DESIGNING AEROBIC EXERCISE INTERVENTIONS FOR STROKE REHABILITATION

by

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Abstract

More than 405,000 Canadians are currently living with the life-altering effects of stroke. Cardiorespiratory fitness is characteristically low after stroke and has negative consequences for functional recovery, cardiovascular risk, and quality of life in this population. Although scientific evidence supports incorporating moderate-intensity aerobic exercise during stroke recovery, these findings have not translated into clinical care where patients are very sedentary and cardiorespiratory fitness levels remain in the "very poor" category. Among the challenges to incorporating aerobic exercise include a lack of access to the specialized equipment needed to accommodate stroke-related impairments. Also, hemiparesis can limit stroke survivors' ability to sustain the workloads needed to reach moderate levels of aerobic intensity. Accordingly, the current thesis aimed to develop exercise strategies that can overcome these barriers.

The first study investigated whether incorporating task-oriented activities typically offered during stroke rehabilitation into circuits that pair more metabolically demanding tasks with less demanding ones is an acceptable method to sustain moderate-intensity aerobic workloads over a single session. The second study evaluated the feasibility and preliminary effects of the task-oriented circuit-training protocol compared to treadmill aerobic exercise over a 10-week intervention period among 40 chronic hemiparetic stroke survivors. The final study investigated the safety and feasibility of pairing treadmill

walking exercise with moderate normobaric hypoxia as a means to increase the cardiovascular strain of submaximal exercise among stroke survivors.

The task-oriented circuit training protocol was associated with at least moderate-intensity aerobic workloads over a single session and, compared to treadmill aerobic exercise, similar proportions of participants were able to maintain the exercise criteria over a 10-week intervention period. One participant reported mild symptoms of nausea during treadmill walking under conditions of moderate normobaric hypoxia. No other adverse events were observed, and participants maintained constant absolute workloads during exercise in normobaric hypoxia, which was associated with a 10% increase in relative effort.

The task-oriented circuit training protocol is a promising strategy to provide moderate-intensity aerobic exercise training stimulus without specialized equipment. Initial data also supports simulated altitude exposure as a safe and feasible method to increase the cardiovascular stress of submaximal exercise among chronic hemiparetic stroke survivors.

Summary

More than 405,000 Canadians are currently living with the life-altering effects of stroke. Physical fitness is low after stroke and increases patients' risk of future hospitalization, decreases individual's ability to complete daily tasks, and negatively impacts their quality of life. Aerobic exercise may remedy poor physical fitness. However, access to this treatment is limited during standard stroke care, and patients remain inactive throughout their recovery. Among the challenges to gaining access to aerobic exercise is the altered movement patterns characteristic of stroke (i.e., hemiparesis), requiring special equipment to make activities accessible. Also, many stroke survivors have a decreased ability to sustain the physical workloads needed to elevate heart rate into the moderate-intensity range. Accordingly, the current thesis aimed to develop exercise strategies that can overcome these barriers.

The first study investigated whether incorporating activities typically offered during stroke rehabilitation into circuits that pair more challenging tasks with less demanding ones is an acceptable method to sustain moderate-intensity aerobic workloads over a single session. The second study examined the extent to which stroke survivors could sustain moderate-intensity aerobic exercise using the circuit training protocol over ten weeks through comparisons with treadmill walking exercise. In the final study, participants breathed air with reduced amounts of oxygen (i.e., normobaric hypoxia) both at rest and during exercise. The safety and feasibility of pairing treadmill walking exercise

with moderate normobaric hypoxia was to increase the cardiovascular strain of submaximal exercise.

Circuit training was associated with moderate-intensity aerobic workloads and compared to treadmill exercise, similar proportions of participants were able to maintain the exercise criteria over a 10-week intervention period. One out of seven participants reported mild symptoms of nausea during treadmill walking under conditions of moderate normobaric hypoxia. No other adverse events were observed, and normobaric hypoxia caused a 10% increase in heart rate reserve for a given treadmill speed/incline.

The circuit training protocol is a promising strategy to provide a moderate-intensity aerobic exercise stimulus without specialized equipment. Initial data also supports normobaric hypoxia exposure as a safe and feasible method to increase the cardiovascular stress of submaximal exercise among chronic hemiparetic stroke survivors.

Acknowledgements

The studies presented in chapters two, three, and four have either been published or are under review. The first study titled “Intensifying functional task practice to meet the aerobic training guidelines in stroke survivors” was published in October 2017 in Frontiers in Physiology-Clinical and Translational Physiology. The second study titled “Task-oriented circuit training as an alternative to ergometer type aerobic exercise training after stroke” was published May 2021 in the Journal of Clinical Medicine. The final study titled “Normobaric hypoxia exposure during treadmill aerobic exercise after stroke: a safety and feasibility study” is currently under review with Frontiers in Physiology-Clinical and Translational Physiology.

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List of Symbols, Nomenclature or Abbreviations

ANOVA: analysis of variance

BP: blood pressure

CET: constant-load ergometer-type training

CHOox: carbohydrate oxidation

CI: confidence interval

CRF: cardiorespiratory fitness

CRP: C-reactive protein

EEE: energy expenditure of exercise

FAME: fitness and mobility exercise program

F_IO_2: fraction of inspired oxygen

GXT: graded exercise test

HDL: high density lipoprotein cholesterol

HI-TM: high-intensity treadmill training

HR: heart rate

HRmax: maximum heart rate

HRpred: predicted maximum heart rate

HRrest: resting heart rate

HRR: heart rate reserve

IFT: intermittent functional training

LDL: low density lipoprotein cholesterol

LILD: low-intensity long duration

LI-TM: low-intensity treadmill training

Lox: lipid oxidation

MET: metabolic equilivant

MISD: moderate-intensity short duration

N: nitrogen

NIHSS: National Institute of Health Stroke Scale

REE: resting energy expenditure

RER: respiratory exchange ratio

RPE: rating of perceived exertion

SD: standard deviation

SpO_2: blood oxygen saturation

SPM: steps per minute

TBRS: total body recumbent stepper

$\dot{V}CO_2$: rate of carbon dioxide production

$\dot{V}O_2$: rate of oxygen uptake

$\dot{V}O_{2max}$: maximum rate of oxygen uptake

$\dot{V}O_2R$: oxygen uptake reserve

W: watts

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Chapter 1: Introduction and Overview

Physical inactivity is among the biggest threats to the health and quality of life of individuals living in the industrialized world. Increased automatization of daily chores (2004), decreased locomotion for daily commuting (Canada, 2017; Hajna et al., 2019), and a shift toward more sedentary work practices (Church et al., 2011; J. A. Levine et al., 2011) have all conspired to decrease the physical requirements of daily living. Consequently, there is a growing trend toward decreased physical work capacity of the general population (J. P. Kelly et al., 2019). This is a major concern given the strong inverse association between cardiorespiratory fitness and all-cause mortality (Blair et al., 1989; Kokkinos et al., 2014). Since the work of Stephen Blair and colleagues in the 1980's, data from the Cooper Center Longitudinal Study has consistently demonstrated an inverse association between midlife cardiorespiratory fitness and the most frequent causes of death and disability globally, which include ischemic heart disease (Berry et al., 2011), dementia (Defina et al., 2013), cancer (Lakoski et al., 2015), and stroke (Pandey et al., 2016). Importantly, the association between cardiorespiratory fitness and many of these chronic conditions is maintained even after controlling for other known cardiometabolic risk factors including obesity, hypertension, dyslipidemia, and hyperglycemia (Berry et al., 2011; Pandey et al., 2016). From this point of view, physical inactivity is a leading cause for the development of chronic disease through its effects on the underlying structure and

function of the human body (Booth, Roberts, Thyfault, Ruegsegger, & Toedebusch, 2017). The Dallas bed rest study, published by Bengt Saltin and colleagues in 1968, clearly demonstrated the impact of extreme physical inactivity on the underlying structures and function of the cardiorespiratory system. In young healthy males, 20-days of bed rest was sufficient to decrease cardiorespiratory fitness by 28%, which was associated with a 11% reduction in heart size and a 26% decrease in cardiac output (Saltin et al., 1968). Participants in this longitudinal cohort study were all able to return to pre-intervention levels of cardiorespiratory fitness, however, it required significant effort (i.e., 11 training sessions a week for 7-8 weeks at intensities ranging from 65 to 100% of maximal heart rate). Importantly, in a follow-up study performed on these same subjects 30-years later, the investigators discovered that 3 decades of aging had less impact on participants physical work capacity than did 20-days of bed rest (McGuire et al., 2001). To this end, population health initiatives must be undertaken to make physical activity participation the easy choice in an environment of minimal physical effort.

National and international physical activity guidelines have been developed to encourage participation in regular physical activity and reduce the high amounts of sedentary behavior prevalent across the globe. The terms physical activity and sedentary behavior describe opposite ends of the energy expenditure continuum; the latter describes waking behaviors below 1.5 times resting energy expenditure (i.e. sitting, lying, and reclined postures) (van der Ploeg & Hillsdon, 2017). Physical activity, on the other hand,

describes any bodily movement that increases energy expenditure above resting (Caspersen, Powell, & Christenson, 1985) and can include light, moderate, and vigorous workloads, which increases energy expenditure 1.5 - 2.9, 3 - 6, and more than 6 times resting energy expenditure, respectively (van der Ploeg & Hillsdon, 2017). Population health guidelines encourage participation in at least 150 minutes of moderate to vigorous intensity aerobic physical activity weekly and to minimize the amount of time engaged in sedentary behaviors (Piercy et al., 2018; Tremblay et al., 2011). Resistance type exercise and good sleep practices are also encouraged due to their unique benefits on bone and brain health, respectively (Tremblay et al., 2016). Although various iterations of these recommendations have been in place for more than three decades, a small fraction of the population meet the target (World Health Organization, 2018). Individuals and populations who do not accumulate 150 minutes of moderate to vigorous intensity physical activity weekly are described as physically inactive (van der Ploeg & Hillsdon, 2017). Recognizing the detrimental effects of physical inactivity on mortality and its link to the development of noncommunicable disease, the World Health Organization (2018) has prioritized this risk factor and set a goal for countries to increase their relative physical activity participation by 15% from 2018 to 2030. The framework disseminated through the action plan includes 20 policies focused on creating active societies, environments, people, and systems. Among these policies is the action for health care providers to implement and strengthen systems of assessment and counselling focused on increasing physical activity

and reducing sedentary behavior (World Health Organization, 2018). However, they fall short on addressing the high amounts of sedentary behavior imposed by the healthcare environment itself. It has been reported across multiple disease states that patients receiving in hospital services are very sedentary (Baldwin, van Kessel, Phillips, & Johnston, 2017) and that patient related factors are only part of the equation (Chastin et al., 2019; Tieges et al., 2015). Such environments normalize physical inactivity and miss an opportunity to enhance health outcomes.

The link between physical inactivity and the development of many noncommunicable diseases (i.e., type 2 diabetes, ischemic heart disease, stroke, etc.) is undeniable. However, among individuals diagnosed with such chronic conditions, it is unlikely that current population health initiatives focused toward increasing daily physical activity levels are sufficient to overcome the underlying structural and function consequences of previous inactivity (Booth et al., 2017). The distinction here is between the use of physical activity interventions for the primary, secondary, and tertiary prevention of chronic diseases. Primary prevention strategies are directed toward apparently healthy individuals where the goal is to prevent the onset of clinical risk factors (i.e., physical inactivity, poor eating behaviours, abdominal obesity, etc.) or even preclinical changes (i.e., increases in blood pressure, blood lipids, blood glucose levels, etc.) (Wolfram & Fuchs, 2008). Whereas secondary prevention strategies are focused on individuals who have already developed risk factors or preclinical disease (Wolfram & Fuchs, 2008).

Tertiary prevention, on the other hand, is focused toward mitigating the health consequences of a clinical disease (e.g., type 2 diabetes, ischemic heart disease, stroke, etc.) (Wolfram & Fuchs, 2008). Current recommendations of 150 minutes of moderate to vigorous intensity physical activity weekly (Piercy et al., 2018; Tremblay et al., 2011), may be appropriate for the primary prevention of noncommunicable diseases (Garber et al., 2011). However, in the case of secondary and tertiary prevention, prescribed physical activity interventions are likely required to reverse the underlying effects of previous inactivity, if such a thing is even possible (Booth et al., 2017). In the context of prescribing physical activity to achieve a desired health outcome, exercise training is the more appropriate term to use. Although the individual movements included in exercise training paradigms are themselves physical activities, they are organized in such a way to maintain or increase physical fitness (Garber et al., 2011). Collectively, the components of physical fitness (i.e., cardiorespiratory fitness, muscle strength and endurance, body composition, flexibility, and neuromotor fitness) govern an individual's ability to carry out daily tasks with ease and vigor (Caspersen et al., 1985; World Health Organization, 2018). When prescribing exercise interventions, the dose of physical activity used (i.e., frequency, intensity, time, and type) is specific to the target outcome. For example, exercise interventions designed to increase cardiorespiratory fitness will differ from ones designed to increase muscular strength in terms of how physical activities are organized within the training program. In terms of health outcomes, exercise interventions focused toward

increasing daily energy expenditure and enhancing cardiorespiratory fitness are the most frequently studied (Garber et al., 2011). An individual's level of cardiorespiratory fitness, or more specifically their aerobic power, describes the capability of structures contained within an interconnected network of organs (i.e., respiratory, cardiovascular, and muscular systems) to extract oxygen from the ambient air, deliver it to tissues throughout the human body that require oxygen and use it to maintain energy supply for the purpose of sustaining vital functions and performing external work (Taylor et al., 1981; Taylor & Weibel, 1981). It is this dependency upon oxygen to perform physical work that makes cardiorespiratory fitness an important marker for health and performance. Accordingly, the gold standard assessment of cardiorespiratory fitness involves measurement of gas exchange (i.e., oxygen uptake and carbon dioxide production) between an individual and their environment during exercise at increasing workloads (Cooper & Storer, 2001). The Dallas bed rest study, described above, clearly demonstrates that cardiorespiratory fitness is not a fixed value. Changes in this component of physical fitness were directly related to structural and functional changes in the oxygen delivery and utilization pathways because of decreases in physical activity, which were later reversed through exercise training (Saltin et al., 1968). It is unclear if individuals diagnosed with chronic medical conditions exhibit the same flexibility in response to exercise training (i.e., restore more normal levels of cardiorespiratory fitness). If so, how much exercise is required and are such interventions acceptable to clinical populations? The answer to these questions will likely depend on the

populations studied, however, they form the foundation of exercise based secondary / tertiary prevention programs.

1.1 Stroke recovery as a model to study the effectiveness of exercise interventions designed to reverse the consequences of a previously inactive lifestyle.

Stroke is a medical emergency occurring when blood flow is disrupted to the central nervous system that results in cell death and is associated with a focal loss of neurological function and may even cause loss of life (Sacco et al., 2013). Transient ischemic attack differs from stroke in that neurological function is returned within 24 hours from the onset of symptoms (Sacco et al., 2013). The early symptoms of stroke include drooping on one side of the face, weakness in one arm, and slurred speech (Hankey, 2017). These symptoms are incorporated in the Heart and Stroke Foundations FAST campaign (F= face, A=arm, S=speech, T=time) to help individuals recognize the signs of stroke and urge them to get immediate medical attention. Advances in the hyperacute management of stroke have reduced the case fatality rate and improved the odds of experiencing less severe impairments (Goyal et al., 2015; Harmel et al., 2019). However, many stroke survivors are left with permanent impairments that limit their ability to maintain functional independence (Winstein et al., 2016). Although hemiparesis is among the most overt symptoms of stroke, the effects are not limited to the motor domain and can include sensory, cognitive, and language impairments along with emotional disturbances (Hankey, 2017; Mukherjee,

Levin, & Heller, 2006). There are two main types of stroke, namely, ischemic and hemorrhagic stroke. Ischemic stroke occurs when there is a lack of blood flow to specific tissues within the central nervous system due to the narrowing or occlusion of a blood vessel supplying them (Sacco et al., 2013). The obstruction is generally caused by a blood clot that was developed in the affected artery itself (thrombus) or embolism that developed as a thrombus from a different area of the circulatory system (thromboembolism) (Sacco et al., 2013). Hemorrhagic stroke occurs when a blood vessel in the brain ruptures causing blood to collect within the brain parenchyma or ventricles (intracerebral hemorrhage) or the subarachnoid space (subarachnoid hemorrhage) that is not caused by trauma (Sacco et al., 2013). Diagnosis of stroke and its subtypes is initially investigated based on clinical symptoms and confirmed by radiological imaging of the brain (Hankey, 2017). It is important to differentiate between ischemic and hemorrhagic stroke as their treatments are very different. Acute ischemic stroke is treated using reperfusion techniques such as the administration of intravenous alteplase and/or endovascular thrombectomy to breakdown the blood clot or remove it using stent retrievers, respectively (Hankey, 2017). Such clot busting drugs could be fatal if wrongly administered to individuals experiencing a hemorrhagic stroke as it would likely lead to expansion of the brain bleed. The immediate goal for treating hemorrhagic stroke is to reduce the bleeding risk, which is focused on blood pressure control, stopping medication that may increase bleeding, and surgical techniques to reduce pressure within the brain (Hankey, 2017).

1.1.1 Why Study Stroke Survivors?

Although most clinical populations could benefit from exercise-based interventions focused on reversing the consequences of their previous inactivity, a unique opportunity exists for individuals recovering from a stroke.

Stroke is a prevalent chronic condition that is associated with high rates of cardiovascular mortality. Globally, the respective incidence and prevalence rates for stroke were estimated to include 13.7 million cases and 80.1 million survivors in 2016 (Krishnamurthi, Ikeda, & Feigin, 2020). Although age-adjusted incidence rates have remained relatively stable (Madsen et al., 2017), the prevalence of stroke is projected to increase due to population growth and decreased case fatality rates. Accordingly, a recent Canadian study estimates that the number of individuals living with the life-altering effects of stroke will increase from 405,000 in 2013 to between 654,000 and 726,000 by 2038 (Krueger et al., 2015). The inadequate management of cardiovascular risk factors is reflected in the high rates of recurrent stroke and major cardiovascular events, the primary cause of premature mortality in this population (Bronnum-Hansen, Davidsen, Thorvaldsen, & Danish, 2001). Therefore, secondary/tertiary prevention of cardiovascular comorbidity is essential in this population, which will be discussed in later.

Physically inactive and sedentary lifestyles predate incident stroke. Physical inactivity is among the leading modifiable risk factors that explain more than 90% of the

population's attributable risk of stroke globally (O'Donnell et al., 2016). Furthermore, poor cardiorespiratory fitness recorded during midlife is strongly predictive of future hospitalization due to stroke (Pandey et al., 2016), which likely reflects lifelong exposure to these risk factors. Given the strong influence of environmental factors on physical activity participation (Sallis et al., 2006), it is unlikely that stroke survivors who were previously inactive and are now living with the effects of stroke will have the support necessary to engage in regular physical activity. Accordingly, high rates of sedentary behavior and physical inactivity are observed in community-living stroke survivors (English, Manns, Tucak, & Bernhardt, 2014).

Stroke survivors have unmatched access to an interdisciplinary health care team during inpatient and outpatient rehabilitation services for a prolonged period (typically between 1 to 3-months) (Hebert et al., 2016; Winstein et al., 2016). Such access to health care providers offers an opportunity to deliver interventions designed to increase cardiorespiratory fitness and facilitate lifelong participation in physical activity.

Poor cardiorespiratory fitness is characteristic of stroke survivors. Maximum oxygen uptake measurements recorded upon completion of formalized stroke rehabilitation (Smith, Saunders, & Mead, 2012) are 40% lower than measures taken in age and sex-matched heart disease patients after completion of cardiac rehabilitation (Banks, Cacoilo, Carter, & Oh, 2019). Some of the discrepancy between the two clinical populations could

be explained by neuromotor impairments, which can limit stroke survivors' ability to achieve validation criteria for assessment of maximum oxygen uptake (Midgley, McNaughton, Polman, & Marchant, 2007; Poole & Jones, 2017) and reduce the amount of active muscle mass (Potempa et al., 1995). However, it must also be recognized that sedentary behaviors dominate the inpatient environment and very little time can be characterized as moderate to vigorous intensity aerobic exercise. Furthermore, stroke survivors discharged from formalized care retain the ability to achieve relatively large increases in cardiorespiratory fitness (i.e., >30%) (Ivey, Stookey, Hafer-Macko, Ryan, & Macko, 2015). Regardless of the reasons for poor cardiorespiratory fitness after stroke, aerobic exercise training is an important treatment modality and has significant implications for functional independence, ongoing cardiovascular risk, and quality of life in this population, which are discussed below

1.1.2 Poor Cardiorespiratory Fitness Can Limit Functional Independence After Stroke

Although hemiparesis is the most overt symptom associated with functional impairments after stroke, poor cardiorespiratory fitness also impacts an individual's ability to perform ambulatory activities. Assessments of cardiorespiratory fitness reveal that peak oxygen uptake is between 12.8- and 20.9-mL min^{-1} kg^{-1} among community living stroke survivors (Saunders et al., 2020; Smith et al., 2012). Given that values less than 18 mL

min^{-1} kg^{-1} are associated with perceived difficulties in completing daily activities among older adults (Morey, Pieper, & Cornoni-Huntley, 1998), such low levels of cardiorespiratory fitness pose a challenge to regaining functional independence after stroke. Furthermore, hemiparesis increases the energy cost of ambulatory activities by a factor of 1.5 to 2 times that of normal gait (S. Kramer, Johnson, Bernhardt, & Cumming, 2016). Together, poor cardiorespiratory fitness and increased energy cost of ambulatory activities conspire to limit what is described as the functional fitness reserve (Macko et al., 2001). To maintain functional independence, this reserve must be sufficient to include the physical requirements for all daily activities. If relatively simple activities, such as walking or getting out of bed, require large fractions of individuals functional fitness reserve, it will be difficult to sustain other daily responsibilities without inducing excessive fatigue. Furthermore, poor cardiorespiratory fitness can limit patient's ability to sustain the intensity of task-oriented therapies required to relearn lost functions after stroke and thus create a potential ceiling for neuromotor recovery (Ploughman & Kelly, 2016). Therefore, interventions targeted toward increasing cardiorespiratory fitness has widespread benefits that extend beyond reducing ongoing cardiovascular risk and must be integrated with therapies designed to increase functional independence among stroke survivors.

