, panel B).

3.2.2.3 Diastolic blood pressure

The best fitting age-adjusted model included a random intercept (variance estimate = 82.9 = (SE= 37.4), 95% CI 34.3, 200.8), and an independent covariance structure. There was a linear relationship between DBP and time post-exercise (β= 0.11 (SE= 0.05), 95% 0.01, 0.21, p=0.03). Despite this, values were not different from rest after Sidak corrections (Figure 7, panel C).

3.2.2.4 Mean arterial pressure

The best fitting age-adjusted model included a random intercept (variance estimate = 76.7 (SE= 35.0), 95% CI 31.4, 187.4), and an independent covariance structure. There was a non-linear relationship between MAP and time post-exercise (β= -0.02 (SE=0.008), 95% CI -0.006, 0.03, p=0.006). However, after Sidak corrections, MAP was not different compared to rest at any timepoint following exercise (Figure 7, panel D).

Table 4. Mixed model analyses on changes in central hemodynamics after peak aerobic exercise.

A) Heart rate (n=10, 255 observations)			
Fixed Effects Variables	***β* (*SE*)**	***95% CI***	***p***
Time post-exercise	2.17 (0.20)	1.77, 2.57	**<0.001**
Time post-exercise$_2$	-0.21 (0.02)	-0.25, -0.17	**<0.001**
Time post-exercise$_3$	0.005 (0.006)	0.004, 0.006	**<0.001**
Covariate: Age	-0.003 (0.29)	-0.58, 0.51	0.91
Constant	73.0 (16.1)	41.4, 104.7	**<0.001**
Random Effects Parameters	***β* (*SE*)**	***95% CI***	
Slope	0.03 (0.02)	0.01, 0.09	
Intercept	95.8 (43.4)	39.4, 233.0	
Residual	3.96 (0.37)	3.30, 4.75	
Model Fit Statistics	***Statistic***		
Log Likelihood	-576.9		
Bayesian Information Criteria	1198.1		

B) Systolic blood pressure (n=10, 241 observations)			
Fixed Effects Variables	***β* (*SE*)**	***95% CI***	***p***
Time post-exercise	-1.42 (0.23)	-1.87, -0.97	**<0.001**
Time post-exercise$_2$	0.06 (0.01)	0.05, 0.08	**<0.001**
Covariate: Age	0.73 (0.41)	-0.07, 1.52	0.07
Constant	76.6 (23.6)	30.3, 122.8	**0.001**
Random Effects Parameters	***β* (*SE*)**	***95% CI***	
Intercept	204.7 (93.1)	83.9, 499.0	
Residual	23.8 (2.21)	19.8, 28.6	
Model Fit Statistics	***Statistic***		
Log Likelihood	-749.3		
Bayesian Information Criteria	1531.5		

C) Diastolic blood pressure (n=10, 245 observations)			
Fixed Effects Variables	***β* (*SE*)**	***95% CI***	***p***
Time post-exercise	0.11 (0.05)	0.01, 0.21	**0.03**
Covariate: Age	0.11 (0.26)	-0.39, 0.62	0.66
Constant	45.7 (15.1)	16.1, 75.2	**0.002**
Random Effects Parameters	***β* (*SE*)**	***95% CI***	
Intercept	82.9 (37.4)	34.3, 200.8	
Residual	15.4 (1.42)	12.8, 18.4	
Model Fit Statistics	***Statistic***		
Log Likelihood	-705.7		
Bayesian Information Criteria	1439.0		

D) Mean arterial pressure (n=10, 243 observations)			
Fixed Effects Variables	***β* (*SE*)**	***95% CI***	***p***

Time post-exercise	-0.39 (0.18)	-0.75, -0.03	**0.04**
Time post-exercise$_2$	-0.02 (0.008)	-0.006, 0.03	**0.006**
Covariate: Age	0.32 (0.25)	-0.17, 0.81	0.200
Constant	55.9 (14.5)	27.5, 84.4	**<0.001**
Random Effects Parameters	***β* (*SE*)**	***95% CI***	
Intercept	76.7 (35.0)	31.4, 187.4	
Residual	15.2 (1.41)	12.7, 18.2	
Model Fit Statistics	***Statistic***		
Log Likelihood	-698.4		
Bayesian Information Criteria	1429.7		