1.1.3 Cardiorespiratory Fitness is an Important Treatment Target for the Secondary Prevention of Cardiovascular Events and Recurrent Stroke

The characteristically low levels of cardiorespiratory fitness observed in stroke survivors has serious implications for ongoing cardiovascular risk. Poor cardiorespiratory fitness is an independent risk factor for future stroke (Pandey et al., 2016). The association between cardiorespiratory fitness and stroke risk was evaluated among 19 815 participants who completed a maximal symptom limited graded exercise test in their 40's as part of the Cooper Centre Longitudinal Study and were later followed up (at ≥ 65 years of age) through Medicare claims. A linear inverse association was observed between cardiorespiratory fitness and stroke hospitalization for both male and female participants, where every 1 metabolic equivalent (i.e., 3.5 mL min^{-1} kg^{-1}) increase was associated with a 7% reduction in risk for stroke hospitalization (Pandey et al., 2016). It is important to note that the average cardiorespiratory fitness level reported among individuals in the lowest fitness category was 29 (SD 4.2) mL min^{-1} kg^{-1}, which is substantially higher than values reported in stroke survivors. Furthermore, adjusting the model for baseline risk factors (body mass index, lipid profile, blood pressure, diabetes) and later diagnosis of hypertension, diabetes, and atrial fibrillation had little effect on the association between midlife cardiorespiratory fitness and stroke hospitalization (Pandey et al., 2016). This is not to say that cardiorespiratory fitness is the only important risk factor for future stroke as hypertension and atrial fibrillation were also independently associated with stroke

hospitalization (Pandey et al., 2016). In fact, a recent multinational case control study evaluated the association between potentially modifiable risk factors and acute stroke among 13,447 cases and 13,472 age and sex matched non-stroke controls (O'Donnell et al., 2016). Collectively, ten risk factors (hypertension, smoking status, waist-to-hip ratio, diet, physical activity, diabetes, alcohol intake, psychosocial factors, cardiac causes (e.g., atrial fibrillation), and lipid profile) were associated with nearly 90% of the population attributable risk of stroke (O'Donnell et al., 2016). Ranked in order of contribution to population attributable risk, hypertension, physical inactivity, and abnormal blood lipids (apolipoprotein levels) were the top three risk factors (O'Donnell et al., 2016). Interestingly, these same modifiable risk factors also explain much of the population attributable risk of myocardial infraction (Yusuf et al., 2004). The challenge for stroke survivors, however, is that the secondary prevention is not prioritized. Accordingly, a recent cross-sectional comparison between patients receiving treatment for stroke and heart disease demonstrated that stroke survivors were less likely to achieve secondary prevention targets for blood pressure and lipid profile (Vanek et al., 2016). Also, as described above, cardiorespiratory fitness is 40% lower among stroke survivors upon completion of formalized rehabilitation compared to heart disease patients (Banks et al., 2019; Smith et al., 2012). Accordingly, the risk of recurrent stroke and death from cardiovascular causes remains high among stroke survivors (Dhamoon, Sciacca, Rundek, Sacco, & Elkind, 2006). A more recent population-based cohort study conducted on nearly half a million Chinese

adults reported that 41% of stroke survivors experienced recurrent stroke within a 5-year period and the authors emphasized the importance of secondary prevention strategies in this population (Chen et al., 2020). To this end, best practice guidelines for the secondary / tertiary prevention of stroke have been developed and treatment targets are outlined for most of the modifiable risk factors described above (Wein et al., 2018). The one exception, however, is cardiorespiratory fitness. Canadian guidelines recommend participation in "dynamic exercise of moderate intensity… 4 to 7 days per week, to accumulate at least 150 minutes in episodes of 10 minutes or more, in addition to routine activities of daily living" to prevent recurrent stroke (Wein et al., 2018). However, there is no target set for increasing cardiorespiratory fitness or even a mention of increasing this component of physical fitness for the purpose of secondary / tertiary prevention, which is surprising considering the literature described above. Also, the recommendations for exercise as part of secondary/tertiary prevention for recurrent stroke are very similar to the physical activity guidelines disseminated for general populations (Wein et al., 2018). This suggests that the amount of physical activity required to prevent future cardiovascular events is similar among apparently healthy individuals as those with known cardiovascular and metabolic comorbidities. The main difference in the dose of aerobic exercise included in both recommendations is a focus on moderate intensity activity after stroke whereas higher intensities are recommended for the general population. A focused review of exercise

interventions implemented in stroke survivors for the purpose of increasing cardiorespiratory fitness is provided in a later section.

1.1.4 The Link Between Cardiorespiratory Fitness and Quality of Life After Stroke

As described above, low levels of cardiorespiratory fitness can limit stroke survivor's ability to achieve functional independence, which has obvious implications for individual's quality of life. Accordingly, exercise induced improvements in quality of life after stroke are often attributed to enhancements in functional performance (Pundik, Holcomb, McCabe, & Daly, 2012). However, its effect on comorbidity should not be overlooked. Nancy Mayo and colleagues (2015) evaluated the Wilson-Cleary health-related quality of life model in stroke survivors (N=678) throughout the subacute phase of recovery. The model describes the casual relationships between five domains in sequential order as follows: biology / physiology, symptoms, function, health perceptions, and quality of life (Wilson & Cleary, 1995). In this model patient reported symptoms are investigated through their link with the underlying biological and physiological abnormalities, and functional status is directly related to symptoms. Additionally, patient's health perceptions are aligned with their functional status and ultimately to their quality of life. Using structural equation modeling, Mayo et al. (2015) found that the model explained much of the variation in health perceptions among stroke survivors, however, they did not find support for a strong link between functional status and health perceptions. Allowing

additional paths from non-adjacent rubrics (i.e., from biology to symptoms and then to health perceptions directly) improved the fit. In their final model, the authors reported strong connections from comorbidity (biology rubric) and impairments (symptoms rubric) to health perceptions, which they interpreted to suggest that interventions during the first 3-months after stroke should be focused on reducing comorbid health conditions and impairments (Mayo et al., 2015). From this point of view, aerobic exercise training is important for addressing impairments related to poor aerobic capacity (biology / physiology) and treating the underlying cardiometabolic dysfunction associated with the development of comorbid conditions in this population (i.e., diabetes, heart disease, peripheral artery disease, etc.).

1.1.5 The Timeline of Stroke Recovery is Well-defined and is Conducive to Studying the Effects of Exercise-based Interventions

The first seven days after the onset of stroke are described as the acute phase of recovery (hyperacute: 0-24hrs) (Bernhardt et al., 2017). Treatments offered during the acute phase are focused toward minimizing the amount of brain tissue damage and preventing further medical complications (Hankey, 2017). Physical activity is limited during the initial phase of recovery and may even be harmful if initiated too early (Bernhardt et al., 2015).

Perhaps, the first opportunity for initiating aerobic exercise training after stroke is in the second week, which marks the beginning of the subacute phase of recovery (early subacute: 7-days to 3-months; late subacute: up to 6-months) (Bernhardt et al., 2017). The subacute phase is when formalized stroke rehabilitation services are typically offered and the focus is on delivering task-oriented therapies (Hebert et al., 2016; Winstein et al., 2016). The goal of such therapies is to help patients regain lost functions through active practice of context-specific motor tasks (e.g., reaching, grasping, walking, etc.) (Pollock et al., 2014). The first three months are regarded as the optimal window for recovery of lost function after stroke because of the injured brains enhanced capacity for structural and functional change during this time (Ward, 2017). Pre-clinical models have begun to describe the neurobiological mechanisms underlying what is commonly referred to as enhanced neuroplasticity during this early stage of recovery (Murphy & Corbett, 2009). Clinical data also supports the idea of increased neuroplasticity during the first 3-months of recovery, which is demonstrated through increased rates of functional recovery followed by slowing or a plateau of recovery after this time (Jorgensen et al., 1995; Nakayama, Jorgensen, Raaschou, & Olsen, 1994). Accordingly, best practice guidelines recommend "three hours per day of direct task-oriented therapy, five days a week, delivered by the interprofessional stroke team throughout the subacute phase" (Hebert et al., 2016). Although such formalized stroke rehabilitation programs are generally considered an intense form of physical rehabilitation, task-oriented therapies typically offered during

inpatient services offer very little cardiovascular stress (Barrett et al., 2018; M. J. MacKay-Lyons & Makrides, 2002). Accordingly, interventions targeting cardiorespiratory fitness during the first 3-months of recovery must incorporate aerobic exercise training in addition to task-oriented therapy or increase the aerobic demands of task-oriented therapy itself.

At the 6-month mark stroke survivors enter the final phase of recovery and are often described as chronic stroke survivors (Bernhardt et al., 2017). Compared to earlier time points, the ability to achieve functional recovery through neural repair mechanisms is reduced and changes in performance measures are generally described as compensatory in nature (i.e., not normal pre-stroke behavior) (Bernhardt et al., 2017). Once recovery of function begins to plateau, it seems reasonable to shift the focus toward treating one of the central causes of stroke in the first place, poor cardiorespiratory fitness. Unfortunately, such services are currently unavailable to stroke survivors after completion of formalized rehabilitation. It is important to recognize that by enhancing cardiorespiratory fitness at this stage of recovery, there are further opportunities to increase functional performance while at the same time decreasing risk for future cardiovascular/cerebrovascular events and enhancing quality of life (Saunders et al., 2020). Accordingly, incorporating functional activities into aerobic exercise interventions may help to translate improvements in cardiorespiratory fitness into enhanced ability to complete daily chores. From a secondary / tertiary prevention point of view, the primary goal of aerobic exercise interventions should be to improve cardiorespiratory fitness and reduce associated risk factors. Increasing this

component of physical fitness is likely a major step forward in helping stroke survivors live a long productive life.

1.2 Aerobic Exercise Training for the Purpose of Increasing Cardiorespiratory Fitness After Stroke: a Focused Review

1.2.1 Objective:

The primary objective of the current literature review is to describe the dosages of aerobic exercise previously prescribed among stroke survivors for the purpose of increasing cardiorespiratory fitness during the subacute and chronic phases of recovery. Secondary objectives involve describing the dose-response effects of such exercise interventions on cardiorespiratory fitness and other know coronary artery disease risk factors.

1.2.2 Search Strategy and Data Reduction Methods:

To be included in this review, studies must have a) used randomized control or waitlist control methodologies, b) included at least one aerobic exercise treatment arm (i.e. sustained physical exercise at prescribed workloads according to heart rate reserve or percentage of peak workload), c) reported cardiorespiratory fitness as the primary or co-primary outcome measure, and d) evaluated cardiorespiratory fitness during a symptom-limited graded exercise tests performed at baseline and post-intervention with direct

measures of gas exchange to determine maximal or peak oxygen uptake. The distinction between maximal and peak oxygen uptake is made because it is unclear if stroke survivors can sustain the workloads required to achieve a valid assessment of maximal oxygen uptake (Howley, Bassett, & Welch, 1995; Midgley et al., 2007; Poole & Jones, 2017). However, both terms are used as the gold standard assessment of cardiorespiratory fitness in the stroke literature. To find relevant peer reviewed publications, the Medline database was searched via PubMed (1947 to July 2020) using the strategy described in Table 1-1 below. Titles and abstracts of all articles published in English returned from the database search were screened for appropriateness based on the above inclusion criteria. After which, the reference lists of the remaining studies and two recent systematic reviews (D'Isabella, Shkredova, Richardson, & Tang, 2017; Saunders et al., 2020) were reviewed for additional publications.

Table 1-1: Search strategy and results

Search #	Search strategy	Items found
#1	"stroke" [Mesh]	134,183
#2	"Exercise" [Mesh]	194,729
#3	"Aerobic Exercise" Title/abstract	9,541
#4	"Physical exertion" [Mesh]	56,302
#5	"Rehabilitation" [Mesh]	304,130
#6	#2 OR #3 OR #4 OR #5	520,842
#7	#1 AND #6	13,427
#8	#7 Filter: Clinical trial; randomized control trial	2,807
#9	"Exercise test" [Mesh]	64,397
#10	"Ergometry" [Mesh]	64,596
#11	"Cardiovascular fitness" Title/abstract	1,355
#12	"physiological outcomes" Title/abstract	682
#13	#9 OR #10 OR #11 OR #12	67,703
#14	#8 AND #13	137

In line with previous literature (Billinger, Boyne, Coughenour, Dunning, & Mattlage, 2015; Garber et al., 2011), the dosage of aerobic exercise studied in each peer reviewed article was described in terms of the frequency (number of sessions per week), intensity (relative effort according maximal/peak oxygen uptake, heart rate reserve, or peak workload), type (ergometer, functional training, constant-load, intermittent exercise, etc.), and time (both duration of individual sessions and total length of the intervention period) of prescribed activities. These parameters were then used to calculate the average energy expenditure of exercise (EEE) for individual sessions and the cumulative weekly metabolic stress. In studies that prescribed aerobic exercise workloads in terms of percentage of peak workload achieved during the baseline graded exercise test, the following formula was used to calculate rate of oxygen uptake ($\dot{V}O_2$) during the prescribed workloads (Cooper & Storer, 2001):

Equation 1-1

$$\dot{V}O_2 = \left(10.3 * \dot{W}\right) + (5.8 * BW) + 151$$

where $\dot{W}$ is the prescribed workloads in watts and BW is participants weight in kilograms. Energy expenditure of exercise was then calculated as follows:

Equation 1-2

$$EEE = \dot{V}O_2 * t * Q_{ox}$$

where t is the time spent at each workload and Q_{ox} is the energy equivalent for oxygen assuming a respiratory exchange ratio of 0.9 (i.e., 5.1 kcal/L) (F. Peronnet & Massicotte, 1991). The same formula was used to determine EEE in studies that prescribed workloads based on heart rate reserve. However, $\dot{V}O_2$ was determined through calculation of oxygen uptake reserve and multiplying by the prescribed intensity for heart rate reserve (e.g., 60%) according to the following equation:

Equation 1-3

$$\dot{V}O_2 = \left(\dot{V}O_{2\,max/peak} - RMR\right) * prescribed\ intensity(\%) + RMR$$

where $\dot{V}O_{2\,max/peak}$ is the highest value reported for $\dot{V}O_2$ during the baseline graded exercise test, and RMR is resting metabolic rate, which was estimated to be 3.5 mL min^{-1} kg^{-1} (Cooper & Storer, 2001). Accordingly, EEE is a composite score that considers both the prescribed intensity and volume of exercise, which reflects total metabolic stress imposed by each study intervention. The advantage of calculating EEE is that we can compare the doses of exercise between studies that vary in more than one of the 'FITT' parameters described above.

1.2.3 Results:

Of the 137 studies returned from the database search, 37 studies were excluded because they did not use randomized control methods, an additional 50 studies were excluded because they did not include an aerobic exercise treatment arm (body-weight

supported treadmill training was excluded if prescribed intensity was not based on heart rate or percentage of peak workload determined during the baseline graded exercise test), a further 35 studies were excluded because cardiorespiratory fitness was not reported as the primary or co-primary outcome measure, and finally four studies were excluded because they did not perform symptom-limited exercise tests with gas analysis to determine maximal or peak oxygen uptake. In total, 16 studies met the inclusion criteria.

1.2.3.1 Aerobic Exercise Workloads Previously Prescribed to Increase Cardiorespiratory Fitness After Stroke

Of the studies included in this review, the majority (12/16) involved stroke survivors in the chronic phase of recovery. The FITT parameters and calculated EEE for each study are reported in Table 1-2. At quick glance, the exercise prescription to enhance cardiorespiratory fitness has not changed much over the last 25 years. Cycle and treadmill ergometers were the most frequently used modalities to achieve the prescribed level of aerobic stress. However, circuit training protocols were also implemented and included functional activities performed in the water (Chu et al., 2004) and over-ground (Pang, Eng, Dawson, McKay, & Harris, 2005). Most of these studies incorporated aerobic exercise 3 days/week (range: 3 to 5 sessions) for 30 min per session (20 to 50 min) over a 12-week period (range: 3 to 24 weeks). On average, this involved 100 min (SD 22) of aerobic exercise weekly. In terms of exercise intensity, more recent studies have implemented

higher relative workloads during steady state exercise (Globas et al., 2012; Ivey et al., 2015) compared to the seminal work (Potempa et al., 1995) and have moved toward high intensity interval training protocols (Munari et al., 2018). The average estimated EEE was 155 (SD 56) kcal/session and ranged from 276 to 950 kcals/week. Given that the prescribed weekly volume of aerobic exercise is relatively consistent between studies, it is not surprising that EEE was higher among studies that implemented the highest relative efforts (Globas et al., 2012; Munari et al., 2018).

Table 1-2: Dose of aerobic exercise implemented in each study

Study	Frequency	Intensity	Type	Time	Energy Expenditure of Exercise
Potempa et al. (1995)	3 days / week	30 to 50% of max effort (4 weeks); highest training load (last 6 weeks)	Cycle ergometer	30 min per session over 10 weeks	~157 kcal / session ~472 kcal / week
Rimmer, Riley, Creviston, and Nicola (2000)*	3 days / week	5-15 bpm lower than HR associated with RER= 1 during GXT	Multiple types of ergometers	30 min per session over 12 weeks	~174 kcal / session ~523 kcal / week
Chu et al. (2004)‡	3 days / week	Progressive increase in intensity (50 to 80% of HRR)	Water-based exercise	30 min / session over 8 weeks	~166 kcal / session ~497 kcal / week
Macko et al. (2005)	3 days / week	Progressive increase in intensity (40 to 70% of HRR)	Treadmill walking	40-min / session over 6 months	~160 kcal/session ~479 kcal/week
Pang et al. (2005)‡	3 days / week	Progressing from 40-50 up to 70-80% of HRR	Functional exercise (FAME)	Up to 30 min / session over 19 weeks	~92 kcal/session ~276 kcal/week
Ivey, Ryan, Hafer-Macko, Goldberg, and Macko (2007)	3 days / week	60 to 70% of HRR	Treadmill walking with body-weight support	40-min / session over 6 months	~141 kcal/session ~422 kcal/week
Rimmer, Rauworth, Wang, Nicola, and Hill (2009)	3 days / week	LILD: <50% HRR MISD: 40 to 69% of HRR	Cycle erg or recumbent stepper	LILD: 30-60 min MISD: 30 min over 14 weeks	LILD: ~129 kcal/session LILD: ~386 kcal/week MISD: ~141 kcal/session MISD: ~422 kcal/week
Tang, Sibley, et al. (2009)†	3 days / week	50 to 70% of peak workload or RPE 4-6 / 10	Semi-recumbent cycle erg	Up to 30 min / session for average 3 weeks	~125 kcal/session ~374 kcal/week

Letombe et al. (2010)*†	4 days / week	70 to 80% of peak power	Semi-recumbent cycle erg	~20 min per session over 4 weeks	~110 kcal/session ~441 kcal/week
Globas et al. (2012)	3 days / week	Progressing to 60-80% of HRR	Treadmill walking (0% grade)	Progressing to 30-50 min per session over 12 weeks	~218 kcal/session ~654 kcal/week
(Jin, Jiang, Wei, Chen, & Ma, 2013)	5 days / week	Progressing to 50-70% of HRR	Limb-loaded cycling exercise	Progressing to 40 min per session over 12 weeks	~74 kcal/session ~371 kcal/week
M. Mackay-Lyons, McDonald, Matheson, Eskes, and Klus (2013)†	5 days / week for first 6 week, then 3 days / week	Progressing to 60-75% of $\dot{V}O_{2peak}$ over first 4 weeks	Bodyweight supported treadmill starting at 70-90% of self-selected speed	At least 20 min per session over 12 weeks	~108 kcal/session ~430 kcal/week
Tang et al. (2014)	3 days / week	Progressed from 40% to 70-80% of HRR	Multimodal: cycle erg., over ground walking, functional exercise.	Progressing to 30-40 min of continuous exercise (completed in bouts of 10 min if needed) over 6 months	~148 kcal/session ~444 kcal/week
Ivey et al. (2015)	3 days / week	High Intensity Treadmill (HI-TM): progressed to 80-85% HRR Low Intensity Treadmill (LI-TM): <50% HRR	Treadmill	HI-TM: 30 min per session LI-TM: progressing from 30 to 50 min over 6 months	~156 kcal/session ~468 kcal/week
Stoller et al. (2015)†	3 days / week	The aim was 40-60% of HRR. Post analysis determined that average HRR was 40%	Robot-assisted treadmill walking	30 min per session over 4 weeks	~102 kcal/session ~307 kcal/week
Munari et al. (2018)	3 days / week	High-intensity Treadmill Training (HI-TM): 85-95% $\dot{V}O_{2peak}$ Low-intensity Treadmill Training (LI-TM): 60% $\dot{V}O_{2peak}$	Treadmill walking (with grade, intermittent)	HI-TM: 5 x 5 min intervals with 3-5 min active recovery at 50% $\dot{V}O_{2peak}$ between intervals LI-TM: 40 min Both interventions occurred over 12 weeks	HI-TM: ~317 kcal/session HI-TM: ~950 kcal/week LI-TM: ~233 kcal/session

					LI-TM: ~700 kcal/week

* Interventions lasted 60-min per session and included other exercises in addition to aerobic exercise (i.e., range of motion, balance, strength training, etc.), only the aerobic exercise portion is described in the table; † Subacute phase of recovery; ‡ completed in the community (i.e., recreational facility)

Most studies (12/16) reported the results of symptom-limited graded exercise tests as peak oxygen uptake rather than maximal oxygen uptake. As displayed in Table 1-3, the primary validation criterion for achieving maximal or peak workloads was volitional exhaustion. In terms of other validation criteria, two studies reported on whether or not a plateau in $\dot{V}O_2$ was achieved (Chu et al., 2004; Stoller et al., 2015), five studies reported respiratory exchange ratios recorded at the end of the graded exercise test (Chu et al., 2004; M. Mackay-Lyons, McDonald, et al., 2013; Pang et al., 2005; Potempa et al., 1995; Rimmer et al., 2000; Stoller et al., 2015), and three studies reported percentage of age predicted max heart rate achieved (Chu et al., 2004; M. Mackay-Lyons, McDonald, et al., 2013; Stoller et al., 2015). At baseline, $\dot{V}O_{2peak}$ scores ranged from 11.2 (SD 0.5) to 14.8 (SD 5.6) and 12.6 (SD 4.2) to 22.5 (SD 5.2) mL min^{-1} kg^{-1} during symptom-limited grated exercise tests performed during subacute and more chronic phases of recovery, respectively. Three studies reported no statistically significant changes in $\dot{V}O_{2peak}$ after the intervention period compared to baseline (Rimmer et al., 2009; Rimmer et al., 2000; Tang et al., 2014) and one study reported no difference in treatment effects between the aerobic exercise and usual care groups when implemented during inpatient rehabilitation (Tang, Sibley, et al., 2009). The remaining 12 studies reported a statistically significant time by group interaction effects in favor of aerobic exercise where pre to post changes in $\dot{V}O_{2peak}$ ranged from 2.0 to 5.5 mL min^{-1} kg^{-1}. Using simple linear regression analysis, variability in the dose-response effects of aerobic exercise was observed in the small non-statistically

significant association with change in $\dot{V}O_{2peak}$ (R^2 = 0.27; p= 0.081). The predicted association between weekly EEE and change in $\dot{V}O_{2peak}$ along with the 95% CI of the error are displayed in Figure 1-1.

Table 1-3: Graded exercise testing outcomes for each of the included studies

Study	Sample Size	Validity Criteria	Oxygen Uptake (Max / Peak)	
			Baseline (ml min^{-1} kg^{-1})	**Post (ml min^{-1} kg^{-1})**
Potempa et al. (1995)*†	Intervention: 19 Control: 23	Volitional exhaustion and RER > 1.15	Intervention: 16.6 (1.0) Control: 15.1 (1.0)	Intervention: 18.8 (1.1) Control: 15.2 (0.9)
Rimmer et al. (2000)†	Intervention: 18 Control: 17	Volitional exhaustion, RER > 1.0, and HR > 90% age predicted max	Intervention: 13.3 (4.2) Control: 14.1 (3.0)	Intervention: 14.4 (4.0) Control: 12.7 (2.6)
Chu et al. (2004)*†	Intervention: 7 Control: 5	RER> 1.15, plateau (1.5 ml min-1 kg-1), or volitional exhaustion.	Intervention: 17.3 (3.0) Control: 17.1 (3.2)	Intervention: 21.2 (2.3) Control: 17.6 (4.7)
Macko et al. (2005)‡	Intervention: 25 Control: 20	volitional exhaustion	Intervention: 14.9 (0.9) Control: 14.7 (1.0)	Intervention: 17.3 (1.0) Control: 14.9 (1.0)
Pang et al. (2005)*†	Intervention: 32 Control: 31	volitional exhaustion	Intervention: 22.5 (5.2) Control: 21.5 (4.3)	Intervention: 24.5 (5.3) Control: 21.8 (4.5)
Ivey et al. (2007)‡	Intervention: 26 Control: 20	volitional exhaustion	Intervention: 13.7 (0.9) Control: 14.8(0.9)	Intervention: 15.7 (1.1) Control: 14.4 (1.0)
Rimmer et al. (2009)†	LILD: 14 MISD: 14 Control: 13	RER> 1.1, HR> 90% of age predicted, volitional exhaustion	LILD:13.3 (3.6) MISD: 15.1 (7.4) Control: 12.6 (4.2)	LILD: 14.0 (3.9) MISD: 15.7 (7.6) Control: 12.2 (3.6)
Tang, Sibley, et al. (2009)†	Intervention: 23 Control: 22	Volitional exhaustion	Intervention: 11.6 (0.7) Control: 11.2 (0.5)	Intervention: 13.1 (0.9) Control: 12.1 (0.8)
Letombe et al. (2010)†	Intervention: 9 Control: 9	Volitional exhaustion	Intervention: 11.5 Control: 12.0	Intervention: 14.0 Control: 12.5
Globas et al. (2012)‡	Intervention: 18 Control: 18	Volitional exhaustion	Intervention: 18.9 (4.6) Control: 21.7 (7.8)	Intervention: 24.4 (6.6) Control: 20.9 (7.8)
(Jin et al., 2013)†	Intervention: 65 Control: 63	Volitional exhaustion	Intervention: 13.2 (0.9) Control: 13.2 (1.0)	Intervention: 16.8 (1.6) Control: 13.3 (1.0)
M. Mackay-Lyons, McDonald, et al. (2013)‡	Intervention: 22 Control: 23	volitional exhaustion	Intervention: 14.2 (4.3) Control: 14.5 (3.5)	Intervention: 18.4 (4.0) Control: 15.6 (4.2)
Tang et al. (2014)†	Intervention: 22 Control: 23	volitional exhaustion	Intervention: 16.9 (7.1) Control: 16.9 (6.1)	Intervention: 17.4 (7.0) Control: 16.6 (5.3)
Ivey et al. (2015)‡	HI-TM: 18	volitional exhaustion	HI-TM: 15.9 (1.7)	Intervention: 21.3 (1.6)

	LI-TM: 16		LI-TM: 16.6 (1.2)	Control: 17.5 (1.2)
Stoller et al. (2015)‡	Intervention: 7 Control: 7	volitional exhaustion	Intervention: 14.3 (4.9) Control: 14.8 (5.6)	Intervention: 17.5 (6.2) Control: 18.0 (5.9)
Munari et al. (2018)*‡	HI-TM: 8 LI-TM: 7	volitional exhaustion	HI-TM: 20.9 (5.3) LI-TM: 20.5 (5.6)	HI-TM: 25.5 (4.0) LI-TM: 19.6 (2.9)

*Reported results of the graded exercise test as V̇O2max; † Cycle erg; ‡ Treadmill

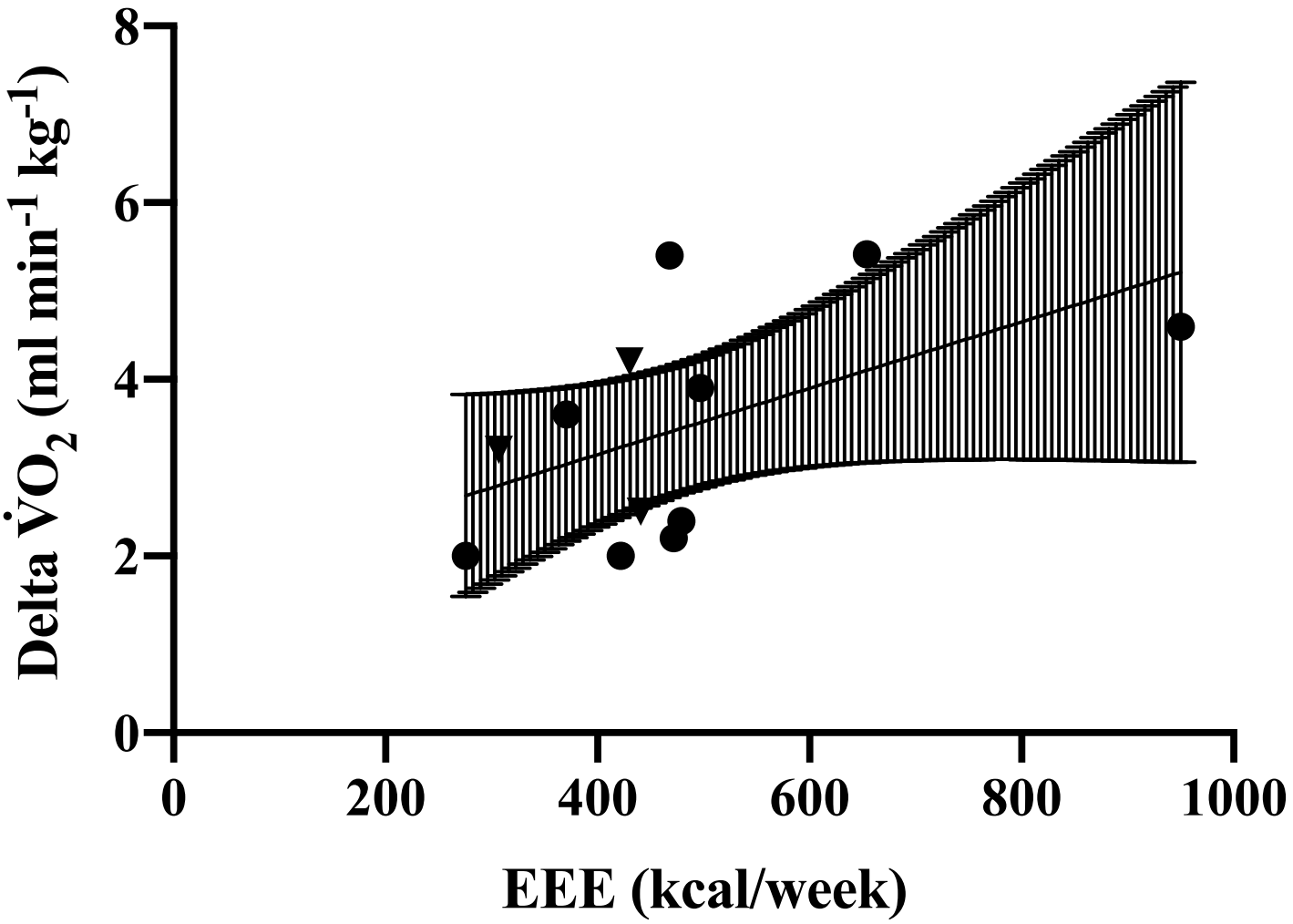


Figure 1-1: Association between weekly energy expenditure of exercise and pre to post changes in peak oxygen uptake. The line of best fit is displayed along with the 95% CI of the error (shaded area). Triangles and circles are used to differentiate between studies initiated during the subacute and more chronic phases of recovery, respectively.

In addition to evaluating the effects of aerobic exercise training on cardiorespiratory fitness, three studies also explored its effect on blood glucose control (Ivey et al., 2007; Tang et al., 2014) and lipid profile (Rimmer et al., 2009; Tang et al., 2014). In the study by Ivey and colleagues (2007), pre to post changes in $\dot{V}O_{2peak}$ (+15%) was associated with reduced total insulin response (-24%) during the 3-hour glucose tolerance test. Importantly, the observed improvements in insulin sensitivity were reported to be greatest for individuals with the most pronounced insulin response at baseline (Ivey et al., 2007). Among individuals with type 2 diabetes and impaired glucose tolerance at baseline, 7/12 in the intervention group and 1/11 in the control group improved their glucose tolerance status. Accordingly, 63% of individuals with impaired glucose tolerance improved to normal levels (5/8) and half of those with type 2 diabetes (2/4) reverted to impaired glucose tolerance status upon completion of the exercise intervention whereas one participant in the control group improved from impaired glucose tolerance to normal levels (Ivey et al., 2007). The study by Tang et al. (2014) also reported improvements in glucose control. However, the observed changes in fasting glucose levels were less likely to be exercise induced because the pre to post effect was larger in the control group and the aerobic exercise intervention failed to provide sufficient metabolic stress as it had little effect on $\dot{V}O_{2peak}$ (<3%) (Tang et al., 2014). Accordingly, the authors reported that a third of their participants were unable to achieve the prescribed exercise intensity (Tang et al., 2014). The intensity dependent effects of aerobic exercise training on blood pressure and lipid

profile were evaluated in a preliminary study that cluster randomized participants to a moderate intensity aerobic exercise program (see Table 1-2 for details), low intensity aerobic exercise matched for EEE, or nonaerobic therapeutic exercise among chronic stroke survivors with diabetes and other comorbidities (Rimmer et al., 2009). Group by time effects were reported in favor of moderate intensity aerobic exercise to decrease total cholesterol, low-density lipoprotein, and diastolic blood pressure (Rimmer et al., 2009). However, baseline values for these markers of coronary artery disease were within acceptable limits and although statistically significant it is unclear if such changes reduce risk. Furthermore, the dosage of aerobic exercise implemented was insufficient to address the very low levels of cardiorespiratory fitness observed in this cohort, which is perhaps a stronger predictor of future events and all-cause mortality (Blair et al., 1989; Pandey et al., 2016).

1.2.4 Discussion

The main outcome of the current review was consolidated data confirming the limited variability in dosages of aerobic exercise previously prescribed to increase cardiorespiratory fitness among stroke survivors. Interestingly, the amount of physical activity incorporated in these studies was below current recommendations for older adults (Tremblay et al., 2011). Unless participants engaged in an additional 50 minutes per week outside the study protocols, they would still meet the definition of being physically inactive

(van der Ploeg & Hillsdon, 2017). The exercise volume (i.e., frequency x time) is remarkably similar between studies. Perhaps the one component of exercise prescription that has changed over the last 25 years is a shift toward increasing the relative intensity of physical activities. Accordingly, participants enrolled in more recent studies (Ivey et al., 2015; Munari et al., 2018) likely achieved physical activity recommendations as they incorporated vigorous intensity activities (Piercy et al., 2018; Tremblay et al., 2011). However, among individuals with such poor levels of cardiorespiratory fitness, increasing relative effort has little effect on the total metabolic stress imposed. For example, in a typical 70-year-old male stroke survivor with a body weight of 80 kg and a $\dot{V}O_{2peak}$ of 16 mL kg^{-1} min^{-1}, a 20% increase in relative effort will cause an additional 30 kcal to be expended over a 30-minute period. To put it in perspective, this increase is about 2% of resting metabolic rate estimated in the same individual (Mifflin et al., 1990). Much higher increases in EEE are likely possible through increases in exercise volume (i.e., frequency and duration) while holding the exercise intensity relatively constant (i.e., 40 to 60% of HRR). For example, increasing the duration of an exercise session from 30 minutes up to 60 minutes at the same relative intensity will double the EEE. Given the limited ability to increase EEE through increments in exercise intensity, the feasibility and acceptability of incorporating higher exercise volumes through increased frequency and duration of individual sessions should be investigated.

Exercise induced changes in cardiorespiratory fitness observed in this focused review were consistent with a recent Cochrane review (Saunders et al., 2020). Comparing the post intervention $\dot{V}O_{2peak}$ scores between stroke survivors randomized to aerobic exercise (N= 223) versus the control condition (N=215), the authors reported a mean difference and 95% confidence interval (CI) for the difference in $\dot{V}O_{2peak}$ of 3.4 mL min^{-1} kg^{-1} (CI 2.98 to 3.83) (Saunders et al., 2020). Although the treatment effects appear rather large, many of these individuals remain below the threshold needed to perform ambulatory activities without inducing excessive fatigue (Morey et al., 1998) and very few stroke survivors achieved the 8 MET threshold (i.e., 28 mL min^{-1} kg^{-1}) reported to offer protection from cardiovascular events (Pandey et al., 2016). It is important to note that average levels of cardiorespiratory fitness for male and female adults 60 years of age and older is in the range of 26 to 32 and 21 to 24 ml min^{-1} kg^{-1}, respectively (Cooper & Storer, 2001). Accordingly, the extent to which stroke survivors can reverse the consequences of a previous inactive lifestyle is currently unknown.

The small non-statistically significant association observed between EEE and pre to post changes in $\dot{V}O_{2peak}$ is difficult to interpret. Having a p-value larger than 0.05 means that the observed association may be reached by chance. However, if we accept that a p-value of 0.08 is providing some evidence indicating that the association is not by chance, then we must also accept that much of the variability in the response to exercise training (i.e., pre to post change in $\dot{V}O_{2peak}$) is not explained by the variability in prescribed EEE

(i.e., >70% of the variability unexplained). There are likely many explanations for this weak association. Firstly, the observed variability in the baseline $\dot{V}O_{2peak}$. Given that relative intensity (i.e., percentage of $\dot{V}O_{2peak}$ or HRR) is used for prescribing exercise, then one prescription (e.g., 30 minutes at 60 % of HRR, 3-days per week over a 10-week period) can have vastly different EEE depending on participants' baseline level of cardiorespiratory fitness. Secondly, most studies do not describe the workloads maintained throughout the study period. This is a problem because we do not know the actual EEE. For example, Tang et al. (2014) reported that a third of their participants were unable to achieve the prescribed aerobic exercise workloads. Thirdly, the duration of the intervention period varied between studies. For example, Ivey et al. (2015) observed similar changes in $\dot{V}O_{2peak}$ over a 6-month period as did Munari et al. (2018) over three months, however, this was achieved at a much lower EEE. Finally, the validity of $\dot{V}O_{2peak}$ for assessing changes in cardiorespiratory fitness must be questioned. If stroke survivors are unable to reach the criteria of $\dot{V}O_{2max}$, then, how do we interpret pre to post changes in graded exercise testing? To what extent do these changes represent a learning effect? From the studies included in this review, aerobic exercise training performed on the treadmill can improve walking ability (Ivey et al., 2015; M. Mackay-Lyons, McDonald, et al., 2013; Macko et al., 2005). Also, a large multicenter randomized control trial demonstrated that bodyweight supported treadmill walking improved self-selected walking speed to a similar extent as did structured physiotherapy among stroke survivors in the subacute phase of recovery (Duncan et al.,

2011). Accordingly, the extent to which the observed pre to post changes in $\dot{V}O_{2peak}$ reflect underlying structural and functional changes in the cardiorespiratory system itself is unclear. Collectively, these limitations indicate that studies with more robust methods for evaluating changes in cardiorespiratory fitness and monitoring/reporting the actual workloads achieved throughout the study period are required to fully elucidate the dose response effects of aerobic exercise training in the stroke population.

Given the limitations discussed above, if we assume the dose-response effects reported in Figure 1-1 to be true, we can then begin to address the question of how much aerobic exercise training is needed to enhance cardiorespiratory fitness to average levels observed in age and gender matched non-stroke population. Again, using the same 70-year-old stroke survivor described previously and setting the target $\dot{V}O_{2peak}$ at 28 ml min^{-1} kg^{-1} (Pandey et al., 2016; Riebe, Ehrman, Liguori, & Magal, 2018), this individual would need to expend 7023 kcal/week over an average of 12 weeks. At an average intensity of 60% of HRR, this corresponds to more than 26 hours of structured aerobic exercise each week. Accordingly, current aerobic exercise recommendations may need to increase by a factor of at least 10 to realize its true potential for enhancing functional performance and reducing cardiometabolic risk among stroke survivors. Although likely an overestimation, the above data highlights the need for future studies to investigate the tolerable and acceptable dosages of aerobic exercise among stroke survivors.

The type of activity used to sustain the prescribed workloads can also influence the dose response effects of aerobic exercise interventions. As displayed in Table 1-2, treadmill and cycling ergometers were the primary types of activities implemented to increase cardiorespiratory fitness in stroke survivors. The type of ergometer used does not appear to be influenced by participants' phase of recovery or level of impairment as similar proportions of studies implemented treadmill versus cycling ergometer interventions in both the subacute and chronic phase of recovery. However, it is difficult to draw conclusions based on the small sample sizes used in these interventions and only four studies recruited participants within the first 30-days of their recovery (Letombe et al., 2010; M. Mackay-Lyons, McDonald, et al., 2013; Stoller et al., 2015; Tang, Sibley, et al., 2009). Two of the earlier subacute studies incorporated low levels of metabolic stress (i.e., 110 to 125 kcal/session) on the semi-recumbent cycle ergometer, which resulted in relatively small gains in cardiovascular fitness (Letombe et al., 2010; Tang, Sibley, et al., 2009). Recognizing the limits that poor cardiorespiratory fitness imposes on walking ability and the focus on task-oriented relearning of walking during the subacute phase of recovery, M. Mackay-Lyons, McDonald, et al. (2013) designed and implemented an exercise intervention that progressively increased both the metabolic demands and walking speed imposed during body weight supported treadmill training. Although novel in design, the intervention imposed similar levels of metabolic stress as the previous studies. Participants in the intervention group achieved relatively large changes in $\dot{V}O_{2peak}$

compared to the previous work in subacute stroke (Letombe et al., 2010; Tang, Sibley, et al., 2009), which were maintained up to one year after the intervention period and statistically different from changes observed in the usual care group (M. Mackay-Lyons, McDonald, et al., 2013). Although clinically meaningful changes in over ground walking speed were also observed, they do not explain the enhanced effect of body weight supported treadmill training on $\dot{V}O_{2peak}$ as similar changes in walking speed were observed between groups. The same trend is observed among chronic stroke survivors, with treadmill aerobic exercise displaying enhance effects (Ivey et al., 2015) compared to similar dosages of aerobic exercise performed on the cycling ergometer (Tang et al., 2014). It is unclear why enhanced effects are observed after treadmill aerobic exercise training compared to similar levels of metabolic stress imposed on the recumbent cycle ergometer. Maybe it is the increased amount of muscle mass used on the treadmill, or increased daily ambulatory activities due to the task-oriented nature of treadmill exercise, or increased ability / willingness to maintain the target workload on the treadmill, or a combination of these and other effects?