*CI = Confidence Interval, SE = Standard Error, *P<0.05*

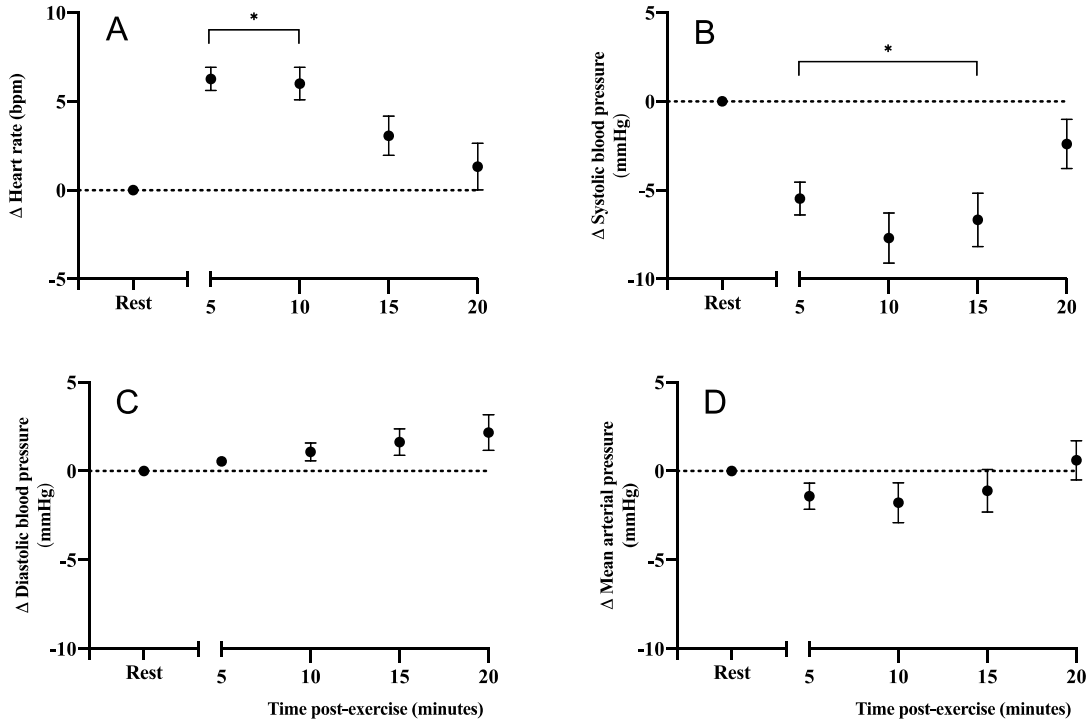


Figure 7. Changes in central hemodynamics at rest and after peak aerobic exercise for A) heart rate, B) systolic blood pressure, C) diastolic blood pressure, and D) mean arterial pressure. Data points are presented as predicted margins with standard error. Significantly different from resting values *P<0.05.

Table 5. Carotid-femoral pulse wave velocity and central hemodynamics up to 20 minutes after peak aerobic exercise.

Variable	Rest	5 minutes	10 minutes	15 minutes	20 minutes
cfPWV (m/s)	9.0 ± 0.53	**9.9 ± 0.52#**	**10.1 ± 0.53#**	**9.9 ± 0.54†**	**9.9 ± 0.57***
HR (bpm)	71.2 ± 3.2	**77.4 ± 3.1#**	**77.2 ± 3.2#**	74.2 ± 3.2	72.5 ± 3.3
SBP (mmHg)	117.3 ± 4.7	**111.8 ± 4.6#**	**109.6 ± 4.6#**	**110.6 ± 4.6#**	114.9 ± 4.6
DBP (mmHg)	52.1 ± 3.0	52.6 ± 2.9	53.1 ± 2.9	53.7 ± 2.9	54.2 ± 2.9
MAP (mmHg)	73.9 ± 2.9	72.5 ± 2.8	72.1 ± 2.8	72.8 ± 2.8	74.5 ± 2.8

*Values represent Mean ± SE; Significantly different from rest *p<0.05, †p<0.01, #p<0.001 cfPWV = carotid-femoral pulse wave velocity; m/s = meters per second; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure.*

3.3 Secondary Objective: Associations between response and recovery of cardiovascular outcomes with functional outcomes

Mean response and post-exercise recovery of cfPWV and central hemodynamics are presented in Table 6.

Table 6. Exercise response and recovery of central hemodynamics after peak aerobic exercise

Variable	n	Value (mean ± SD)	Range (min, max)
Carotid-femoral pulse wave velocity			
cfPWVr (m/s)	9	0.95 ± 0.69	1.86 (-0.04, 1.90)
β cfPWV (m/s per minute)	9	-0.02 ± 0.05	0.16 (-0.07, 0.09)
Heart rate			
HRR (bpm)	10	66.0 ± 28.56	104 (11, 115)
HR_{60s} (bpm)	10	19.8 ± 11.4	34 (1, 35)
HR_{120s} (bpm)	10	30.6 ± 16.0	52 (3, 55)
HR_{300s} (bpm)	10	58.4 ± 22.7	78 (9, 87)
HR_{600s} (bpm)	10	59.7 ± 22.5	78 (12, 90)
Systolic blood pressure			
SBPr (mmHg)	10	58.0 ± 27.1	84 (-4, 81)
SBP_{rec} (mmHg)	10	0.84 ± 0.11	0.30 (0.70, 1.0)

cfPWV = carotid-femoral pulse wave velocity; cfPWVr = cfPWV reserve; β cfPWV = cfPWV recovery slope HRR = heart rate reserve; HR_{60s} = heart rate recovery at 60 seconds; HR_{120s} = heart rate recovery at 120 seconds; HR_{300s} = heart rate recovery at 300 seconds; HR_{600s} = heart rate recovery at 600 seconds; bpm = beats per minute; SBP =systolic blood pressure; SBPr = SBP reserve; SBP_{rec} = 1-minute SBP recovery ratio

Bivariate analyses revealed no associations between cfPWVr and measures of cardiorespiratory fitness or functional outcomes (Table 7). Additionally, there was no association between cfPWV recovery and measures of cardiorespiratory fitness or functional outcomes (Table 8).

Table 7. Bivariate correlations between cfPWVr and functional outcomes (n=9)

	Pearson's r	***95% CI***	***p***
Gait speed (m/s)	0.34	-0.42, 0.82	0.37
6MWT distance (m)	0.06	-0.73, 0.78	0.90
$\dot{V}O_{2peak}$ (mL/kg/min)	-0.12	-0.72, 0.59	0.77

CI = Confidence Interval; cfPWV = carotid-femoral pulse wave velocity; 6MWT = 6-minute walk test

Table 8. Bivariate correlations between β cfPWV, with cardiorespiratory fitness and functional outcomes (n=9)

	Pearson's r	***95% CI***	***p***
Gait speed (m/s)	0.50	-0.25, 0.87	0.18
6MWT distance (m)	0.36	-0.54, 0.88	0.43
$\dot{V}O_{2peak}$ (mL/kg/min)	-0.51	-0.88, 0.23	0.16

CI = Confidence Interval; cfPWV = carotid-femoral pulse wave velocity; 6MWT = 6-minute walk test

There were strong positive correlations between HRR and cardiorespiratory fitness (r=0.74, *p*=0.02, Table 9). There were also strong positive correlations between each of the fast- and slow-phases of heart rate recovery (HR_{60s}, HR_{120s}, HR_{300s} and HR_{600s}) and cardiorespiratory fitness (r=0.80, *p*=0.005; r=0.79, *p*=0.006; r=0.72, *p*=0.02; r=0.75, *p*=0.01, respectively, table 9). Scatterplots depicting these relationships are presented in Figure 8.