In conclusion, stroke survivors retain the ability to achieve relatively large improvements in cardiorespiratory fitness during both the subacute and chronic phases of recovery. However, the doses of aerobic exercise implemented to date are insufficient to restore cardiorespiratory fitness to levels observed in age and sex matched healthy controls.

Future studies should focus on methods to enhance the effects of task-oriented activity on cardiorespiratory fitness throughout the continuum of stroke recovery.

1.3 What Opportunities Currently Exist for Incorporating Aerobic Exercise Training During Stroke Recovery?

Before we begin to design interventions that can overcome the consequences of previous inactivity on cardiorespiratory fitness among stroke survivors, we must first understand the target populations' previous exposure to aerobic exercise training. It is important to stress here that given the strong association between poor cardiorespiratory fitness and future cardiovascular/cerebrovascular events (Pandey et al., 2016), high rates of sedentary behavior likely predate incident stroke. Accordingly, formalized stroke rehabilitation services likely include most survivors' experience with structured aerobic exercise training. As a subproject during my doctoral studies, we evaluated the metabolic demands imposed during formalized stroke rehabilitation services offered at our tertiary rehabilitation hospital. Measurements were taken 24 hours a day over 7-days during patients' first and last week of inpatient services. Having two monitoring periods allowed us to evaluate changes in the total workload performed within the inpatient environment over the course of the patient's recovery. A 1-lead electrocardiography device with built-in accelerometer (Actiheart, CamNtech Inc., England, UK) was placed on participants chest according to manufacturer instructions to continuously record heart rate and activity

counts (i.e., 15-sec epochs 24 hrs. per day), which were later converted to metabolic equivalents. In line with previous literature (van der Ploeg & Hillsdon, 2017), activities below 1.5 metabolic equivalents were described as sedentary and 3 metabolic equivalents was used as the minimum threshold for moderate intensity physical activity. In total, 28 patients were approached to participate in the study; 19 completed the first monitoring period and 8 participants completed both (Barrett et al., 2018). The main findings of this study were that participants engaged in very little activity beyond 1.5 metabolic equivalents and most of their awake time was characterized as either lying in bed or seated rest (Barrett et al., 2018). In fact, only one participant sustained activity levels beyond 3 metabolic equivalents for 20 min or more per day during the first and/or last week of their inpatient stay. It is important to note that among patients who participated in both monitoring periods, no obvious change in metabolic demand was observed either during supervised task-oriented therapies themselves or with respect to total daily metabolic demands (Barrett et al., 2018). The observed data contrast with a recent report, which suggests that most stroke rehabilitation programs across Canada follow best practice recommendations for incorporating aerobic exercise training during their inpatient/outpatient services (Nathoo et al., 2018). However, our data is consistent with previous reports conducted in Canada (M. J. MacKay-Lyons & Makrides, 2002) and across the globe (Bernhardt, Dewey, Thrift, & Donnan, 2004). Furthermore, the level of cardiorespiratory fitness recorded among stroke survivors who have previously completed formalized stroke rehabilitation and are

discharged into the community remains very low (M. J. Mackay-Lyons & Makrides, 2004; Tang, Sibley, et al., 2009).

Given the high amounts of sedentary behavior recorded in our observational study, parallels can be drawn between the immobility imposed during the Dallas Bed Rest Study and the amount of metabolic stress achieved during inpatient stroke rehabilitation. Accordingly, aerobic exercise training must first overcome the detrimental effects of such environments on the underlying structures and function of the cardiovascular system (Saltin et al., 1968) before measurable improvements in cardiorespiratory fitness can be observed. It is important to recall the amount of structured aerobic exercise that young healthy participants had to complete in order to restore cardiorespiratory fitness to levels recorded prior to the 21 days of bed rest, which included 200 to 400 minutes per week of interval training and continuous aerobic exercise at intensities ranging from 60 to 100 % of $\dot{V}O_{2max}$ over a 7 to 8-week period (Saltin et al., 1968). A conservative estimate of the weekly EEE is in the range of 3200 to 6400 kcal/week, which is getting close to the predicted workloads described above to achieve normal levels of cardiorespiratory fitness in stroke survivors. However, it is currently unknown if stroke survivors can sustain such workloads, especially during the subacute phase of recovery. Although the feasibility of incorporating aerobic exercise training during inpatient rehabilitation has been established (Biasin et al., 2014), the dosages of aerobic exercise studied thus far remain relatively low (M. Mackay-Lyons, McDonald, et al., 2013; Tang, Sibley, et al., 2009). The tolerability of

increasing dosages of aerobic exercise among stroke survivors has not been empirically evaluated and is currently under investigation (S. F. Kramer, Cumming, Johnson, Churilov, & Bernhardt, 2020). In either case, when you compare the observed metabolic demand of the inpatient environment with the amounts of aerobic exercise needed to increase cardiorespiratory fitness to normal levels, a fundamental shift in the service delivery model will be required.

Recognizing the limited access to progressive aerobic exercise programs and other secondary/tertiary prevention strategies during formalized stroke rehabilitation services, a transition of care has been proposed where stroke survivors are referred to cardiac rehabilitation upon completion of traditional stroke rehabilitation (Marzolini, 2018). The core components of comprehensive cardiac rehabilitation programs include a) patient assessment, b) nutrition counseling, c) weight management, d) blood pressure management, e) lipid management, f) diabetes management, g) tobacco cessation, h) psychosocial management, i) physical activity counseling, and j) exercise training (Balady et al., 2007). With respect to exercise training, the scientific statement from the American Heart Association includes both aerobic and resistance activities 3-5 and 2-3 days per week, respectively (Balady et al., 2007). Compared to stroke best practices (Wein et al., 2018), slightly higher aerobic exercise intensities (i.e., 50 to 80% of heart rate reserve) and volumes (3 to 5 days per week for 20 to 60 min per session) are recommended during cardiac rehabilitation (Balady et al., 2007). The feasibility and preliminary effectiveness of

such comprehensive secondary prevention programs has been described among individuals who have experienced a transient ischemic attack or nondisabling minor stroke (Prior et al., 2011). In fact, changes in cardiorespiratory fitness (+ 31.4%), body mass index (-0.53 kg/m^2) blood pressure (systolic: -3.2 mmHg; diastolic -2.34 mmHg), and cholesterol (total/high density lipoprotein: -11.6%) are like those observed in coronary heart disease patients (Mitchell et al., 2019). The challenge, however, is adapting such programs for individuals with stroke related impairments (Tang, Closson, et al., 2009). Lennon, Carey, Gaffney, Stephenson, and Blake (2008) randomized 48 chronic stroke survivors to receive a cardiac rehabilitation program (i.e., 20 x 30-min sessions of cycle ergometry at 50-60% of HRR over 10-weeks, and 2 life skills sessions focused on stress management) or usual care. The relatively low dose of aerobic exercise implemented in the study (60 minutes per week at 50 to 60% of heart rate reserve over 10 weeks) lead to statistically significant between group changes in cardiorespiratory fitness (+ 13%) and within group changes in Framingham cardiac risk score (- 1.5 points), which lead the authors to conclude that adapted cardiac rehabilitation is a feasible and effective method to decrease cardiovascular risk among chronic stroke survivors. The reported decrease in cardiovascular risk is likely overstated given that the post intervention $\dot{V}O_{2peak}$ remained very low (12.0 ml min^{-1} kg^{-1}) in the cardiac rehab group and no change in cardiometabolic profile was observed. Also, it is unclear how the cardiac rehabilitation program was adapted for stroke survivors; especially given that most participants were independently ambulatory. Using repeated

measures pre-post study designs, two Canadian studies also evaluated the feasibility and effectiveness of integrating stroke survivors into an adapted cardiac rehabilitation program, which involved lower staff to participant ratios and smaller class sizes compared to usual (Marzolini, Tang, McIlroy, Oh, & Brooks, 2014; Tang, Marzolini, Oh, McIlroy, & Brooks, 2010). The programs were 6-months in length and involved once-weekly 90 min sessions of education and supervised exercise along with four prescribed workouts to be completed at home each week. Individually prescribed aerobic exercise was intended to be progressed up to 30-60 minutes per session at intensities between 60 to 80% of heart rate reserve. Based on self-reported information collected in activity logs, participants engaged in 76 min (SD 52) of aerobic exercise each week at an intensity of 48.9% of heart rate reserve (SD 23.2). The actual amount of aerobic exercise performed was substantially lower than the target training load and was like workloads previously described (Lennon et al., 2008). Accordingly, small pre to post changes in cardiorespiratory fitness were observed (Marzolini et al., 2014; Tang et al., 2010) with little to no effect on cardiometabolic profile (Tang et al., 2010). It is important to point out here that although participants were recruited for these studies based on having incomplete recovery from stroke, almost all were independently ambulatory over flat surfaces with or without a gait aid. Therefore, it is unclear why stroke survivors with mild to moderate levels of impairment have such poor response to cardiac rehabilitation compared to individuals recovering from transient ischemic attack or nondisabling stroke (Prior et al., 2011). In either case, we need novel

interventions to increase the aerobic stress imposed during task-oriented activities. Two potential methods are introduced below and evaluated in the subsequent chapters.

1.4 A Pragmatic Method to Increase the Cardiometabolic Stress Imposed During Task-oriented Activities After Stroke: Circuit Training

Best practice recommendations include 15 hours per week of direct task-oriented therapy throughout the subacute phase of stroke recovery (Hebert et al., 2016). In addition to practicing goal directed functional movements, stroke survivors are encouraged to accumulate 150 minutes of structured aerobic exercise training each week (Wein et al., 2018). However, as described above, much higher dosages of aerobic exercise are likely required to optimize its effect on secondary / tertiary prevention and functional performance in stroke survivors. Given the large amounts of task-oriented therapy recommended during stroke recovery, could some of the activities typically offered during formalized therapy be structured in such a way to maintain at least moderate levels of aerobic stress? If so, this would offer a pragmatic solution to increasing the cardiometabolic stress imposed during impatient rehabilitation and will increase access to aerobic exercise once stroke survivors are discharged from formalized rehabilitation. The obvious starting point is with ambulatory rehabilitation activities. However, many stroke survivors are left with impairments that limit their ability to walk even short distances and assistive devices such as body-weight support (M. Mackay-Lyons, McDonald, et al., 2013) or robotic

exoskeletons (Stoller et al., 2015) are often required to sustain moderate intensity aerobic workloads. Access to such specialized equipment has repeatedly been reported as a barrier to incorporating aerobic exercise among stroke survivors (Biasin et al., 2014; Brown et al., 2014; Moncion et al., 2020). Accordingly, aerobic exercise interventions that are not dependent upon the use of specialized equipment are needed. Several group-based exercise classes that incorporate functional activities specific to stroke related impairments have been developed (Marsden et al., 2016; Pang et al., 2005; Richardson et al., 2018; Salbach et al., 2004; van de Port et al., 2009). Such classes are typically offered at the community level and organize functional activities into workstations that include warm-up activities followed by exercises directed toward increasing muscle strength, endurance, and balance, and finishing with cooldown activities. Although such group-based exercise classes have been reported to increase cardiorespiratory fitness and reduce metabolic risk markers (Moore et al., 2015; Pang et al., 2005), the reproducibility of their findings must be questioned given that the work to rest ratios are not well defined and workloads are generally not prescribed in terms of percentage of max effort (i.e., % heart rate reserve, or max heart rate). A relatively large (N=250) multicenter randomized control trial evaluated the effects of incorporating functional activities into circuits employing a 1:1 work to rest ratio (3 minutes functional activities followed by 3 minutes of recovery) over a 60-minute session 2 days per week over 12 weeks compared to usual physiotherapy on walking ability (van de Port, Wevers, Lindeman, & Kwakkel, 2012). The authors reported that circuit

training was associated with significantly higher scores in walking speed and distance covered during the six-minute walk test (van de Port et al., 2012). The observed improvements in six-minute walk distance may indicate an improvement in cardiorespiratory fitness, however, more work is needed to better understand the amount of aerobic stress imposed during such interventions and the extent to which they can improve metabolic risk markers in stroke survivors throughout the continuum of care. The development of a circuit training protocol and evaluation of the aerobic workloads sustained are the focus of Chapter 2. In Chapter 3, the effects of the circuit training protocol on cardiorespiratory fitness and metabolic profile are evaluated among chronic stroke survivors with multiple cardiovascular and metabolic comorbidities.

1.5 Normobaric Hypoxia Conditioning as a Potential Method to Increase the Aerobic Strain Imposed During Task-oriented Activities After Stroke

Rather than increasing the amount of work performed in a given time period, the aerobic stress imposed during task-oriented exercise could also be increased by performing such activities under environmental conditions of either reduced partial pressure of inspired oxygen (i.e. hypobaric hypoxia) or reduced fraction of inspired oxygen (i.e., normobaric hypoxia). Given that atmospheric pressure decreases with increasing distance above sea level (Mazzeo, 2008), hypobaric hypoxia is a natural phenomenon experienced by individuals who ascend to higher altitudes for recreational activities such as skiing and

trekking. Accordingly, the severity of environmental hypoxia exposure can be described in terms of distance above sea level; “low altitude” refers to elevations below 2000 meters, “moderate altitude” describes elevations between 2000 and 3000 meters, “high altitude” is between 3000 to 5500 meters, and “extreme altitude” for elevation beyond 5500 meters (Bartsch & Saltin, 2008). For perspective, the partial pressure of oxygen at sea level is approximately 160 mmHg, which decreases to 125, 110, and 79 kPa at elevations of 2000, 3000, and 5500 meters, respectively (Peacock, 1998). In terms of duration of hypoxia exposure, the following terminology and definitions have been proposed: a) “native”, which describes populations that have lived at altitude for generations, b) “permanent”, which describes individuals who have been exposed to hypoxic conditions from birth to death, c) “long-term”, which describes continuous exposure that last from weeks to months; d) “short-term”, which describes continuous exposure lasting from minutes to hours, and e) “intermittent hypoxia” exposure that includes short periods of hypoxia (i.e. minutes) interspaced with similarly short periods of normoxia (Hoppeler, Vogt, Weibel, & Fluck, 2003). Together, the severity and duration of hypoxia exposure determine its dose (Navarrete-Opazo & Mitchell, 2014). It is obviously not practical to bring stroke survivors who live near sea level to higher altitudes for therapeutic purposes. Accordingly, hypobaric chambers and hypoxicators can be used at sea level to simulate altitude exposure (Serebrovskaya, Manukhina, Smith, Downey, & Mallet, 2008). In specialized rooms called hypobaric chambers, barometric pressure is reduced to simulate the partial pressure of

inspired oxygen experienced at the target distance above sea level. In contrast, hypoxicators produce hypoxic gas mixtures either by infusing supply air with nitrogen or using a deoxygenating technique such as filtering to simulate the level of environmental hypoxia experienced at the target altitude (Serebrovskaya et al., 2008). Translating the severity of environmental hypoxia exposure to fraction of inspired oxygen, the descriptions of "moderate", "high", and "extreme" altitude correspond to fractions of inspired oxygen of 16 to 14%, 13 to 11%, and <10%, respectively (Bartsch & Saltin, 2008). In terms of using environmental hypoxia exposure for therapeutic (Navarrete-Opazo & Mitchell, 2014) or ergogenic purposes (B. D. Levine, 2002), moderate to high levels of simulated or natural altitude exposure are typically used.

Performing exercise under conditions of hypobaric or normobaric hypoxia poses an additional metabolic stress that must be overcome to sustain activities (Hoppeler, Klossner, & Vogt, 2008; L.P. Kelly & Basset, 2017). Accordingly, breathing frequency, minute ventilation, and heart rate are elevated at altitude compared to performing similar workloads at sea level (L.P. Kelly & Basset, 2017). A shift in substrate partitioning toward carbohydrate energy sources (i.e., glycogen, glucose, lactate) and an increased reliance on intramuscular energy stores are also observed (F Peronnet et al., 2006). Elevations in minute ventilation and heart rate act to maintain arterial oxygen supply (Bartsch & Gibbs, 2007; Bartsch & Saltin, 2008; Mazzeo, 2008), while changes in substrate partitioning aid in oxidative energy production as less oxygen is required per mole of carbohydrate

compared to lipids (Brooks et al., 1991; Mazzeo, 2008). These mechanisms are limited, however, and maximal rates of oxygen uptake decrease by approximately 7% for every 1000-meter increase in elevation (Fulco, Rock, & Cymerman, 1998). Accordingly, a 14 to 21% increase in relative exercise intensity is observed when a given workload is performed at moderate altitude compared to sea level. The increased relative effort is a hindrance to athletic performance at altitude (B. D. Levine, 2002). However, it may provide an opportunity to enhance cardiorespiratory and metabolic outcomes among populations such as stroke survivors who have impairments that limit their ability to perform external work (L.P. Kelly & Basset, 2017).

Exercise interventions performed under conditions of short-term moderate normobaric hypoxia, are associated with similar or even enhanced effects on cardiorespiratory fitness and metabolic outcomes among sedentary adults compared to higher absolute workloads performed under typical sea level conditions (Hobbins, Hunter, Gaoua, & Girard, 2017). As described above, maximal oxygen uptake decreases with increasing altitude (Fulco et al., 1998) and, therefore, lower absolute workloads are needed under normobaric hypoxia to match for relative exercise intensity. Accordingly, Haufe, Wiesner, Engeli, Luft, and Jordan (2008) randomized 20 healthy adults to complete 12 sessions of aerobic exercise (60 min each) over 4 weeks at the same relative exercise intensity under conditions of moderate normobaric hypoxia or normoxia. Although the prescribed workloads were 20% higher under typical atmospheric conditions, participants

randomized to the normobaric hypoxia intervention achieved similar changes in exercise tolerance and experienced enhanced effects on maximal oxygen uptake, body fat mass, blood triglyceride levels, and insulin sensitivity (Haufe et al., 2008). This led the authors to suggest that exercise training in hypoxia elicits a similar cardiovascular stimulus to exercise under normoxic conditions but at lower absolute workloads (Haufe et al., 2008). Many of these findings were reproduced in overweight / obese adults (Netzer, Chytra, & Kupper, 2008; Wiesner et al., 2010), individuals with metabolic syndrome (Klug et al., 2018), and among patients with multiple sclerosis (Mahler et al., 2018). Such normobaric hypoxia conditioning protocols that minimize the external work performed while maintaining moderate to high levels of cardiometabolic stress may provide a therapeutic benefit for individuals who are at increased risk of injury during weight bearing activities such as those with morbid obesity and the frail elderly (Pramsohler et al., 2017). However, for populations such as stroke survivors, the question is not how do we reduce the amount of work performed, but rather, how do we maximize the effects of task-oriented activities given participants limited ability to perform external work? Although more is needed to determine the safety and feasibility of maintaining absolute workloads under conditions of environmental hypoxia among clinical populations with preexisting cardiovascular conditions (Parati et al., 2018), normobaric hypoxia conditioning is a potential method to increase the aerobic stress imposed during task-oriented activities in stroke survivors. In addition to its proposed secondary / tertiary prevention benefits, normobaric hypoxia

exposure may even enhance recovery from stroke related impairments. Using a randomized cross-over study design, Hayes et al. (2014) studied the effects of daily intermittent hypoxia exposure (15 x 90 sec cycles of normobaric hypoxia [9% oxygen] and normoxia) followed by over ground walking or seated rest on 5 consecutive days on walking performance among individuals with incomplete spinal cord injury. Intermittent hypoxia exposure alone was associated with statistically significant improvements in walking speed compared to the sham exposure (i.e., normoxia) (Hayes et al., 2014). Furthermore, over ground walking was associated with enhanced effects on walking endurance when preceded by intermittent hypoxia exposure compared to sham exposure (Hayes et al., 2014). The enhanced effects of preceding walking practice with intermittent hypoxia exposure on walking speed and endurance were later reproduced on a body weight supported treadmill among patients with incomplete spinal cord injury (Navarrete-Opazo, Alcayaga, Sepulveda, Rojas, & Astudillo, 2017). Although the methods employed in these studies are not consistent with normobaric hypoxia conditioning (i.e., exercise was not performed under normobaric hypoxia), they stimulate further interest in studying the effects of pairing normobaric hypoxia exposure with task-oriented activities during stroke recovery. More work is needed to evaluate the safety and feasibility of normobaric hypoxia exposure and to develop protocols that are appropriate for use in stroke survivors. Chapter 4 of this thesis is dedicated to beginning to address some of these questions.

1.6 The Following Questions are Addressed in the Chapters that Follow:

- Chapter 2:
    a. Can functional task practice, which includes activities typically employed during stroke recovery and does not require the use of specialized equipment, be organized in such a way to achieve workloads associated with at least moderate aerobic exercise intensity?
- Chapter 3:
    a. Among chronic stroke survivors with persistent hemiparesis and multiple risk factors for coronary artery disease, does such intermittent functional training methods lead to similar levels of metabolic stress as progressive aerobic exercise training performed on a body weight supported treadmill when implemented 3-days per week over a 10-week period?
    b. Are similar patterns for change in cardiorespiratory fitness, metabolic risk factors, and resting whole body energy metabolism observed for individual randomized to intermittent functional training as those randomized to treadmill aerobic exercise training?
- Chapter 4:

a. Among chronic stroke survivors with persistent hemiparesis and multiple risk factors for coronary artery disease, is normobaric hypoxia exposure a safe and feasible method to increase the metabolic stress of submaximal constant-load aerobic exercise performed on a body weight supported treadmill?

1.7 Co-authorship Statement

Chapters two, three, and four describe three separate research studies that are currently under peer review or have been published. Along with my supervisors Dr. Michelle Ploughman and Dr. Fabien Basset, I set the research objectives of the three studies and designed the experiments. I was responsible for delivering the exercise interventions and data collection with assistance from the lab manager and other trainees. I reduced the data, performed the statistical analysis, prepared the figures and tables, and wrote the manuscript. My supervisors provided feedback and edited the manuscript prior to submission. The authors list and contributions for each study are provided below as they were submitted for publication.

The first study titled "Intensifying functional task practice to meet the aerobic training guidelines in stroke survivors" was published October 2017 in Frontiers in Physiology - Clinical and Translational Physiology. Authors: Liam P. Kelly, Augustine J. Devasahayam, Arthur R. Chaves, Elizabeth M. Wallack, Jason McCarthy, Fabien Andre Basset and Michelle Ploughman. Contributions: *"LK conceived of and designed experiment, collected data, analyzed data, interpreted findings, and wrote the manuscript. AD screened subjects, collected the data and edited manuscript. AC conceived of experiment and edited manuscript. EW recruited participants and edited manuscript. JM designed the experiment and screened subjects. FB interpreted*

findings and edited manuscript. MP conceived of and designed the experiment, screened subjects, and edited manuscript."

The second study titled "Task-oriented circuit training as an alternative to ergometer type aerobic exercise training after stroke" was published June 2021 in Journal of Clinical Medicine. Authors: Liam P. Kelly, Augustine J. Devasahayam, Arthur R. Chaves, Marie E. Curtis, Edward W. Randell, Jason McCarthy, Fabien A. Basset and Michelle Ploughman. Contributions: "*Study design and conceptualization, L.P.K. and M.P.; data collection, L.P.K., A.J.D., A.R.C. and J.M.; blood collection and analysis, L.P.K., M.E.C., and E.W.R.; data analysis and interpretation L.P.K. and F.A.B.; L.P.K.; original draft preparation, L.P.K.; review and editing, L.P.K., M.P., F.A.B., and E.W.R.; supervision: M.P., F.A.B., and J.M. All authors have read and agreed to the published version of the manuscript."*

The final study titled "Normobaric hypoxia exposure during treadmill aerobic exercise after stroke: a safety and feasibility study" was published August 2021 in Frontiers in Physiology-Clinical and Translational Physiology. Authors: Liam P. Kelly, Fabien A. Basset, Jason McCarthy, and Michelle Ploughman. Contributions*: "LPK, FAB, JM, and MP contributed to the conception and design of the study. LPK and JM collected the data. LPK performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version."*

Chapter 2: Intensifying Functional Task Practice to Meet Aerobic Training Guidelines in Stroke Survivors

2.1 Abstract

Objective: To determine whether stroke survivors could maintain workloads during functional task practice that can reach moderate levels of cardiometabolic stress (i.e., ≥40% oxygen uptake reserve ($\dot{V}O_2R$) for ≥ 20 min) without the use of ergometer-based exercise.

Design: cross-sectional study using convenience sampling.

Setting: research laboratory in a tertiary rehabilitation hospital.

Participants: chronic hemiparetic stroke survivors (>6-months) who could provide consent and walk with or without assistance.

Intervention: a single bout of intermittent functional training (IFT). The IFT protocol lasted 30 min and involved performing impairment specific multi-joint task-oriented movements structured into circuits lasting approximately 3 min and allowing 30-45 sec recovery between circuits. The aim was to achieve an average heart rate (HR) 30-50 beats above resting without using traditional ergometer-based aerobic exercise.

Outcome measures: attainment of indicators for moderate intensity aerobic exercise. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and HR were recorded throughout the 30 min IFT protocol. Values were reported as percentage of $\dot{V}O_2R$, HR reserve (HRR) and HRR calculated from age predicted maximum HR (HRRpred), which were determined from a prior maximal graded exercise test.

Results: Ten (3-female) chronic (38 ± 33 months) stroke survivors (70% ischemic) with significant residual impairments (NIHSS: 3 ± 2) and a high prevalence of comorbid

conditions (80% ≥ 1) participated. IFT significantly increased all measures of exercise intensity compared to resting levels: $\dot{V}O_2$ (Δ 820 ± 290 L min^{-1}, $p < 0.001$), HR (Δ 42 ± 14 bpm, $p < 0.001$), and energy expenditure (EE; Δ 4.0 ± 1.4 kcal min^{-1}, $p < 0.001$). Also, mean values for percentage of $\dot{V}O_2R$ (62 ± 19), HRR (55 ± 14), and HRRpred (52 ± 18) were significantly higher than the minimum threshold (40%) indicating achievement of moderate intensity aerobic exercise ($p = 0.004$, 0.016, and 0.043, respectively).

Conclusion: Sufficient workloads to achieve moderate levels of cardiometabolic stress can be maintained in chronic stroke survivors using impairment-focused functional movements that are not dependent on ergometers or other specialized equipment.

2.2 Introduction

Stroke mortality rate continues to decrease thanks to advances in medical management (Thrift et al., 2017) and emergency medical care (Crichton, Bray, McKevitt, Rudd, & Wolfe, 2016). However, the amount of recovery observed after disabling stroke remains largely unchanged and the number of individuals living with life-altering physical and cognitive impairments due to stroke is increasing (Krueger et al., 2015). A major challenge to regaining function after disabling stroke is the limited time window for optimal recovery, which is thought to occur within the first 3 months (Cramer, 2008; Murphy & Corbett, 2009). This sensitive period for enhanced plasticity and subsequent plateau of recovery follows well-defined neurobiological processes that involve upregulation of growth-promoting factors followed by their downregulation with concurrent increases in growth-inhibiting factors (Murphy & Corbett, 2009). Substantial resources are currently being employed to develop interventions that extends this time window and possibly even enhance repair mechanisms through use of stem cells, brain stimulation, and other pharmaceutical therapies (Ward, 2017). However, it is unclear whether the plateau of recovery observed post-stroke is due to a failure of the mechanisms underlying spontaneous biological recovery or if it is related to suboptimal dosage of physical and behavioral therapies (Ward, 2017). Animal models of stroke reinforce the critical importance of intense therapeutic exercise combined with an enriched environment

to optimize the efficacy of pharmaceutical, and stem cell interventions (Hicks et al., 2009; Johansson, 2000; Ploughman et al., 2009; Sale, Berardi, & Maffei, 2014). Therefore, stroke rehabilitation must be optimized to not only take advantage of intrinsic mechanisms for recovery but also to enhance the effects of emerging therapies.

Unfortunately, current inpatient stroke rehabilitation is of insufficient intensity to promote optimal recovery. Studies from across the globe consistently report that stroke patients spend most of their time "inactive and alone" (Bernhardt et al., 2004) throughout the acute and subacute phases of recovery (Astrand et al., 2016). Also, the total amount of work performed during structured therapy is below levels required to maintain functional fitness (Macko et al., 2005) and reduce cardiovascular risk (M. J. MacKay-Lyons & Makrides, 2002). Accordingly, patients in both the acute and chronic phases of recovery demonstrate levels of cardiorespiratory fitness that are about half (~16 ml min^{-1} kg^{-1}) of those observed in age and gender matched populations (Ivey et al., 2015; M. Mackay-Lyons, McDonald, et al., 2013; Potempa et al., 1995; Smith et al., 2012). In addition to increasing risk for recurrent stroke (M. Mackay-Lyons, Thornton, Ruggles, & Che, 2013), such levels of physical deconditioning limit patients' ability to participate in structured therapy (Billinger et al., 2015; Tang, Sibley, et al., 2009) and may even contribute to a ceiling for neuromotor recovery (Ploughman & Kelly, 2016). Given the inverse association between cardiorespiratory fitness and stroke risk (Pandey et al., 2016), premorbid physical activity levels also contribute to the poor aerobic capacity observed after rehabilitation.

Regardless, the low intensity nature of the inpatient environment must be addressed to optimize recovery.

Several studies have proposed adding ergometer-based aerobic training to inpatient rehabilitation (M. Mackay-Lyons, McDonald, et al., 2013; Tang, Sibley, et al., 2009; Wang, Wang, Fan, Lu, & Wang, 2014), while others have suggesteed that practice of gross motor skills could produce a training effect if there was adequate attention to heart rate monitoring (Marsden et al., 2017; Outermans, van Peppen, Wittink, Takken, & Kwakkel, 2010; van de Port et al., 2012). In either case, stroke best practice guidelines have advised therapists to provide aerobic training in addition to a minimum of 3 hours per day of skilled task training (Billinger et al., 2014; Hebert et al., 2016). In practice, however, there are many challenges to implementing such recommendations including insufficient time, lack of resources, patient level of impairment, and concern for ongoing cardiovascular risk (Bayley et al., 2012; Biasin et al., 2014; Prout, Mansfield, McIlroy, & Brooks, 2016). Rehabilitative strategies that are individualized to level of impairment, addressing multiple targets (i.e. relearning of functional tasks and cardiorespiratory fitness), and which do not rely on specialized equipment are urgently needed. The purpose of the current study was to determine whether functional task practice could be structured in such a way to maintain sufficient workloads to reach moderate levels of cardiometabolic stress (i.e. $\geq$ 40% oxygen uptake reserve ($\dot{V}O_2R$) for $\geq$ 20 min) without the use of ergometers. As a first step, an impairment-based intermittent functional training (IFT) protocol was developed to answer

this question among chronic stroke survivors. It was hypothesized that (1) workloads maintained during IFT would cause significant elevations in cardiometabolic responses compared to resting values, and (2) the increased cardiometabolic demands of IFT would be within a range needed to increase cardiorespiratory fitness (i.e. moderate-to-vigorous intensity).

2.3 Methods

2.3.1 Participants

Chronic stroke survivors (>6 months post-stroke) were recruited from a discharge registry of a tertiary inpatient rehabilitation center as part of an ongoing clinical trial. The local Health Research Ethics Authority approved the study (see Appendix A) and participants provided written informed consent. Inclusion criteria were: (1) diagnosis of disabling stroke requiring physical rehabilitation, (2) able to provide consent, and (3) able to walk at least with assistance.

2.3.2 Experimental Design

Participants visited the laboratory on two separate occasions, with at least 72-hours between sessions to avoid any carryover effect. During the first visit, anthropometrics and stroke characteristics (type of stroke, co-morbid conditions, severity of stroke [National Institutes of Health Stroke Scale] (Goldstein, Bertels, & Davis, 1989), and level of

impairment [Chedoke-McMaster Impairment Inventory for Leg and Foot] (Gowland et al., 1993) were recorded prior to performing a maximal graded exercise test (GXT). The GXT was performed to determine maximal oxygen uptake ($\dot{V}O_{2max}$) and maximum heart rate (HRmax) as described below. The second session lasted approximately 50 min and included a 10 min seated rest period, followed by 30 min of IFT (described below), finishing with a 10 min seated recovery period. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), breathing frequency, and tidal volume, were recorded breath-by-breath throughout the experimental sessions using a portable metabolic cart (VmaxST, Sensor Medics, FL, USA). Heart rate was collected in line with respirometry data using a chest strap sensor (H10, Polar Electro Inc., NY, USA) wirelessly connected to the portable metabolic cart.

2.3.3 Graded Exercise Testing

Prior to performing the GXT, participants were assessed for cardiovascular risk by the study physician using a standardized medical history form. A physician was available during all GXTs. Participants performed the GXT on either a body weight supported treadmill or total body recumbent stepper.

The total body recumbent stepper GXT protocol was adapted from previous work in this population (Billinger, Tseng, & Kluding, 2008). Briefly, after familiarizing participants with the TBRS and adjusting the ergometer for arm and leg length, participants

maintained 80 steps per minute (SPM) while the load level was gradually increased to level 3. This workload (~ 20 W) was maintained for the first 2 min, which was then increased by one load level every 2 minutes at 80 SPM (~20 W increments) until exhaustion or completion of load level 10. If exhaustion was not reached after load level 10, SPM was increased in increments of 10 SPM every 2 min until exhaustion.

The body weight supported treadmill GXT protocol was based on the AEROBICS guidelines, (MacKay-Lyons M, 2012) which involved: 2 min stages beginning with walking at self-selected speed and 0% treadmill grade for 2 min, followed by a 2.5% increase in grade every 2 min until an incline of 10% was reached and, thereafter, a .05 m s^{-1} increase in speed every 2 min, until test termination. A <10 % bodyweight support was used during the GXT to prevent falls.

Both exercise tests were terminated using predefined criteria: (1) volitional exhaustion, (2) no increase in $\dot{V}O_2$ or HR despite increases in workload, (3) inability to maintain workload and (4) signs of excessive fatigue. Achievement of $\dot{V}O_{2max}$ was assessed based on attainment of at least two of the following criteria: (1) a plateau in $\dot{V}O_2$ (<80 mL min^{-1}) despite increasing workload; (2) respiratory exchange ratio (RER; $\dot{V}CO_2/\dot{V}O_2$) above 1.10; and (3) HRmax ±10 beats min^{-1} of predicted maximum HR ($HRmax_{pred}$) calculated as 206.9 – (0.76 x age) or 164 – (0.7 x age) if prescribed beta blockers (Medicine, 2010).

2.3.4 Intermittent Functional Training (IFT*)*

The IFT protocol involved performing multi-joint task-oriented movements (i.e. sit-to-stand, lying-to-sitting, kneeling-to-stand, etc.) structured into circuits lasting approximately 3 min and allowing 30-45 sec recovery between circuits. Selection of functional tasks were determined based on participant's individual impairments as determined by two registered physiotherapists (MP, and AJD). There was 1:1 supervision during IFT and participants were encouraged to minimize rest time within each circuit. The aim was to achieve an average HR 30-50 beats above resting throughout the IFT protocol. As displayed in figure 1, more metabolically demanding tasks were paired with less demanding ones and consideration was given to minimize task setup and transfer time to maintain the target HR range

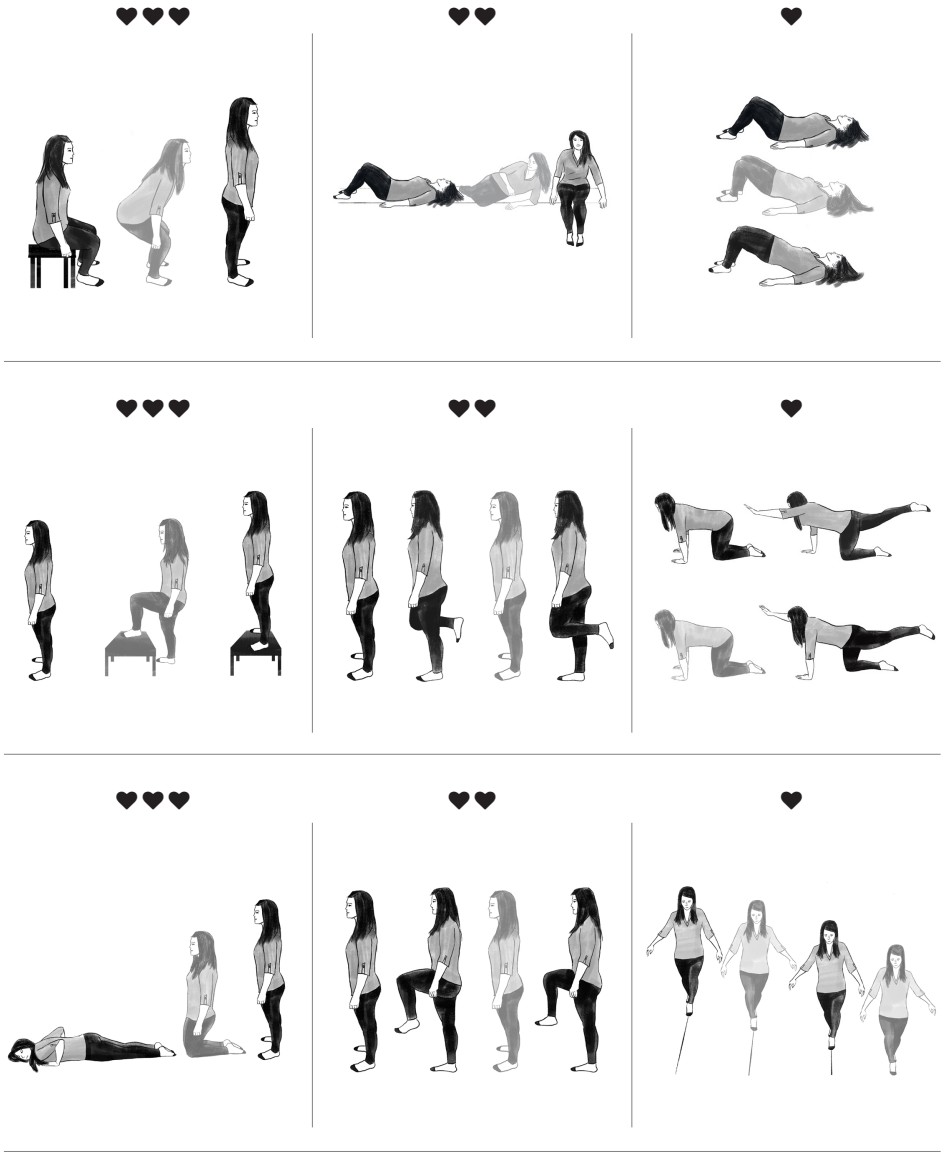


Figure 2-1: Illustration of a typical intermittent functional training session. Participants completed 3 circuits of 3 functional tasks. Each circuit was completed twice, with 30-45 sec recovery between sets, before moving onto the next circuit. Circuit 1: A) sit-to-stand (15-20 reps), B) lying-to-sit (7/side), and C) hip bridge (15-20 reps). Circuit 2: A) step-up-to-stand (10-15 reps), B) alternate 1-leg balance (5 sec hold 7/leg), C) alternate-arm and alternate-leg (5 sec hold 7/side). Circuit 3: A) lying-to-standing (15-20 reps), B) high-knees (15-20 reps), C) tandem walking (10 meters). Participants were instructed to move from one exercise to the next with minimal rest. ♥ = 15-30 bpm above resting, ♥♥= 30-45 bpm above resting, and ♥♥♥= 45-60 bpm above resting

2.3.5 Calculations

Attainment of the minimum intensity to be considered moderate intensity exercise (MacKay-Lyons M, 2012; Medicine, 2010) was determined after completion of the IFT protocol. The following equations were used to determine if the minimum threshold criteria were exceeded based on 40% of $\dot{V}O_2$ reserve ($\dot{V}O_2R$), HR reserve (HRR), and HRR calculated from age predicted maximal HR (HRR_{pred}):

Equation 2-1:

$$\dot{V}O_2R = \left[\left(\dot{V}O_{2max} - \dot{V}O_{2rest}\right) \times 40\%\right] + \dot{V}O_{2rest}))$$

Equation 2-2:

$$\text{HRR} = [(\text{HR}_{max} - \text{HR}_{rest}) \times 40\%] + \text{HR}_{rest}$$

Equation 2-3:

$$\text{HRR}_{pred} = \left[\left(\text{HR}_{pred} - \text{HR}_{rest}\right) \times 40\%\right] + \text{HR}_{rest}$$

Where $\dot{V}O_{2max}$ and HR_{max} were the highest values recorded for oxygen uptake and heart rate during the GXT, respectively. Resting heart rate (HR_{rest}) and oxygen uptake ($\dot{V}O_{2rest}$) were recorded immediately prior to IFT in the seated position. Age-predicted maximal heart rate (HR_{pred}) was calculated as describe above. Energy expenditure (EE) at rest and during IFT was calculated based on previously published data (Jeukendrup & Wallis, 2005).

2.3.6 Data Reduction and Statistical Analysis

Heart rate and respirometry data were recorded breath-by-breath and later smoothed using a 30-point box averaging technique. Maximal oxygen uptake was determined during the last 30 secs of the GXT and all parameters were reported for the same time point. A mean value representing the 10 min resting periods before and after IFT was reported for all parameters. During IFT both a mean value representing the entire 30 min data collection period and a mean value after removing seated rest time were recorded. Lastly, the cardiometabolic demands of the individual tasks during IFT were reported for the most frequently used tasks.

Due to non-random selection of participants and small sample size, non-parametric statistical tests were used (Graph-Pad Prism, Version 7). Friedman's statistical test was used to detect differences in the cardiometabolic demands at rest, during IFT, and recovery. When appropriate, *a priori* post hoc analysis were performed using the Dunn's multiple comparisons test. The Wilcoxon signed rank test was used to test for differences in relative exercise intensities based on $\dot{V}O_2R$, HRR, and HRR_{pred} compared to the minimum threshold criteria (Medicine, 2010). Data are reported as means and standard deviation. Statistical significant was set at $p < 0.05$.