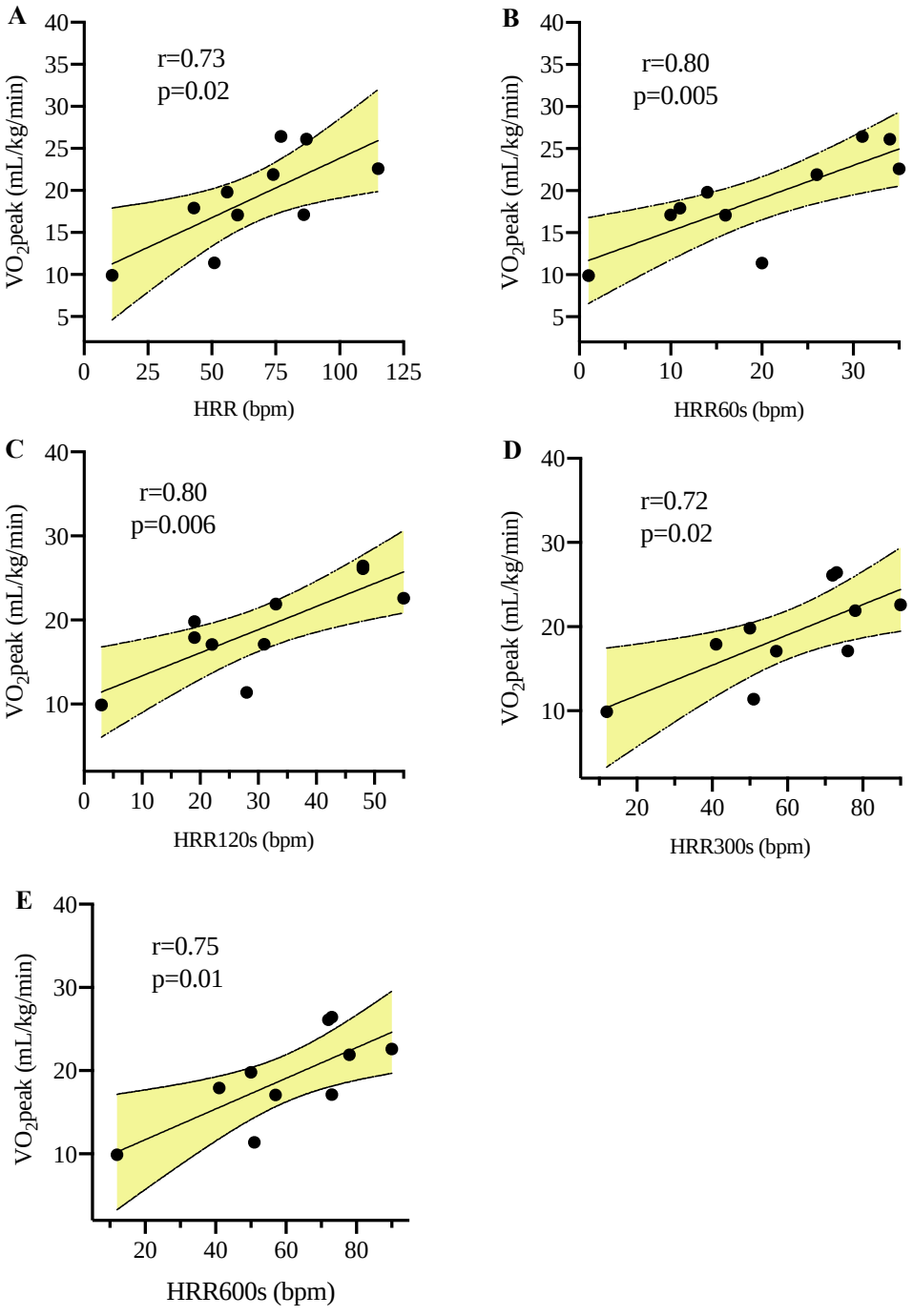
Table 9. Bivariate correlations between changes in central hemodynamics and cardiorespiratory fitness (n=10)

	Pearson's r	***95% CI***	***p***
HRR (bpm)	0.73	0.18, 0.93	**0.02***
HR_{60s} (bpm)	0.80	0.35, 0.95	**0.005***
HR_{120s} (bpm)	0.79	0.33, 0.95	**0.006***

HR_{300s} (bpm)	0.72	0.18, 0.93	**0.02***
HR_{600s} (bpm)	0.75	0.22, 0.94	**0.01***

*CI = Confidence Interval; HRR = heart rate reserve; HR_{60s} = heart rate recovery at 60 seconds; HR_{120s} = heart rate recovery at 120 seconds; HR_{300s} = heart rate recovery at 300 seconds; HR_{600s} = heart rate recovery at 600 seconds; bpm = beats per minute *P<0.05*

Figure 8. Bivariate correlations with 95% CI confidence bands between cardiorespiratory fitness (VO_2peak) and (A) heart rate reserve (HRR), (B) fast-phase of heart rate recovery (HR_{60s}), (C) slow-phase of heart rate recovery (HR_{120s}), and (D) slow-phase of heart rate recovery (HR_{300s}), (E) slow-phase of heart rate recovery (HR_{600s}).


A
r=0.73
p=0.02
VO2peak (mL/kg/min)
HRR (bpm)
B
r=0.80
p=0.005
VO2peak (mL/kg/min)
HRR60s (bpm)
C
r=0.80
p=0.006
VO2peak (mL/kg/min)
HRR120s (bpm)
D
r=0.72
p=0.02
VO2peak (mL/kg/min)
HRR300s (bpm)
E
r=0.75
p=0.01
VO2peak (mL/kg/min)
HRR600s (bpm)

CHAPTER 4: DISCUSSION

To our knowledge, this was the first study to comprehensively characterize the exercise response and post-exercise recovery of arterial stiffness and central hemodynamics in individuals with stroke, identifying that increases in cfPWV in response to aerobic exercise remain elevated for up to 20 minutes post-exercise, independent of changes in blood pressure and heart rate. Individuals with stroke appear to have preserved fast-phase heart rate recovery (HR_{60s}) but impaired slow-phase of heart rate recovery (HR_{120s}).