2.4 Results

Seven of the ten participants recruited were male and seven experienced ischemic strokes. As displayed in Table 1, significant residual impairments were observed in participants between 12- and 131-months' post stroke on both the NIHSS and the Chedoke-McMaster Impairment Inventory (leg & foot). Most participants were overweight, based on the body mass index (BMI), and eight had at least one comorbid condition. Physiological responses to the GXT and minimum threshold criteria are reported in Table 2. All participants could complete the GXT and $\dot{V}O_{2max}$ was between 14- and 29-mL min^{-1} kg^{-1}, with a mean value of 20.6 ± 5.4 mL min^{-1} kg^{-1}. These values fall within the very poor category according to normative data published by the American College for Sports Medicine (Medicine, 2010). Maximal HR recorded during the GXT was 150 ± 26 bpm, which was within 2% of age-predicted values. Average RER recorded at $\dot{V}O_{2max}$ was 1.06 ± 0.06. The minimum threshold criteria based on 40% of: $\dot{V}O_2R$, HRR, and HRR_{pred} were 0.85 ± 0.28L min^{-1}, 103 ± 17 bpm, and 104 ± 14 bpm, respectively.

Table 2-1: Participant characteristics

Participant	Age (years)	Sex (M,F)	Weight (kg)	BMI (kg m^{-2})	Stroke type	Months since stroke	NIHSS (/42)	Combined Chedoke (/14)	Hypertension	Diabetes	Dyslipidemia
01	61	M	119	35.9	Ischemic	24	1	13	✓	✓	✓
02	43	M	64	20.4	Ischemic	27	7	4	✓	✗	✓
03	62	M	82	26.2	Ischemic	33	4	7	✗	✗	✗
04	69	M	85.3	27.2	Ischemic	26	1	13	✗	✓	✗
05	49	F	85	30.5	Hemorrhagic	12	5	9	✓	✗	✗
06	79	F	60.6	28.0	Ischemic	24	0	12	✗	✗	✗
07	76	M	78.5	25.1	Ischemic	131	3	11	✗	✓	✗
08	67	M	90.3	29.8	Ischemic	32	3	12	✗	✓	✓
09	59	F	65	23.0	Hemorrhagic	40	2	9	✓	✗	✗
10	81	M	81.9	27.4	Hemorrhagic	31	3	12	✓	✗	✓

NIHSS: National Institute of Health Stroke Scale

Table 2-2: Physiological responses recorded during graded exercise test and calculated minimum threshold criteria.

								Minimum threshold criteria		
Participant	Resting HR (min^{-1})	Resting $\dot{V}O_2$ (ml min^{-1})	$\dot{V}O_{2max}$ (ml min^{-1})	RER at max	$\dot{V}O_{2max}$ (ml min^{-1} kg^{-1})	HR_{max}(min^{-1})	HR_{pred}(min^{-1})	$\dot{V}O_2R$ (ml min^{-1})	HRR (min^{-1})	HRRpred (min^{-1})
01	91	393	2950	1.01	24.7	150	161	1415	115	119
02	80	279	1640	1.08	24.5	185	173	823	122	117
03	66	410	2570	1.11	29.4	172	160	1274	108	104
04	80	303	1760	1.07	20.2	168	154	886	115	110
05	94	320	1190	1.03	14.0	171	170	668	125	124
06	60	213	840	0.91	13.9	122	147	464	85	95
07	63	124	1670	1.11	21.5	148	149	742	97	97
08	62	306	1710	1.13	18.9	138	156	868	92	100
09	61	243	1670	1.11	25.1	137	162	814	91	101
10	54	462	1150	1.02	14.1	98	107	737	72	75

Throughout IFT, participants spent more than 80% of the time engaged in task-oriented exercise and less than 5 min was characterized as seated rest time (see Table 3). As displayed on Figure 2, IFT significantly increased all measures of workload compared to resting levels: $\dot{V}O_2$ (Δ 0.82 ± 0.29 L min^{-1}, $p<0.001$), HR (Δ 42 ± 14 bpm, $p<0.001$), EE (Δ 4.0 ± 1.4 kcal min^{-1}, $p<0.001$), and RER (Δ 0.06 ± 0.04, $p<0.001$). Although not significantly different from pre-exercise values, three of the four measures remained elevated during the 10 min seated post-exercise recovery period: $\dot{V}O_2$ (Δ 0.17±0.09 L min^{-1}, $p=0.051$), HR (Δ 22±8 bpm, $p=0.051$), and EE (Δ 0.8±0.4 kcal min^{-1}, $p=0.051$).

All participants could achieve at least one of the minimum threshold criteria during IFT (Table 3). In fact, mean values for percentage of $\dot{V}O_2R$ (62±19%), HRR (55±14%), and HRR_{pred} (52±18%) were significantly higher than the minimum threshold (40%) indicating moderate intensity exercise ($p=0.004$, 0.016, and 0.043, respectively; Figure 3). Also, the metabolic equivalents (MET) for individual task-oriented exercises when completed in a circuit with minimal rest periods were greater than 2.5 (see Figure 4). Practice of standing up from ½ kneel position and stepping-up to stand on 15-20-inch box were the most metabolically challenging tasks at 4-4.5 METs

Table 2-3: Participant responses to intermittent functional training excluding rest time.

Participant	Time (mm:ss)	HR (min^{-1})	$\dot{V}O_2$ ($ml\ min^{-1}$)	MET	Achievement of minimum threshold criteria		
					HR	HRpred	$\dot{V}O_2$
01	21:05	115	1664	4.23	Yes	No	Yes
02	23:43	125	954	4.28	Yes	Yes	Yes
03	23:03	109	1240	4.02	Yes	Yes	No
04	21:11	126	710	2.36	Yes	Yes	No
05	29:23	91	922	4.07	No	No	Yes
06	19:28	149	1309	4.32	Yes	Yes	Yes
07	25:13	118	1363	5.00	Yes	Yes	Yes
08	19:58	95	833	3.89	No	Yes	No
09	24:50	121	1212	3.84	Yes	Yes	Yes
10	19:50	81	1003	3.50	Yes	Yes	Yes

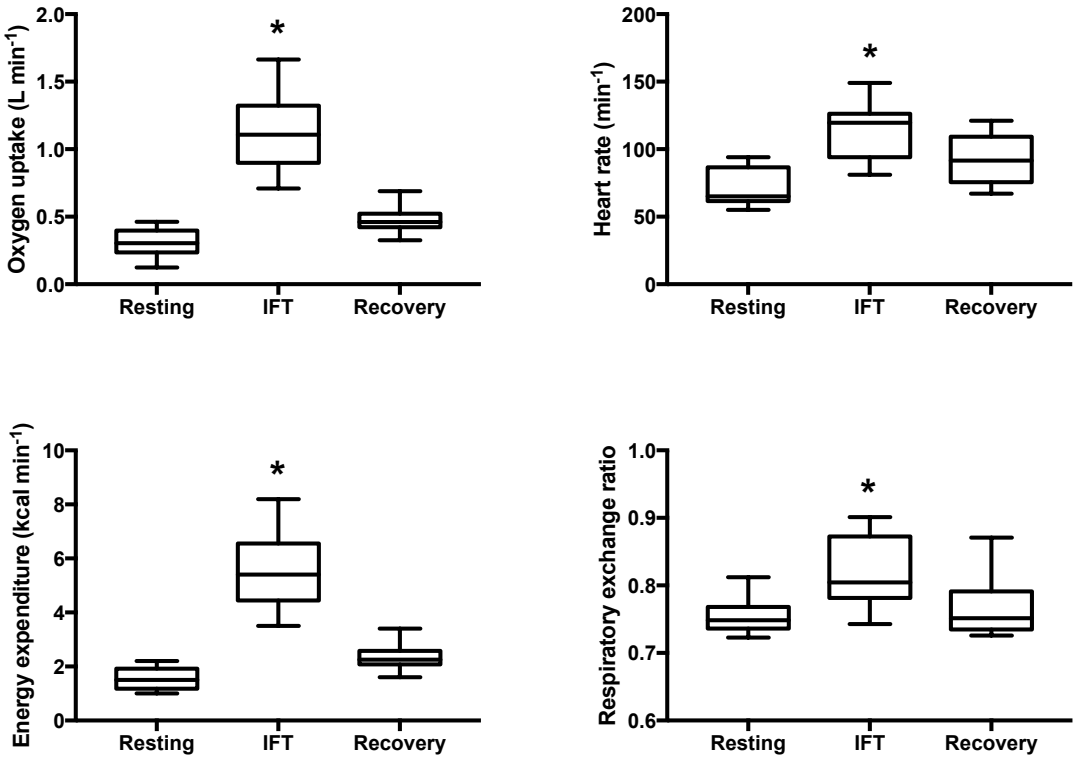


Figure 2-2: Cardiometabolic responses to intermittent functional training. Box and whisker plot displaying the median and 5th - 95th percentile. *Significantly different from pre-exercise resting $p < 0.05$.

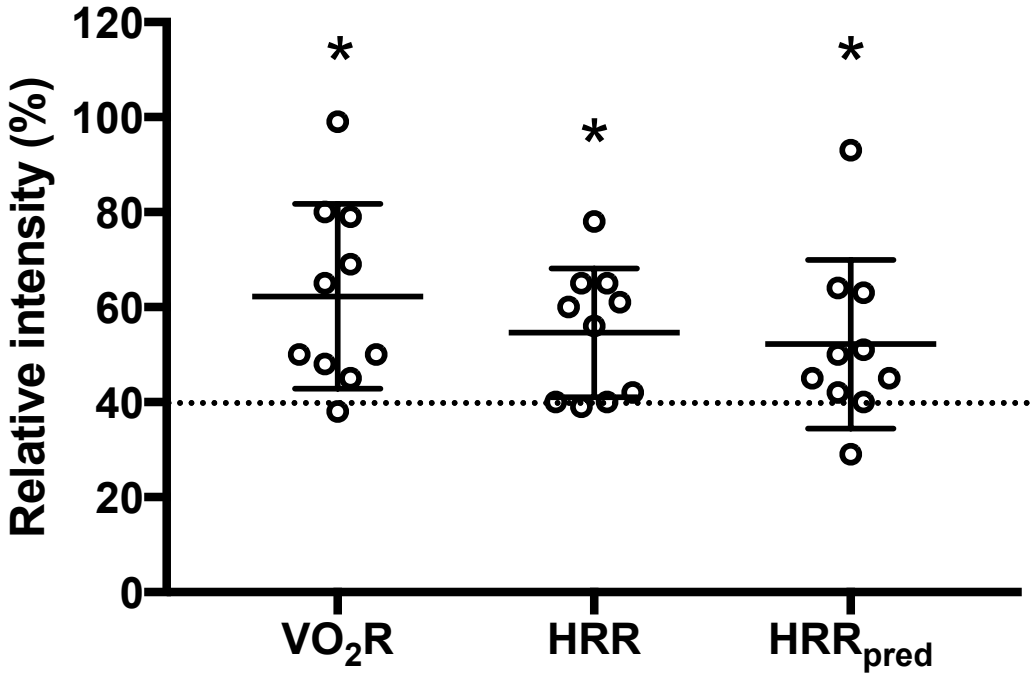


Figure 2-3: Mean response during intermittent functional training based on oxygen uptake reserve ($\dot{V}O_2R$), heart rate reserve (HRR), and HRR using age predicted maximal heart rate (HRR_{pred}). Dashed lines indicate minimum threshold required to be considered moderate intensity aerobic exercise. *$p < 0.05$ compared to 40% threshold.

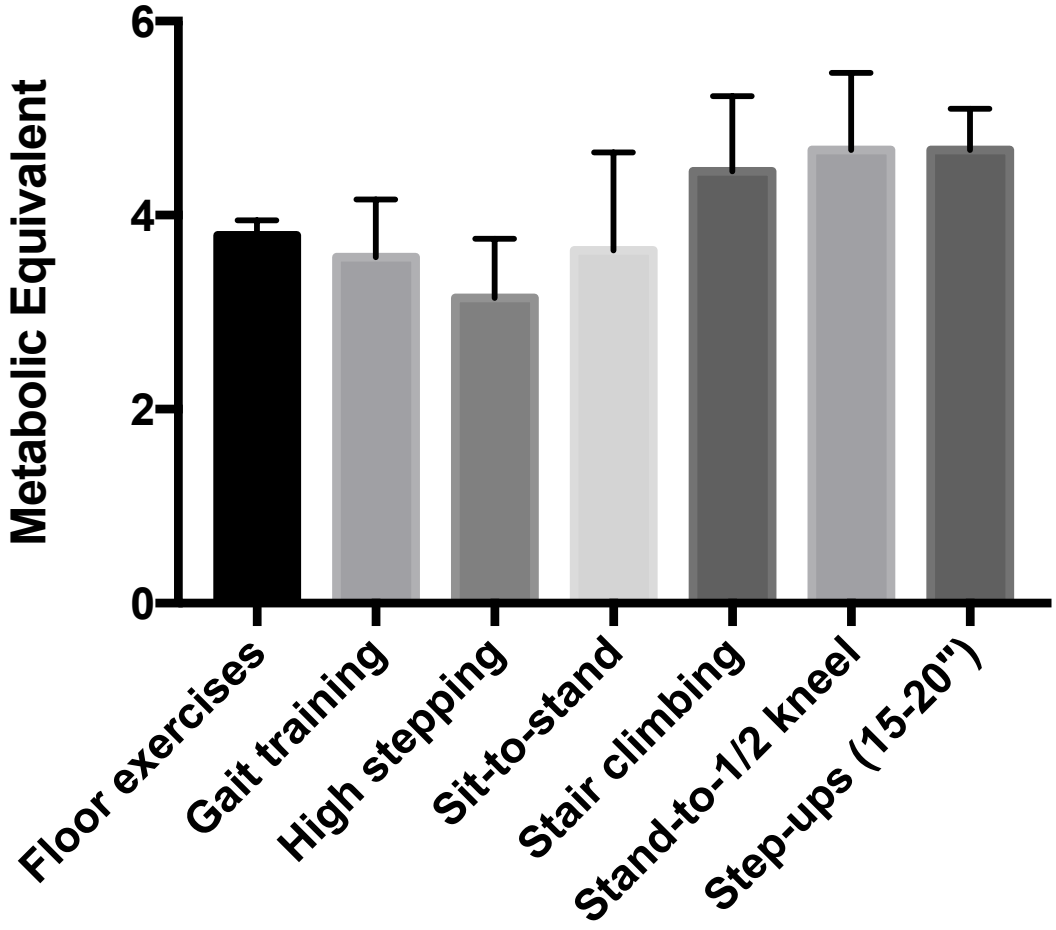


Figure 2-4: Metabolic equivalent (MET) of functional tasks used during intermittent functional training

2.5 Discussion

We aimed to determine whether practice of individualized functional tasks while keeping HR 30-50 beats above resting for 30 min would be sufficient to achieve the minimum intensity and duration of activity needed to be considered moderate intensity aerobic exercise. Our intention was to develop a method that could be used to enrich stroke rehabilitation by targeting both relearning of neuromotor control and cardiorespiratory fitness. The key finding of the current study was that chronic stroke survivors could sustain workloads during the IFT protocol that were beyond the minimum intensity needed to increase cardiorespiratory fitness (Garber et al., 2011) without the use of ergometers or other specialized equipment. All participants reached at least one of the minimum threshold criteria and average HR was between 40 and 80% of HRR. Using similar intermittent training approaches, Marsden et al. (2017) also reported workloads in the moderate to vigorous intensity range using task-oriented exercise in subacute stroke survivors. However, they combined circuits of both functional and ergometer-based exercise to meet aerobic exercise guidelines in this population. Such relative workloads have also been recorded using circuit-based functional movements in populations without acquired brain injury (Miller et al., 2014; Paoli et al., 2013; Schmidt, Anderson, Graff, & Strutz, 2016; Sperlich et al., 2017). During high-intensity circuit training using resistance-based exercise, overweight males were able to maintain workloads corresponding to 85% of maximal HR for 30 min 3 times per week over 4 weeks (Miller et al., 2014). Interestingly,

this strategy was sufficient to improve blood pressure, glucose tolerance, blood lipids, and body composition (Miller et al., 2014). Although we used tasks that are commonly employed during contemporary stroke rehabilitation, the cardiometabolic demands were much higher than those previously reported (M. J. MacKay-Lyons & Makrides, 2002). In the current study, however, more emphasis was placed on the total amount of work performed rather than on the biomechanics and therapists should consider the tradeoff (quality / quantity) before implementing such a program.

The appeal of such intermittent functional training paradigms lies in the fact that it pairs an aerobic exercise stimulus along with task-oriented exercise, which may provide synergetic benefits on ambulatory outcomes in stroke survivors. Outermans et al. (2010), demonstrated that adding 55 min of high intensity task-oriented circuit training to 30 min of usual physiotherapy was more effective than adding the same amount of typical therapy on gait parameters and walking endurance. The safety and efficacy of such therapeutic exercise has also been demonstrated in a relatively large (n= 250) multicenter randomized control trial (van de Port et al., 2012). The authors reported significant improvements in walking speed and endurance using task-oriented circuit training in stroke survivors who had completed inpatient therapy. Although these studies were not designed to elucidate the underlying mechanisms, the authors argued that improvements in ambulatory function were likely related to a higher cardiorespiratory workload during circuit training (Outermans et al., 2010). This would then suggest that changes in walking speed and

endurance resulted from increased cardiorespiratory fitness rather than improved neuromotor control of gait. However, aerobic exercise not only increases capacity for work but it also stimulates structural and functional alterations in the brain after stroke (Ploughman, Austin, Glynn, & Corbett, 2015). It is believed that this beneficial effect is mediated via increased expression of growth factors, such as brain derived neurotrophic factor, which is associated with functional recovery after stroke (Ploughman et al., 2009). It is then conceivable that circuit-based training, which combines task-oriented and aerobic exercise, could enhance neuromotor recovery through synergistic effects on neuroplasticity. This is an important area for future research.

The intermittent functional training protocol described in the current study overcomes three major barriers to implementing aerobic exercise during stroke rehabilitation. Firstly, insufficient time within a single therapy session is consistently reported as a challenge to implementing aerobic exercise recommendations (Biasin et al., 2014; Prout et al., 2016). Therapists have been asked to provide at least 30 min of moderate intensity aerobic exercise three times per week in addition to 3 hrs per day task-oriented training (Billinger et al., 2014; Hebert et al., 2016) without corresponding increases in therapy time (Bayley et al., 2012). Although the tradeoff between quantity and quality of task-oriented exercise performed during the IFT protocol needs to be considered, gradually decreasing rest time and organizing tasks to maintain HR 30-50 beats above resting within a therapy session (e.g. the last 20-30 min) is achievable and may be an effective strategy

to meet best practice guidelines without increasing therapy time. Secondly, many rehabilitation centers do not have structured aerobic exercise programs and access to appropriate ergometers is a significant barrier to implementation (Prout et al., 2016). Unlike other task-oriented circuit training protocols (Marsden et al., 2017; Outermans et al., 2010; van de Port et al., 2012), the current study was performed without any specialized equipment other than a HR monitor and items which are typically available in stroke rehabilitation units (i.e. floor mat, step, and a bed). Furthermore, the minimal equipment requirement makes the IFT protocol transferrable to the community as part of a home-based exercise program. Thirdly, uncertainty on how to progress patients with ongoing cardiovascular risk and comorbid conditions has been identified as a barrier to reaching target HR training zones (Biasin et al., 2014). This is further complicated by recommendations to perform maximal exercise testing with electrocardiography monitoring (MacKay-Lyons M, 2012), which is not routinely available in rehabilitation units. Progression within the IFT protocol could be achieved by increasing the complexity of a given functional task (e.g. practice on unstable surface) rather than increasing the target HR. Although IFT may help to address several challenges to implementation of aerobic exercise recommendations, it is still unknown whether such exercise strategies can replicate the demonstrated benefits observed with ergometer-based aerobic exercise on CRF (Ivey et al., 2015; M. Mackay-Lyons, McDonald, et al., 2013) and cardiometabolic

risk factors (D'Isabella et al., 2017) in stroke survivors. A comparison between the two methods is warranted.

2.5.1 Study Limitations

As a first step toward understanding the potential utility of providing intensive task-oriented exercise during inpatient rehabilitation, we evaluated the cardiometabolic demands of our IFT protocol in chronic stroke survivors. The generalizability of these results to patients at earlier stages into their recovery is a significant limitation. However, it must be realized that tasks were individualized to each participant's level of impairment and such tasks are commonly employed during inpatient rehabilitation. Also, the cardiovascular demands were within the range recommended for patients within the first 3 months (MacKay-Lyons M, 2012) and did not require the use of specialized equipment.

2.6 Conclusion

The level of physical deconditioning observed in stroke survivors not only increases risk for recurrent stroke and development of comorbid conditions but can also limit participation in rehabilitation programs. Stroke best practice guidelines now encourage incorporating aerobic exercise as soon as possible during inpatient rehabilitation and throughout the continuum of care (Billinger et al., 2014; Hebert et al., 2016). However, there are many challenges to implementing aerobic exercise recommendations during

inpatient rehabilitation including access to appropriate ergometers, ability to maintain target heart rate training zone, and assessment of underlying cardiovascular risk. The current analysis revealed that typical functional tasks employed during inpatient rehabilitation can be organized to meet aerobic training guidelines in chronic stroke survivors with significant cardiovascular comorbidities and residual impairments. The advantage of such exercise modalities is that specialized equipment is not required, tasks are individualized to impairments, and progression can be achieved by increasing difficulty of movement rather than only increasing the target HR. When implemented into a progressive training program (Ploughman & Kelly, 2016), IFT has the potential to address multiple targets for regaining function after stroke. More studies are needed to describe the cardiometabolic demands in subacute stroke survivors and to determine the efficacy of such training programs on functional recovery, CRF, and cardiovascular risk factors.

Chapter 3: Task-oriented Circuit Training as an Alternative to Ergometer Type Aerobic Exercise Training After Stroke

3.1 Abstract

Moderate-intensity aerobic exercise training is an important treatment strategy to enhance functional recovery and decrease cardiometabolic risk factors after stroke. However, stroke related impairments limit access to ergometer-type exercise. The aims of the current study were (1) to evaluate whether our task-oriented circuit-training protocol (intermittent functional training; IFT) could be used to sustain moderate-intensity aerobic workloads over a 10-week intervention period, and (2) investigate its preliminary effects on cardiorespiratory fitness and metabolic profile compared to constant-load ergometer-type exercise (CET). Forty chronic hemiparetic stroke survivors were randomized to receive 30-sessions of IFT or CET over ten weeks. Similar proportions of participants randomized to IFT (7/19) and CET (9/18) sustained workloads associated with moderate-intensity aerobic exercise over the study period (p= 0.515). However, CET was associated with more substantial changes in maximal oxygen uptake (MD= 2.79 mL min^{-1} kg^{-1} CI: 0.84 to 4.74) compared to IFT (MD= 0.62 mL min^{-1} kg^{-1} CI: -0.38 to 1.62). Pre-to-post changes in C-reactive protein (-0.9 mg/L; p=0.017), fructosamine (+14.7 µmol/L; p= 0.026), and resting whole-body carbohydrate oxidation (+24.2 mg min^{-1}; p= 0.046) were observed when considering both groups together. Accordingly, IFT can replicate the aerobic intensities sustained during traditional ergometer-type exercise training. More work is needed to evaluate the dose-response effects of such task-oriented circuit training protocols on secondary prevention targets across the continuum of stroke recovery.

3.2 Introduction

Stroke rehabilitative efforts are primarily directed toward the recovery of lost functions. Hence, best practice guidelines include 15 hours of direct task-oriented therapy each week during inpatient/outpatient rehabilitation services (Hebert et al., 2016). Such treatment involves practicing relevant tasks, including moving from lying to sitting, stepping, and walking. As delivered during neurorehabilitation programs focused on restoring more normal movement patterns after stroke, task-oriented activities provide insufficient cardiovascular stress levels (M. J. MacKay-Lyons & Makrides, 2002). Accordingly, practitioners are recommended to incorporate an additional 150 minutes of moderate-intensity aerobic exercise each week during formalized care and encourage stroke survivors to remain active throughout the continuum of recovery (Billinger et al., 2014; Marilyn MacKay-Lyons, 2019). In addition to its implications for functional recovery (Ploughman & Kelly, 2016), moderate-intensity aerobic exercise is an integral component of lifestyle and risk factor management to prevent recurrent stroke and other major cardiovascular events (Wein et al., 2018). Although recent evidence suggests an increased focus on incorporating aerobic exercise recommendations during formalized stroke rehabilitation (Nathoo et al., 2018), sedentary activities remain the dominant behavior of the inpatient environment (Astrand et al., 2016; Barrett et al., 2018; Bernhardt et al., 2004; Sjoholm et al., 2014; West & Bernhardt, 2012). Furthermore, stroke survivors

are not meeting physical activity targets once discharged into the community (English et al., 2014; Moore et al., 2013). The limited treatment time available to each patient, and a lack of access to the specialized equipment needed to adapt traditional ergometer type aerobic exercise for stroke survivors with hemiparesis, are among the barriers to incorporating aerobic exercise during formalized rehabilitation (Moncion et al., 2020). Similarly, stroke related impairments limit access to existing exercise programs available at the community level (Tang, Closson, et al., 2009). Accordingly, practical solutions are needed to increase access to moderate-intensity aerobic exercise throughout the continuum of stroke recovery.

Task-oriented circuit training may be an effective strategy to replicate the intensities and outcomes achieved during traditional aerobic exercise training without using ergometers or other specialized equipment. A relatively large (N= 150) randomized control trial demonstrated that task-oriented circuit training was more effective than usual physiotherapy on gait outcomes in a cohort of stroke survivors who recently completed inpatient rehabilitation (van de Port et al., 2012). Other studies have reported beneficial effects of group-based exercise classes on cardiorespiratory fitness (Marsden et al., 2016; Moore et al., 2015; Pang et al., 2005) and cardiometabolic risk factors (Moore et al., 2015) among community-dwelling stroke survivors. However, the aerobic workloads maintained during such group-based exercise classes are not well defined. Furthermore, the extent to which task-oriented circuit training can achieve the large treatment effects reported for

ergometer-type aerobic exercise interventions (Saunders et al., 2020) needs further investigation.

Building on previous literature (Pang et al., 2005; van de Port et al., 2012), we developed a task-oriented circuit training protocol that included activities typically employed during formalized stroke rehabilitation and did not require the use of ergometers or other specialized equipment. Task-oriented activities were incorporated into circuits that paired more metabolically demanding movements with less demanding ones to maintain a target heart rate range of 30 to 50 beats per minute above resting levels. Indeed, workloads supported during this intermittent functional training (IFT) protocol are sufficient to achieve at least moderate-intensity aerobic exercise criteria over a single session (L. P. Kelly et al., 2017). However, it is unknown whether such workloads are sustainable over a typical treatment period (i.e., 8 to 12 weeks) or if they can replicate the outcomes observed after ergometer-type aerobic exercise training. Accordingly, the current study aimed to evaluate participants' ability to sustain moderate-intensity aerobic workloads during IFT over the 10-week study period and investigate its preliminary effects on cardiorespiratory fitness and metabolic profile compared to ergometer-type aerobic exercise training.

3.3 Methods

3.3.1 Study Design

A parallel-groups randomized comparative study design was employed to evaluate participants' ability to maintain moderate-intensity aerobic workloads during IFT and to investigate its preliminary effects compared to constant-load ergometer training (CET) performed on the treadmill according to best practice recommendations (Marilyn MacKay-Lyons, 2019). Participants who received inpatient and outpatient therapy from the provincial tertiary rehabilitation hospital within the preceding three years were recruited. The following inclusion criteria were used: (1) age ≥18 years, (2) ischemic or hemorrhagic stroke>6 months, (3) ability to perform 2-step instruction, (4) and ambulatory with or without aid >10 m. Participants were excluded if they presented with any absolute contraindications for graded exercise testing as described elsewhere (Riebe et al., 2018). Allowing for a 20% dropout rate, we enrolled 20 participants per group to retain at least 16 participants in each exercise group. Power analysis based on previous studies employing similar dosages of aerobic exercise training (Macko et al., 2005; Macko et al., 2001) suggested that this sample size would have sufficient power to detect within-group differences in maximum oxygen uptake ($\dot{V}O_{2max}$) over the study period (0.85 power, α = 0.05). Experimental procedures were approved by the regional Health Research Ethics Board (HREB# 2018.082) (see Appendix A), and all participants provided written

informed consent following TCPS 2: Ethical Conduct for Research Involving Humans (Canadian Institutes of Health Research, 2018). Participants were randomized in permuted blocks of 6-8 (using an opaque envelope) to receive either the IFT or CET interventions 3-days per week over ten weeks. Given the nature of the study, it was not possible to blind participants on group assignments. Participant characteristics (age, sex, height, weight, and list of current medications), stroke history (date of onset, type of stroke), and the severity of residual impairment using the National Institutes of Health Stroke Scale (NIHSS) (Goldstein et al., 1989) and stage of lower limb recovery using the Chedoke McMaster scale (Gowland et al., 1993) were recorded after randomization.

3.3.2 Interventions

Resting heart rate (HR) and blood pressure were recorded before each 30-minute session of IFT and CET using a digital blood pressure monitor (Essentia, Physiologic, Montreal, Quebec). As described previously (L. P. Kelly et al., 2017), IFT sessions involved performing 6-9 circuits of task-oriented exercises (3 different tasks per circuit) focused on improving functional ability. Circuits lasted approximately 3-min each, pairing more metabolically demanding tasks with less demanding ones in such a way to maintain an HR range 30-50 bpm above resting. This target HR range is associated with at least moderate levels of aerobic intensity (i.e., >40% of heart rate reserve, HRR) in chronic stroke survivors (L. P. Kelly et al., 2017) and reflects a 3 to 5-fold increase in HR compared

to current inpatient rehabilitation practices (Barrett et al., 2018). Task-oriented exercises were selected based on each participant's functional limitations, and difficulty was progressed throughout IFT (i.e., increasing the number of repetitions within a given time frame, increasing step height, incorporating unstable surfaces, etc.). Exercises included practicing rolling side-to-side on a mat, moving from lying to sitting and sitting to standing, stepping and transferring from standing position to the floor and back. Among participants randomized to CET, sessions were performed on a motorized treadmill (Trackmaster TMX58, Full Vision Inc, KS, USA) with harness support (<10% of body weight, PneuWeight, Pneumex, ID, USA) unless contraindicated and the total body recumbent stepper (T4r, Nustep, LLC, MI, USA) was used instead. Treadmill speed and incline (or load-level and steps-per-min) were adjusted to achieve a target HR range corresponding to 40 to 60% of HRR as tolerated. The target HR range was calculated as follows:

Equation 3-1:

$$40\%\ \mathrm{HRR} = (\mathrm{HRmax} - \mathrm{HRrest}) * 0.40 + \mathrm{HRrest}$$

Equation 3-2:

$$60\%\ \mathrm{HRR} = (\mathrm{HRmax} - \mathrm{HRrest}) * 0.60 + \mathrm{HRrest}$$

Where maximum HR (HRmax) was recorded during the baseline graded exercise test and resting HR (HRrest) was measured before each exercise session. In terms of progression, the focus was on increasing treadmill workload (i.e., speed and incline).

Continuous verbal encouragement was provided throughout both interventions to sustain workloads >40% of HRR.

3.3.3 Outcome Measures

The primary outcome measure was proportions of participations sustaining the prescribed moderate-intensity aerobic workloads (i.e., >40% of HRR) in 80% or more of the exercise sessions. Participants wore a chest strap HR transmitter (T31-Coded, Polar Electro Oy, Kempele, Finland) and a wrist-worn wireless receiver (FT2, Polar Electro Oy, Kempele, Finland) during each session to monitor HR response. Average HR was recorded for each 30-min IFT and CET session.

Secondary outcomes included comparing proportions of participants in the IFT and CET groups who achieved the *a priori* threshold for change in $\dot{V}O_{2max}$ and pre to post changes in parameters related to metabolic profile. The threshold for meaningful change in $\dot{V}O_{2max}$ was set at >1.4 mL min^{-1} kg^{-1} based on the results of previous studies in chronic hemiparetic stroke survivors (Ivey et al., 2007; Macko et al., 2005; Macko et al., 2001). Using similar treadmill aerobic exercise training methods to the current research, Macko et al. (2005) reported a mean difference and 95% confidence interval for the difference between pre-and post-graded exercise tests of 2.1 mL min^{-1} kg^{-1} (95% CI: 1.4 to 2.7) over a 3-months. Other measures of cardiometabolic risk included changes in body mass index (BMI), resting blood pressure, resting HR, serum C-reactive protein (a measure of chronic

inflammation), serum lipids [triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL)], and serum fructosamine (short term glycemia). As an exploratory outcome, pre to post changes in whole-body resting energy expenditure was evaluated in a subset of the participants. Assessments of $\dot{V}O_{2max}$ and resting energy expenditure were performed over two sessions (at least 3-days apart) at baseline and after the intervention period. Participants were instructed to refrain from structured physical activities for 24-hr and consume no food at least 4-hr before each assessment. In an attempt to reduce biological variation, assessments were performed at the same time of day, and participants were instructed to take medications as prescribed throughout the trial.

3.3.3.1 Maximum Oxygen Uptake:

A calibrated indirect calorimetry system (Moxus, AEI Technologies, Pittsburgh, PA, USA) was used to assess $\dot{V}O_{2max}$ and resting whole-body energy metabolism. Symptom-limited graded exercise tests were performed on either the treadmill (with 10% body weight support) or total-body recumbent stepper to determine $\dot{V}O_{2max}$. The first two cohorts of participants in each group (n =14) performed pre-and post-graded exercise tests on the treadmill, and the remaining assessments were performed on the total-body recumbent stepper. The decision to switch to a total-body recumbent stepper early in the study was made due to challenges in determining the oxygen uptake/workload relationship

on the treadmill. Although the bodyweight support harness was used and participants were instructed not to hold onto the handrail, participants felt unsteady with increasing workloads and repeatedly held onto the handrails. Participants were interfaced with the metabolic cart using 51 mm diameter corrugated tubing (2.74 m) connected to a silicone oro-nasal face mask (8900 series) with a two-way non-rebreathing valve and headgear (Hans Rudolph Inc., Shawnee, KS, USA). Ventilatory parameters (tidal volume, breathing frequency, and minute ventilation) and expired gas concentrations (fraction of expired oxygen and fraction of expired carbon dioxide) were recorded breath by breath to determine rates of oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). The HR response to graded exercise testing was recorded in line with ventilatory parameters using a telemetry system (Polar Electro Oy Kempele, Finland) or electrocardiography device (CardioCard, Nasiff Associates Inc., Central Square, NY, USA), which were integrated with the indirect calorimetry system. Electrocardiography was only used when deemed necessary by the study physician. Rating of perceived exertion was taken during the last 30-sec of each stage using the Borg CR10 scale (Borg & Kaijser, 2006; G. Borg, 1982). The treadmill graded exercise test protocol was based on best-practice recommendations (Marilyn MacKay-Lyons, 2019), which involved walking at a self-selected speed and 0% incline for 2 min, followed by a 2.5% increase in grade every 2 min until a slope of 10% was reached and, after that, a 0.05 m/s increase in speed every 2 min, until test termination. The total-body recumbent stepper protocol was adapted from previous work in this

population (Billinger et al., 2008) and involved increments in workload (~20 W) every 2 min through load-level or step frequency changes. All testing was terminated according to established criteria (Riebe et al., 2018). Achievement of $\dot{V}O_{2max}$ was assessed based on the attainment of at least two of the following criteria (Howley et al., 1995): (i) a plateau in $\dot{V}O_2$ (<2.1 mL min^{-1} kg^{-1}) with increasing workload, (ii) respiratory exchange ratio greater than 1.15, and (iii) HRmax >90% of age-predicted maximum heart rate calculated as (Brawner, Ehrman, Schairer, Cao, & Keteyian, 2004; Gellish et al., 2007):

Equation 3-3

$$HRmax = 207 - (0.7 * age)$$

Equation 3-4

$$HRmax(beta\ blockers) = 164 - (0.7 * age)$$

Equation 3-4 was used to predict HRmax in participants receiving beta-adrenergic blockade therapy.

3.3.3.2 Resting Metabolic Rate:

To explore exercise-induced changes in whole-body energy metabolism, resting metabolic rate was added to the experimental protocol after the first two blocks of participants completed the intervention period. Briefly, the protocol involved participants lying comfortably on an adjustable bed with their head supported by a single pillow in a temperature-controlled (22-24 ^{o}C) and dimly lit room. Participants were instructed to

minimize movements during the test and not to fall asleep. The indirect calorimetry system was adapted for resting metabolic rate measurements, which included the use of a flow-through canopy place over the participant's head and a flow meter (Moxus, AEI Technologies, Pittsburgh, PA, USA). According to manufacturer instructions, the flow rate was adjusted to maintain a fraction of expired oxygen between 0.7 and 1.0. The data collection period lasted 40-min; of which the first 15-min and last 5-min were discarded. The remaining 20-min were averaged to determine $\dot{V}O_2$ and $\dot{V}CO_2$. Measurements were then used to calculate resting energy expenditure (REE), lipid oxidation rate (Lox), and carbohydrate oxidation rates (CHOox) according to the following formulas (Simonson & DeFronzo, 1990):

Equation 3-5

$$REE = 3.91\,\dot{V}O_2 + 1.10\,\dot{V}CO_2 - 1.93\,N$$

Equation 3-6

$$Lox = 1.69\,\dot{V}O_2 - 1.69\,\dot{V}CO_2 - 2.03\,N$$

Equation 3-7

$$CHOox = 4.57\,\dot{V}CO_2 - 3.23\,VO_2 - 2.60\,N$$

Where urinary nitrogen excretion rate (N) was estimated to be 0.01 g min^{-1} (Simonson & DeFronzo, 1990). Resting metabolic rate was also predicted (REEpred) using

the Mifflin-St Jeor equations (Frankenfield, Roth-Yousey, & Compher, 2005; Mifflin et al., 1990):

Equation 3-8

$$\text{REEpred (males)} = 10 * \text{weight} + 6.25 * \text{height} - 5 * \text{age} + 5$$

Equation 3-9

$$\text{REEpred (females)} = 10 * \text{weight} + 6.25 * \text{height} - 5 * \text{age} - 161$$

Where weight is measured in kg, height in cm, and age in years.

3.3.3.3 Blood analysis:

Blood samples were taken immediately before the graded exercise tests performed at baseline and post-intervention (3 days after the last exercise session). A 10 mL sample was obtained from the antecubital vein using (no additive) Vacutainer tubes (BD, Canada). The blood was left to clot at room temperature for 30-min, spun at 2,200 rpm for 10 min, blood serum was aliquoted into microcentrifuge tubes, and placed at -80°C until blood chemistry tests were performed. Upon completing data collection, samples were thawed and analyzed at a local clinical laboratory using the methodologies described below. Briefly, CRP, total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, and fructosamine were measured on Architect c16000 clinical chemistry systems (Abbott Diagnostics, Abbott Park, IL, USA). All testing reagents were purchased from Abbott Diagnostics. The CRP method was calibrated for high sensitivity CRP determination. The

Friedwald Equation was used to calculate LDL-Cholesterol concentrations (LDL (mmol/L) = total cholesterol (mmol/L) – HDL (mmol/L) – [triglycerides (mmol/L) / 2.2]) (Friedewald, Levy, & Fredrickson, 1972; Vujovic et al., 2010). Fructosamine analysis included reference values between 205 and 285 μmol / L as normal average blood glucose levels (Vujovic et al., 2010). The reference values for risk stratification based on CRP were as follows: <1 mg/L= low risk, 1-3 mg/L= moderate risk, and > 3 mg/L= high risk of CVD (Ridker, 2003). The recommendations of the Expert Panel on Detection and Treatment of High Blood Cholesterol in (2001) were used for risk assessment based on lipid profile.

3.3.4 Statistical Analysis

Continuous data were first inspected for outliers, and distribution tested for normality using the T D'Agostino-Pearson normality test. Differences between IFT and CET groups at baseline were evaluated using the independent samples T-test for continuous data, the Mann-Whitney U tests for ordinal data, and the Fisher's exact test for nominal data. Differences in proportions of individuals maintaining at least moderate-intensity aerobic exercise workloads over the intervention period between IFT and CET were evaluated using the Fisher's exact test. Similarly, the Fisher's exact test was used to test for differences in proportions of individuals exceeding the 1.4 mL min^{-1} kg^{-1} threshold set for changes in $\dot{V}O_{2max}$ between the two groups. Within-group changes over the intervention period were evaluated using the paired samples T-test. The Wilcoxon

matched-pairs test was used to evaluate blood markers' changes due to this data's non-continuous nature. Bland-Altman analysis was performed to assess the agreement between measured and predicted resting energy expenditure. Spearman correlation coefficients (rs) were used to evaluate associations between changes in $\dot{V}O_{2max}$ and changes in other metabolic markers. Statistical significance was set at $p < 0.05$. All statistical analysis and figures were performed in Prism 8 for MacOS (GraphPad Software, CA, USA).

3.4 Results

Of the 40 participants [65 years of age (SD 9)] randomized to receive either IFT or CET, 37 completed at least one session of their allocated treatment. As reported in Figure 3-1, no dropouts were observed among participants randomized to IFT, while 3 participant dropouts were observed in the CET group. Furthermore, two participants could not safely complete 30-min of walking on the treadmill and were switched to the total body recumbent stepper (participant numbers CET08 and CET15). As reported in Table 3-1, 35 % of the randomized participants were female, and most suffered an ischemic stroke (31 / 40). No statistically significant group differences were observed for baseline characteristics. The average BMI was 27.8 kg m^{-2} (SD 4.7), corresponding to the overweight category based on the American College of Sports Medicine classifications (Riebe et al., 2018). Although participants were, on average, 34 months (SD 29) since their first disabling stroke, many survivors were left with significant impairment. Accordingly, 63 % of participants had

NIHSS scores > 5 or Chedoke-McMaster Stage of Recovery Leg or Foot scores <6, indicating moderate levels of impairment (Gowland et al., 1993; Kwakkel et al., 2010). On average, participants had very poor levels of cardiorespiratory fitness 16.0 mL min^{-1} kg^{-1} (SD 5.0) according to age and sex-based normative data (Riebe et al., 2018). In fact, 60% had scores below the minimum threshold required for completing daily activities without inducing excessive fatigue (i.e., 18 to 20 mL min^{-1} kg^{-1}) (Macko et al., 2001; Morey et al., 1998). Accordingly, the current cohort represents the full range of impairments and functional limitations observed in community-dwelling stroke survivors.