This was also the first study to explore the associations between the changes in arterial stiffness or central hemodynamics following peak exercise, and cardiorespiratory fitness and functional outcomes in individuals with stroke. We found that HRR and all markers of heart rate recovery are strongly correlated with cardiorespiratory fitness but not functional outcomes.

4.1 Response and recovery of cfPWV and central hemodynamics

4.1.1 Carotid-femoral pulse wave velocity

Transient increases in cfPWV acutely following peak aerobic exercise have been reported in studies across a range of populations. A recent systematic review of 43 studies and 1,089 adults without CVD or CVD risk factors found that the acute changes in cfPWV following exercise are largely time-sensitive, whereby cfPWV increases substantially within the first 5 minutes post-exercise, but returns to baseline levels thereafter (Mutter et al. 2017). In the current study, participants with stroke experienced increased cfPWV of 0.95 ± 0.69 m/s following cessation of peak-effort aerobic exercise, that are similar to values previously reported in individuals with hypertension

(Gkaliagkousi et al. 2014). However, in contrast to previous literature in non-CVD populations, individuals with stroke in the current study demonstrated an impaired capacity to return to baseline levels. While this is the first study to report recovery rates for cfPWV, we observed that individuals with stroke recover at an average rate of 0.02 ± 0.05 m/s per minute, and thus by 20 minutes, cfPWV values were still elevated compared to baseline. The delayed recovery is similar to what is observed in individuals with hypertension (Gkaliagkousi et al. 2014), obesity (Bunsawat et al. 2017) and smokers (Doonan et al. 2011). This indicates that individuals with stroke may have similarly impaired cardiovascular recovery from peak aerobic exercise to populations with risk factors for CVD.

Interestingly, we also found that the prolonged trajectory of recovery of arterial stiffness following peak exercise is independent of changes in central hemodynamics (blood pressure and heart rate). These findings are similar to previous literature in individuals with risk factors for CVD and stroke (Doonan et al. 2011; Gkaliagkousi et al. 2014; Bunsawat et al. 2017). Historically, it was believed that blood pressure has large influences on cfPWV (Chirinos 2012) but with the recent application of a novel technique called lower-limb venous occlusion, it has been demonstrated that the increase in cfPWV may in fact occur in response to SNS activation, independent of changes in blood pressure (Faconti et al. 2019). Increases in SNS activity during exercise is typical, however overactivation of the SNS is characteristic of individuals with stroke (Myers et al. 1981) and in populations with CVD risk factors such as hypertension (Mancia and Grassi 2014), obesity (Lambert et al. 2010) and smokers (Middlekauff et al. 2014).

Indeed, studies suggest that these populations exhibit similar patterns of blood pressure-independent elevations of cfPWV in exercise recovery as our sample with stroke (Doonan et al. 2011; Gkaliagkousi et al. 2014; Bunsawat et al. 2017). Supported by our findings in heart rate recovery outcomes, it is likely that excessive SNS activation in exercise recovery inhibits cfPWV from returning to baseline levels.

4.1.2 Central hemodynamics: heart rate and blood pressure

We found that peak heart rate from the CPET among our participants with stroke was 136 ± 27 bpm, or approximately 82% of age-predicted maximal heart rate. Interestingly, these values were considerably higher than those reported in a scoping review of peak exercise responses in stroke with mild or no symptoms (120 ± 14 bpm). This may be attributed to choice of exercise modality, where the present study used a recumbent stepper, which allows four limbs to be engaged and higher intensities to be achieved (Billinger et al. 2008). In contrast, 80% of studies in the review by Gäverth and colleagues (2015) used either treadmill (n=15/40, 38%) or cycle ergometer (n=17/40, 42%) exercise test protocols. Typically, treadmill tests elicit greater peak exercise responses compared to cycle ergometry as walking is generally a more familiar activity. However, many studies use cycle ergometers because the spectrum of peripheral neuromuscular deficits in this population may limit exercise performance for treadmill exercise tests (van de Port et al. 2015). Cycle ergometer exercise tests may also underestimate exercise capacity as they engage only lower limbs and thus less muscle mass compared to protocols using recumbent steppers. Recumbent steppers allow for use of upper and lower limbs, allowing individuals with upper and/or lower limb hemiparesis

to generate greater power outputs and exercise at higher intensities. Because of this modality, our sample was likely better able to reach higher intensities of exercise.

Upon exercise termination, after reaching peak intensities, the cardiovascular system enters the recovery phase. Pertaining to heart rate, the fast-phase of heart rate recovery (HR_{60s}) primarily represents increases in PNS activation whereas the slow-phase of heart rate recovery is mostly representative of SNS withdrawal. The present study found that individuals with stroke may have impaired heart rate recovery after peak aerobic exercise in the slow- but not fast-phase. Aligned with preserved 1-minute SBP_{rec}, we observed that HR_{60s} exceeded the 12-bpm threshold representative autonomic dysfunction (Cole et al. 1999) but in the slow-phase (HR_{120s}), values were lower than reference values (<42 bpm) in the general population without CVD. Our findings are consistent with previous literature in stroke and TIA that have also reported impaired slow-phases of recovery but a preserved fast phase (Jin et al. 2013; Francica et al. 2015; Li et al. 2019). Combined with our findings of prolonged cfPWV elevation post-exercise, the impaired slow-phase of heart rate recovery (HR_{120s}) provides additional evidence of SNS overactivity after exercise in people with stroke with a relatively normal functioning PNS.

Moreover, the present study extended the findings in fast- and slow-phases of heart rate recovery to longer periods of follow-up of 5 (HR_{300s}) and 10 minutes (HR_{600s}) following exercise termination. There are few studies that have examined heart rate recovery to this length of time post-exercise, and to our knowledge, this was the first study to report these lengths of recovery in individuals with stroke. Our sample produced

HR_{300s} values (58 ± 23 bpm) that were similar to individuals with TIA (Li et al. 2019) and diabetes (Cheng et al. 2003), but substantially lower than adults without CVD or CVD risk factors (HR_{300s} >70 bpm (Bosquet et al. 2008; Li et al. 2019)). Arguably, HR_{300s} >70 bpm reported by Li et al (2019) may be due to differences in higher peak exercise intensities achieved in their study (162 ± 14 bpm versus 136 ± 27 bpm in the current study) which would also result in higher values for HR_{300s}. While there is no established cut-off value for abnormal HR_{300s} or HR_{600s} responses, Cheng and colleagues (2003) found a dose-response relationship between cardiovascular health and HR_{300s} among 2,333 men with diabetes whereby those with the lowest quartile of HR_{300s} (<55 bpm) had the highest all-cause and cardiovascular mortality rates compared to the other quartiles (Cheng et al. 2003). It is possible that individuals with stroke present similar impairments in heart rate recovery that is characteristic of populations with impaired autonomic function such as TIA and diabetes. Future research is warranted to identify appropriate cut-off values indicative of autonomic dysfunction in the slow-phases of post-exercise recovery.

Lastly, to our knowledge, this was the first study to examine blood pressure recovery of individuals with stroke. In contrast to our hypothesis, we found that individuals had 1-minute SBP_{rec} values that were similar to (Miyahara et al. 1990) or lower than (Tsuda et al. 1993) those reported in adults without CVD. Indeed, this time course of post-exercise recovery of SBP in stroke is aligned with our findings in cfPWV and heart rate, suggesting that individuals with stroke are able to effectively reactivate

PNS activity immediately post-exercise, allowing them to return blood pressure towards baseline levels following intense exercise.

Taken together, the hemodynamic response of cfPWV, heart rate and blood pressure following intense aerobic exercise are suggestive of one-sided ANS dysfunction, wherein the PNS appears to be preserved in spite of an overactive SNS. ANS dysfunction is a common characteristic of individuals with stroke (Dorrance and Fink 2015). There is increased SNS activity post-stroke, where nearly twice the amount of circulating norepinephrine has been reported in individuals with acute ischemic stroke compared to as age-matched controls (Myers et al. 1981), which may persist into the chronic phase of stroke recovery (Dütsch et al. 2007; Xiong et al. 2013). Higher levels of norepinephrine post-stroke may increase the risk of cardiovascular mortality (Sander et al. 2001), as excessive SNS activity is linked to the development of hypertension (Esler et al. 1989), endothelial cell damage (Pettersson et al. 1990) and increased left ventricular mass (Simpson 1983).

Much less is known about PNS function among individuals with stroke. It appears that the presence of PNS dysfunction may depend on the acuity of the stroke. Individuals with acute stroke (~1 week post-stroke) may have altered PNS function, measured by heart rate and blood pressure responses to deep breathing (Korpelainen et al. 1994). However, whether this impairment persists into the chronic phases (>6 months) post-stroke is less clear. In a very early study, Korpelainen et al. (1994) reported that at 6-months post-stroke, PNS function is comparable to controls without stroke but more recent studies (Dütsch et al. 2007; Xiong et al. 2013) using more sensitive measures such

as resting heart rate variability have found overactive SNS and reduced PNS activity in the chronic phase of stroke. Arguably, the discrepancies in the literature may also be partially explained by the differences in participants' age between studies, whereby PNS dysfunction was observed in older individuals with stroke (mean age=68 (Dütsch et al. 2007) and 67 years old (Xiong et al. 2013) vs. 51 (Korpelainen et al (1994) and the current study 57 years). Age itself is known to be associated with autonomic dysfunction (Parashar et al. 2016). With further investigations with larger sample sizes and across wider age ranges, we may better understand the relationship between age and ANS dysfunction in stroke in the future.

4.2 Relationship between response, recovery, cardiorespiratory fitness and function

In partial agreement with our hypothesis, we found strong, positive correlations between cardiorespiratory fitness, HRR and all-phases of heart rate recovery, but no relationship between the response or recovery of cfPWV and cardiorespiratory fitness or walking function. Moreover, there was no association between response and recovery of central hemodynamics and walking function.

While previous studies have established strong relationships between HRR and cardiorespiratory fitness in individuals with (Brawner et al. 2002; Carvalho et al. 2008) and without CVD (Dalleck and Kravitz 2006), this is the first study to observe this relationship in individuals with chronic stroke. Because we used a recumbent stepper protocol to assess cardiorespiratory fitness, we were able to accommodate for a wide range of motor abilities which allowed participants to achieve higher intensities of exercise compared to previous reports in stroke (Gäverth et al. 2015). Thus, selecting the

appropriate exercise test modality is important for approximating maximal (vs. peak) exercise capacity in populations where other functional impairments may affect exercise test performance. Because of this, we were able to establish a positive relationship between HRR and cardiorespiratory fitness even with concurrent post-stroke motor impairments. Our findings extend the established associations between cardiorespiratory fitness and HRR in other CVD populations (Brawner et al. 2002; Carvalho et al. 2008) to those with chronic stroke, in spite of motor limitations.

In contrast to the well-established relationship between HRR and cardiorespiratory fitness, less is known regarding the association between heart rate recovery and cardiorespiratory fitness. Jin et al (2013) first demonstrated that the fast-phase of heart rate recovery (HR_{60s}) is positively correlated with cardiorespiratory fitness ($r=0.69$) in 128 individuals with chronic stroke, which is aligned with the findings from the current study ($r=0.80$). Moreover, the present study expands on the study by Jin et al (2013) by also demonstrating that the positive relationship between cardiorespiratory fitness and heart rate recovery persists into the slow-phases of heart rate recovery HR_{120s}, HR_{300s} and HR_{600s}).

It is known that endurance training is known to improve cardiorespiratory fitness in stroke (Saunders et al. 2020). In the general population, aerobic exercise training may also increase parasympathetic activity and reduce sympathetic activity, such that endurance-trained individuals have lower resting heart rates and greater heart rate recovery (Carter et al. 2003). The present study extends this to individuals with stroke, where greater SNS withdrawal (i.e. slow-phases of heart rate recovery) was associated

with greater cardiorespiratory fitness. Future prospective trials may examine the potential of aerobic exercise training to improve cardiorespiratory fitness and concurrently mediate the effects of ANS dysfunction in stroke.

In contrast to our hypothesis, we did not find a relationship between the response and recovery of SBP with cardiorespiratory fitness or walking ability in individuals with stroke. This was surprising because of known associations between exaggerated blood pressure responses to exercise and poor cardiovascular health (Le et al. 2008), and between SBP_{rec} and endothelial dysfunction (Nishiyama et al. 2014). While peak heart rate values were higher than what was previously reported in stroke (Gäverth et al. 2015), they were still much lower than age-predicted values. It is likely that, despite the use of a recumbent stepper, the motor impairments resulting from stroke were still able to limit high exercise intensities that elicits an exaggerated SBP response. In fact, mean SBP_{peak} in our study was only 184 mmHg, with a similar range (130 to 222 mmHg) to studies in a systematic review of individuals with stroke (van de Port et al. 2015) and lower than age-matched values of those without stroke (Daida et al. 1996). Lower SBP_{peak} in this study may explain seemingly preserved 1-minute SBP_{rec} which may in fact reflect a floor effect. Previous reports demonstrated that individuals with hypertension and impaired 1-minute SBP_{rec} had large increases in SBP in response to peak exercise reaching up to 251 mmHg (Miyahara et al. 1990). However, in our sample, it is possible that our sample did not achieve high enough SBP and that individuals with an exaggerated blood pressure response (n=3 with values exceeding 190 mmHg) were underrepresented in this sample. Because of low SBP responses observed in this sample, it is difficult to draw conclusions

regarding the associations between SBP response and recovery, with cardiorespiratory fitness and walking ability.

There are known associations between walking function and cardiorespiratory fitness among individuals with stroke (Pang et al. 2005; Tang et al. 2006a) and based on these findings, we expected that these associations would carry over to hemodynamic response and recovery with walking ability. However, in contrast to our hypothesis, there were no relationships between any of the measures of central hemodynamics and walking ability. Lower-limb motor function may be a possible explanation for finding no relationship between the two. While they found a relationship between cardiorespiratory fitness and walking ability, Pang et al (2005) confirms that balance, knee extensor strength and spasticity may also influence the relationship. While cardiorespiratory fitness and walking ability were related, Tang et al (2006) also found that 6MWT distance is also more closely related to gait-speed than cardiorespiratory fitness. The present study confirms their findings, demonstrating a strong, positive correlation between 6MWT distance and self-selected gait-speed (r=0.73) (Appendix III). We anticipated that by using a recumbent stepper CPET protocol, motor limitations may have had less of an effect on exercise test performance and thereby, resulting in a similar hemodynamic response to exercise to those without stroke. However, the limitations that affect their ability to exercise may have persisted beyond the adaptive protocol and may explain the absence of a relationship between response and recovery of hemodynamic variables and walking ability. While this study did not assess lower-limb motor function, it may still mediate the relationship between the response of central hemodynamics and walking

ability. Future studies should examine the effects of lower-limb function on these relationships.

4.3 Strengths & Limitations of the Thesis

There are several strengths to this study, primarily related to our methods of data collection. First, we examined post-exercise changes in arterial stiffness and central hemodynamics using recommended standards of assessment (cfPWV (Townsend et al. 2015), heart rate recovery (Shetler et al. 2001), SBP_{rec} (Le et al. 2008)). The non-invasive methods used for the assessment of these outcomes generate values that are comparable to invasive measures, and have shown to hold prognostic significance. These measurement techniques were feasible to conduct due to their non-invasive nature, and provide preliminary evidence to establish their potential application to clinical settings.

In our data acquisition of the post-exercise cfPWV recovery response, we note that this study is one of the few studies to measure cfPWV continuously over time. Whereas many studies reported the acute effect of exercise on arterial stiffness at discrete timepoints often with large gaps (often up to 10 minutes) between measurements, the present study collected data continuously for over 15 minutes which enabled us to capture all small and time-dependent changes that occur during exercise recovery (Mutter et al. 2017). Similarly, we were able to capture continuous changes in heart rate and blood pressure throughout the recovery phase, which also helped us determine whether changes in cfPWV occurred independently of central hemodynamics.

The most prominent limitation in this study was its small sample size. We originally determined that we would require 36 individuals with stroke to detect a

moderate to large effect in change in cfPWV (80% power, alpha of <0.05) but were unable to achieve this sample size due to the restrictions set in place by McMaster University in response to the COVID-19 pandemic. We also acknowledge that the current sample of 10 individuals with stroke did not allow us to adjust for other important factors such as sex and cardiorespiratory fitness. However, the use of mixed model analyses appropriately allowed us to model changes in cfPWV and central hemodynamics over recovery despite the small sample, as they are able to handle variation of time between measurements and missing data (Detry and Ma 2016). Future studies should include a larger sample of individuals with stroke to clarify our findings. The present study was also limited by the absence of a comparison group of individuals without stroke to determine if the changes observed in cfPWV and central hemodynamics were due to the presence of stroke or were characteristic of aging in general. Lastly, we acknowledge that individuals with stroke are a highly heterogenous population whereby differences in functional mobility would contribute to heterogeneity in the length of time moving from the recumbent stepper at peak exercise and to the examination table for collection of post-exercise cfPWV. We attempted to minimize the time delay as much as possible, and indeed were able to record the first datapoint on average within 6 minutes after peak exercise, which is less than the time reported in studies among older adults or clinical populations (Gkaliagkousi et al. 2014; Akazawa et al. 2018).

4.4 Conclusion

This study was the first to comprehensively assess exercise response and recovery of arterial stiffness and central hemodynamics in individuals with stroke. Moreover, this

study provided novel insights to the prognostic value of examining these patterns of responses and recovery. Our results demonstrate that individuals with chronic stroke may have impaired recovery of arterial stiffness and central hemodynamics following peak aerobic exercise, which may be indicative of autonomic dysfunction. We also demonstrated that all phases of heart rate recovery are related to cardiorespiratory fitness but not walking ability. These findings reinforce the demand for prospective trials aimed at improving cardiorespiratory fitness for individuals with stroke, as they it is shown to be associated with indices of autonomic function.

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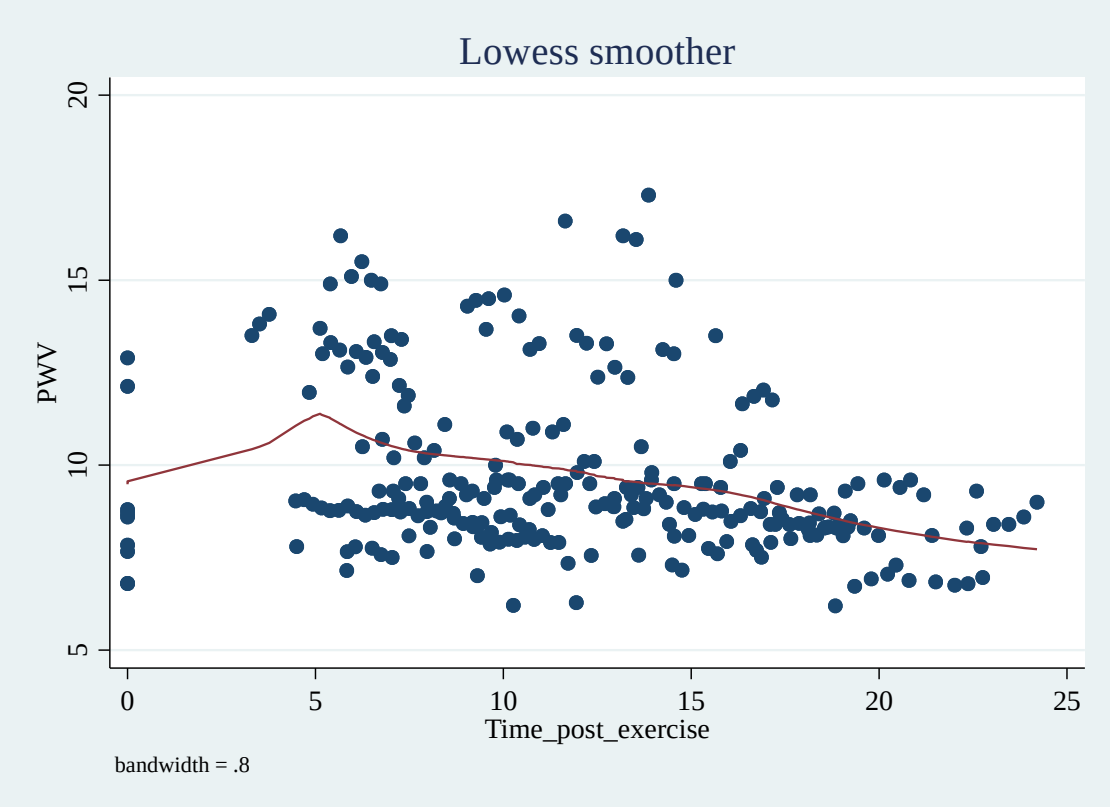
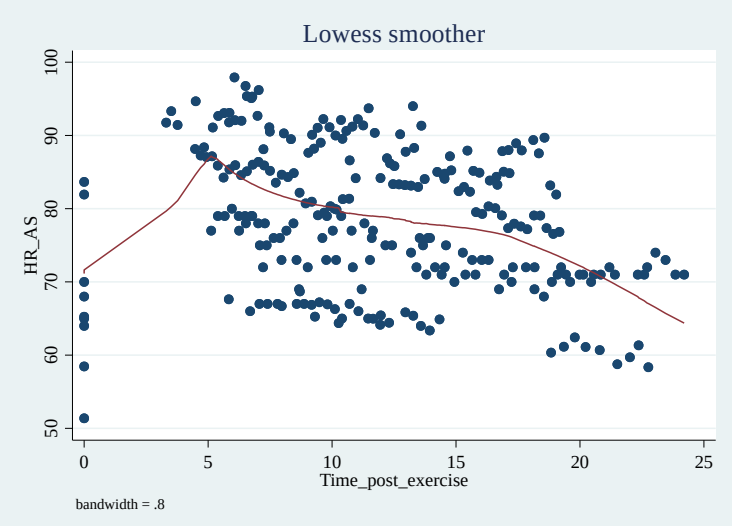
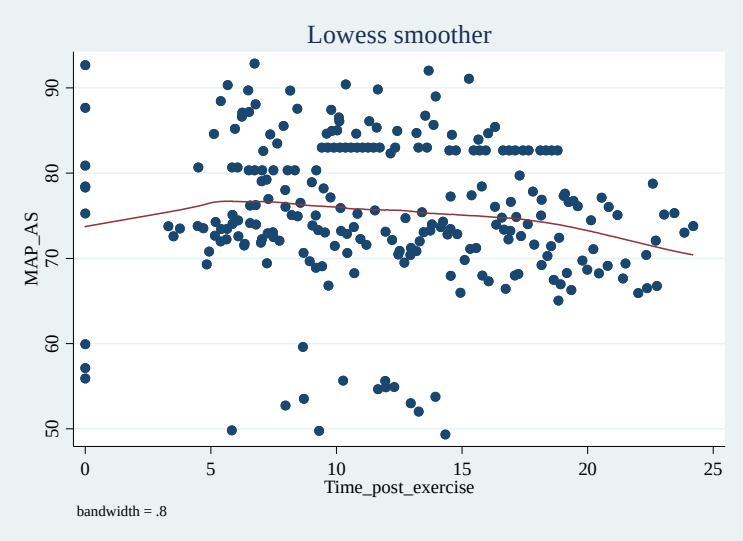
APPENDICES

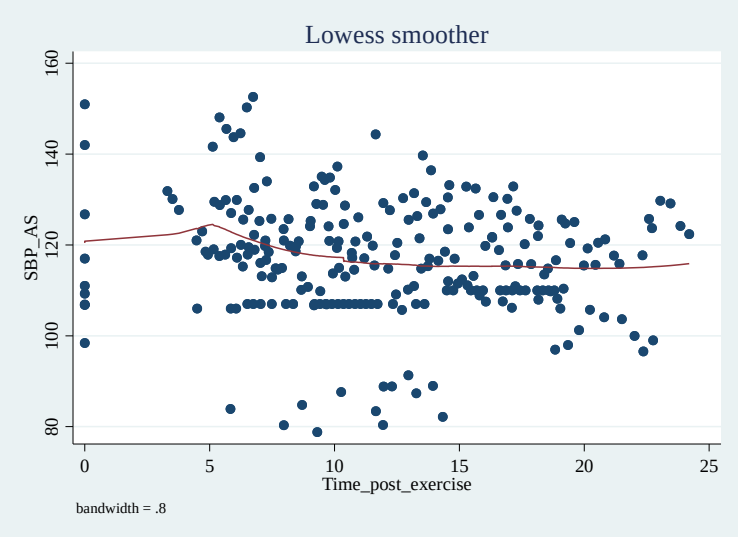
Appendix I. Lowess plot of post-exercise trajectories of cfPWV.



Appendix II. Lowess plots of post-exercise trajectories of central hemodynamics.




Lowess smoother
MAP_AS
50
60
70
80
90
0
5
10
15
20
25
Time_post_exercise
bandwidth = .8


Lowess smoother
SBP_AS
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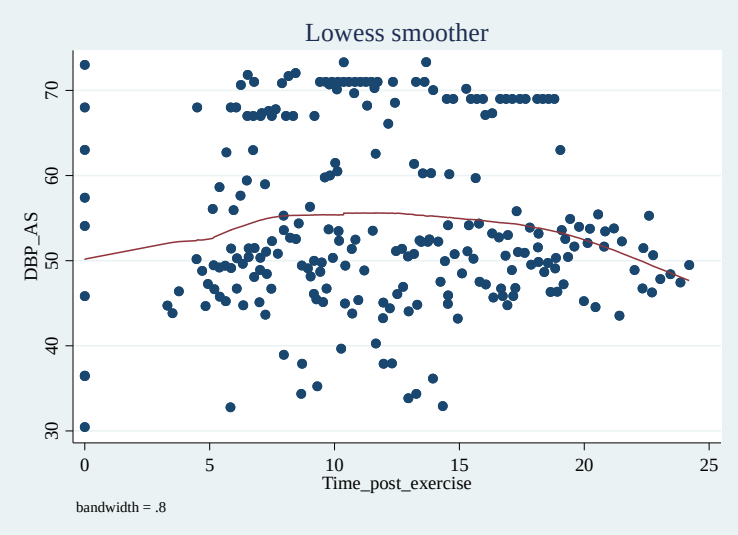
100
120
140
160
0
5
10
15
20
25
Time_post_exercise
bandwidth = .8


Lowess smoother
DBP_AS
30
40
50
60
70
0
5
10
15
20
25
Time_post_exercise
bandwidth = .8

Appendix III. Correlation matrix of all bivariate correlations.

	PWV	PWVr	HRR	HR_{60s}	HR_{120s}	HR_{300s}	HR_{600s}	SBPr	SBP_{rec}	DBPr	DBP_{rec}	Gait speed	6MWT	VO_2peak
PWV	1													
PWVr	-0.3	1												
HRR	-0.1	-0.36	1											
HR_{60s}	-0.5	-0.37	**0.80#**	1										
HR_{120s}	-0.2	-0.47	**0.91#**	**0.94#**	1									
HR_{300s}	-0.1	-0.22	**0.97#**	**0.78#**	**0.88#**	1								
HR_{600s}	-0.2	-0.23	**0.97#**	**0.81#**	**0.90†**	**0.99#**	1							
SBPr	**-0.8**	0.38	0.48	**0.66***	0.48	0.56	0.57	1						
SBP_{rec}	-0.2	-0.2	0.53	0.47	0.41	0.53	0.52	0.55	1					
DBPr	-0.3	0.58	0.3	0.25	0.19	0.46	0.47	0.66	0.49	1				
DBP_{rec}	-0.9	0.31	-0.03	0.34	0.07	-0.04	0.06	0.62	0.21	0.37	1			
Gait speed	0.5	0.34	0.14	-0.23	-0.03	0.27	0.22	-0.03	0.05	0.56	-0.36	1		
6MWT	0.36	0.06	0.45	0.21	0.44	0.57	0.52	0.02	-0.23	0.32	-0.4	**0.73***	1	
VO_2peak	-0.5	-0.12	**0.73***	**0.80†**	**0.79†**	**0.72***	**0.75***	0.57	0.1	0.14	0.23	-0.25	0.2	1

Values represent correlation coefficient (r). PWV = pulse wave velocity; PWVr = pulse wave velocity reserve; HRR = heart rate reserve; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; 6MWT = 6-minute walk test distance. *P<0.05,