Seven participants in the IFT and nine participants in the CET groups maintained > 40 % of HRR in at least 80 % of the sessions (Figure 3-2). Statistical analysis (IFT n = 19, CET n = 18) revealed no differences between groups for proportions of participants meeting the moderate-intensity aerobic exercise criteria (Fisher's exact test; p = 0.515). Also, the impairment level did not appear to explain the relatively high proportions of participants not sustaining the prescribed workloads. For instance, of the participants who did not maintain > 40 % HRR, only 4 / 12 in the IFT group and 3 / 8 in the CET group had NIHSS > 5 suggestive of moderate disability. Participants randomized to CET and switched to total-body recumbent stepper for their training completed 30/30 of their exercise sessions. However, they were unable to maintain workloads > 40 % of HRR.

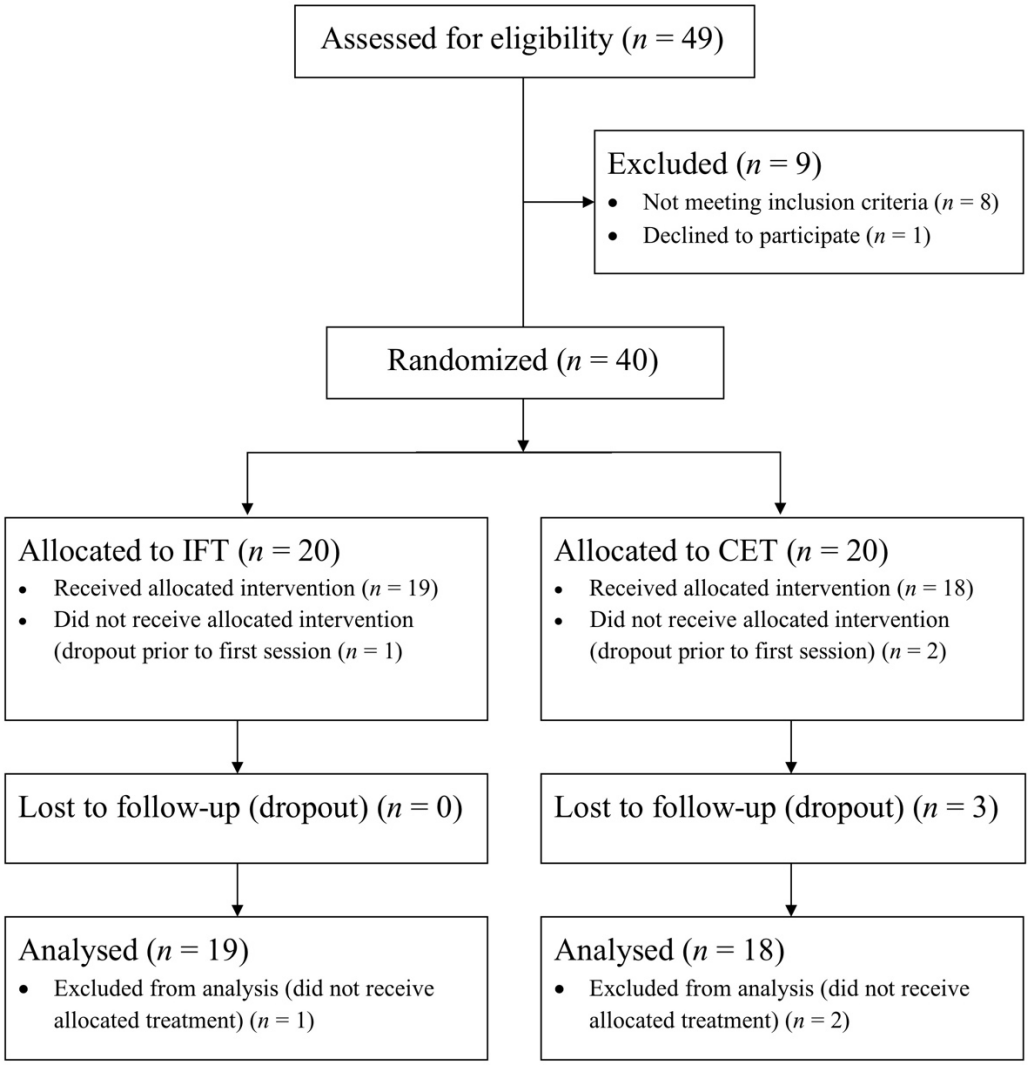


Figure 3-1: Participant flow through each stage of the study

Table 3-1: Baseline Characteristics

ID	Sex	Age	BMI ($kg\ m^{-2}$)	Stroke Type	NIHSS	Chedoke (leg /7)	Chedoke (foot /7)	$\dot{V}O_{2max}$ ($mL\ min^{-1}\ kg^{-1}$)
IFT01	F	58	21.5	Hemorrhagic	2	5	4	22.9
IFT02	M	61	38.9	Ischemic	1	6	7	22.8
IFT03	M	50	27.6	Hemorrhagic	17	3	2	14.6
IFT04	M	75	24.5	Ischemic	3	6	5	23.5
IFT05	M	66	32.1	Ischemic	15	3	1	11.8
IFT06	M	79	28.4	Hemorrhagic	11	3	2	15.9
IFT07	F	79	26.2	Ischemic	0	6	6	14.2
IFT08	M	67	29.6	Ischemic	3	6	6	19.6
IFT09	M	69	28.5	Ischemic	1	-	-	15.8
IFT10	M	81	28.2	Hemorrhagic	3	6	6	9.9
IFT11	M	74	28.0	Hemorrhagic	7	5	5	17.2
IFT12	M	79	29.5	Ischemic	9	3	2	10.8
IFT13	M	54	26.8	Ischemic	9	5	3	14.3
IFT14	M	71	28.4	Hemorrhagic	10	5	4	12.0
IFT15	F	73	24.7	Ischemic	3	5	6	8.0
IFT16	F	63	26.7	Ischemic	2	5	5	19.3
IFT17	F	70	27.9	Ischemic	1	7	7	13.5
IFT18	M	55	32.9	Ischemic	3	7	7	20.2
IFT19	F	64	18.3	Hemorrhagic	0	7	7	19.7
IFT20	M	71	32.9	Ischemic	3	7	7	19.6
CET01	M	71	30.9	Ischemic	6	5	6	15.1
CET02	M	43	24.3	Ischemic	7	3	1	17.6
CET03	M	62	26.9	Ischemic	4	5	2	19.3
CET04	F	49	29.6	Hemorrhagic	5	5	4	14.5
CET05	M	69	26.3	Ischemic	1	7	6	20.0
CET06	M	67	24.2	Ischemic	12	3	4	15.2
CET07	M	69	19.1	Ischemic	6	5	4	19.5
CET08	F	71	35.3	Ischemic	15	1	1	4.9
CET09	M	65	35.6	Ischemic	0	7	7	15.1
CET10	M	52	32.9	Ischemic	1	6	7	23.1
CET11	F	72	24.3	Hemorrhagic	3	5	5	-
CET12	F	72	22.8	Ischemic	5	5	4	10.2
CET13	M	54	29.6	Ischemic	10	3	1	18.4
CET14	M	58	37.8	Ischemic	3	6	5	10.8
CET15	M	78	22.7	Ischemic	9	5	3	7.9
CET16	F	67	21.1	Ischemic	-	-	-	11.8
CET17	M	60	24.1	Ischemic	2	-	-	28.3
CET18	F	52	30.6	Ischemic	0	6	5	18.2
CET19	F	66	26.0	Ischemic	1	6	6	12.0

Six participants in the IFT group and 11 participants in the CET group exceeded the 1.4 mL min^{-1} kg^{-1} threshold for change in $\dot{V}O_{2max}$. The difference in proportions between the two groups did not reach the level of statistical significance (Fisher's exact test; p= 0.103). However, as displayed in Figure 3-3, CET was associated with more consistent and larger cardiorespiratory fitness changes. The mean difference and 95% confidence interval for the difference between pre-and post-measurements were 0.62 mL min^{-1} kg^{-1} (CI: -0.38 to 1.62) and 2.79 mL min^{-1} kg^{-1} (CI: 0.84 to 4.74) for participants randomized to IFT and CET, respectively. In terms of symptom-limited graded exercise testing to evaluate changes in cardiorespiratory fitness, no adverse events were observed, and most participants (n=35) reached volitional exhaustion or were unable to maintain the target workload during the final stage. Two participants stopped the graded exercise test due to leg pain during baseline testing only. Fifty-four and 56 % of participants reached at least 2 of the a priori criteria for determining $\dot{V}O_{2max}$ during the pre-and post-intervention assessments, respectively (see Table 3-2).

Resting blood pressure and BMI measurements remained relatively stable over the study period across both groups [systolic (MD = -6 mmHg, CI: -14 to 2); diastolic (MD = 1 mmHg, CI: -5 to 6); BMI (MD = -0.20 kg m^{-2}, CI: -0.43 to 0.03)]. However, a consistent decrease in pre to post assessments of resting heart rate was observed after IFT (MD = -4.1 bpm, CI: -7.4 to -0.7) and CET (MD = -5.9 bpm, CI: -10.0 to -1.8). Average serum CRP exceeded the high-risk reference values at both time points among participants randomized

to IFT [Pre: 4.3 mg/L (SD 5.1); Post: 3.7 mg/L (SD 4.2)] and CET [Pre: 5.3 mg/L (SD 6.1); Post: 4.0 mg/L (SD 5.7)]. However, four participants in each group dropped their levels into a lower risk category, which was associated with statically significant pre to post changes in CRP across both groups (MD= -0.9 mg/L CI: -1.9 to -0.1). The majority of participants had serum fructosamine levels within the normal range (200 to 285 µmol/L) at both time points (see Table 3-3). However, average values increased after IFT (MD= 11.5 µmol/L, CI: -12.7 to 35.8) and CET (MD= 18.7 µmol/L, CI: 3.2 to 34.1), which suggests an increase in short-term glycemia after the exercise interventions. Similarly, scores for total cholesterol, HDL, LDL, and triglycerides were associated with low risk at baseline and postintervention for both exercise groups. A small but statistically significant increase in total cholesterol was observed after IFT (MD= 0.2 mmol/L, CI: 0.04 to 0.39). In terms of correlations between changes in $\dot{V}O_{2max}$ and metabolic markers, the only statistically significant association observed was with changes in fructosamine (rs= 0.42, p= 0.024).

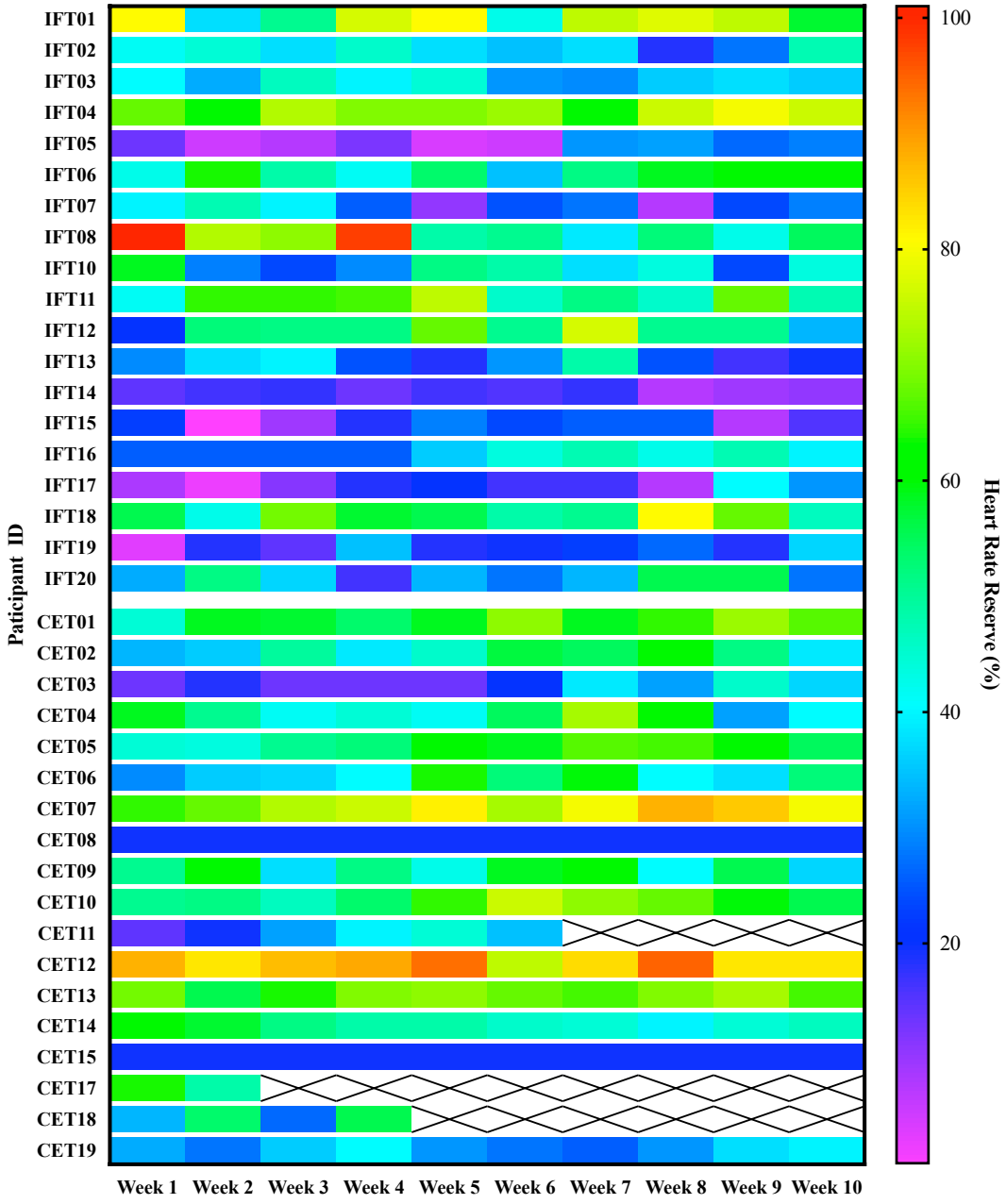


Figure 3-2: Dose analysis. Heatmap displaying participant's average heart rate during each week of aerobic exercise training. The graph's top and bottom halves are separated for intermittent functional training (IFT) and constant-load ergometer training groups (CET), respectively. Dark blue and purple cells indicate workloads below the moderate-intensity aerobic exercise threshold (i.e., <40% HRR).

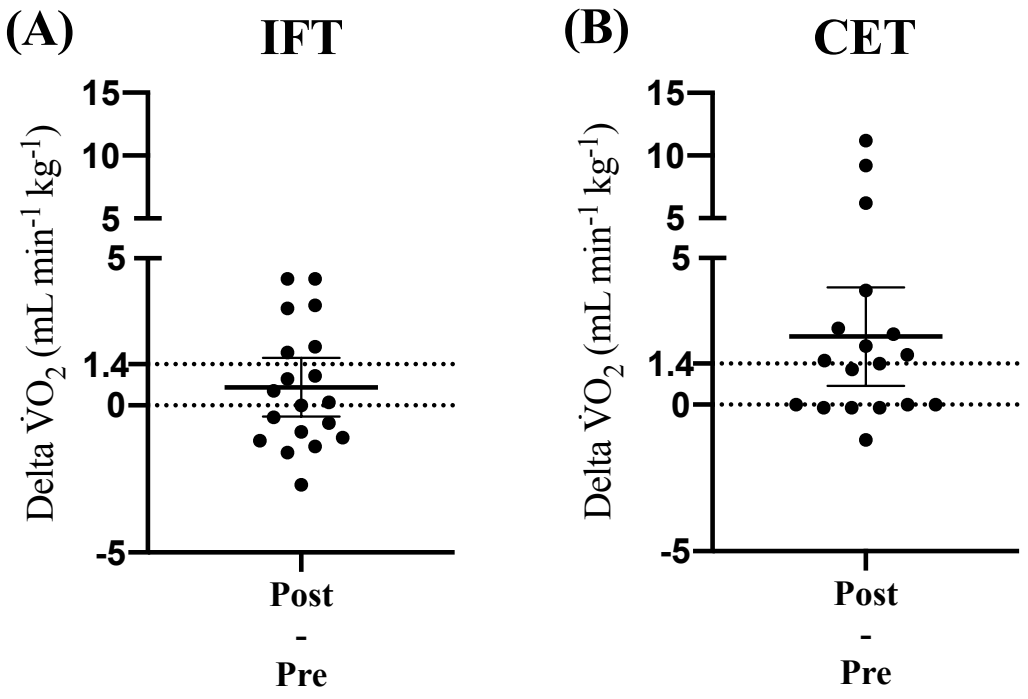


Figure 3-3: Change in maximum oxygen uptake ($\dot{V}O_{2max}$) over the 10-week intervention period among participants randomized to (a) intermittent functional training and (b) constant-load ergometer training. Dotted lines indicate the *a priori* threshold for change in $\dot{V}O_{2max}$ (i.e., 1.4 mL min^{-1} kg^{-1}). Solid lines display the mean difference and 95% confidence interval.

Table 3-2: Participants Maximum Absolute Oxygen Uptake and Achievement of Graded Exercise Testing Criteria at Pre and Post Assessments

		Pre-Graded Exercise Test					Post-Graded Exercise Test				
ID	Ergometer	$\dot{V}O_2$	Plateau Yes/no	RER	HRM	RPE (/10)	$\dot{V}O_2$	Plateau Yes/no	RER	HRM	RPE (/10)
IFT01	Treadmill	1467	yes	1.06	70	4	1716	No	1.06	82	5
IFT02	Treadmill	2878	yes	1.01	98	7	2924	Yes	1.00	93	7
IFT03	Treadmill	1458	yes	0.99	78	10	1540	Yes	1.07	79	10
IFT04	Treadmill	1782	yes	1.05	98	7	1716	No	1.17	82	3
IFT05	Treadmill	1131	yes	0.85	74	8	1331	Yes	0.89	75	10
IFT06	Treadmill	1272	yes	1.03	124	-	1246	Yes	1.09	124	-
IFT07	NuStep	865	yes	0.84	77	5	860	Yes	0.90	88	3
IFT08	NuStep	1776	no	1.12	98	7	1664	No	1.12	94	10
IFT09	NuStep	1348	yes	1.03	104	8	Dropout prior to intervention				
IFT10	NuStep	810	yes	0.97	96	7	1088	Yes	1.02	91	9
IFT11	NuStep	1526	no	1.09	120	5	1481	Yes	1.06	121	9
IFT12	NuStep	1013	yes	0.98	88	9	1017	Yes	1.01	84	5
IFT13	NuStep	1096	yes	1.06	83	5	1162	No	1.08	79	9
IFT14	NuStep	1000	yes	0.99	60	10	1339	No	1.05	67	7
IFT15	NuStep	548	yes	0.92	54	5	605	Yes	0.92	53	8
IFT16	NuStep	1189	no	1.07	94	10	1010	No	1.04	89	5
IFT17	NuStep	950	yes	1.04	74	9	920	Yes	1.05	66	10
IFT18	NuStep	1930	no	1.12	101	7	1745	No	1.07	100	5
IFT19	NuStep	1035	no	1.07	103	10	1260	Yes	1.07	101	10
IFT20	NuStep	1809	no	1.22	88	10	1727	No	1.23	87	7
CET01	Treadmill	1391	no	1.05	94	6	1250	Yes	1.10	93	5
CET02	Treadmill	1270	yes	0.96	77	8	1845	No	1.04	103	5
CET03	Treadmill	1676	no	0.94	80	6	2431	Yes	1.06	106	6
CET04	Treadmill	1204	yes	1.01	98	5	1290	Yes	1.01	98	5
CET05	Treadmill	1702	no	0.99	103	7	2235	Yes	1.07	104	2
CET06	Treadmill	1089	no	0.92	75	5	1217	Yes	0.97	96	-
CET07	Treadmill	1126	yes	1.21	91	10	1253	Yes	1.26	98	5
CET08	NuStep	397	yes	0.80	60	3	524	Yes	0.87	55	-
CET09	Treadmill	1804	yes	0.94	93	10	1836	No	1.05	93	10
CET10	NuStep	2350	no	0.97	90	10	2685	No	1.02	95	7
CET11	NuStep	1370	yes	1.0	83	7	Dropout during intervention				
CET12	NuStep	589	yes	1.07	77	5	588	Yes	1.16	70	4
CET13	NuStep	1647	no	1.17	84	10	1755	No	1.16	87	10
CET14	NuStep	1193	yes	1.07	76	7	1597	No	0.94	79	9
CET15	NuStep	587	yes	1.05	88	4	580	Yes	1.14	74	5
CET16	NuStep	680	yes	0.83	67	7	Dropout prior to intervention				
CET17	NuStep	2146	yes	1.05	84	7	Dropout during intervention				
CET18	NuStep	1591	yes	1.09	88	9	Dropout during intervention				
CET19	NuStep	818	no	1.12	98	7	976	Yes	1.09	93	7

Table 3-3: Pre to Post Changes in Short-term glycemia and lipid profile during intermittent functional training and constant-workload ergometer exercise

	Fructosamine (µmol/L)		Total cholesterol (mmol/L)		High-density Lipoprotein (mmol/L)		Low-density lipoprotein (mmol/L)		Triglycerides (mmol/L)	
ID	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
IFT01	244.4	261	5.017	5.475	1.322	1.203	3.195	3.71	1.101	1.237
IFT03	279.6	281.7	3.606	3.782	1.137	1.11	1.889	2.026	1.275	1.422
IFT04	238.2	261	3.094	3.609	1.04	1.184	1.758	2.119	0.652	0.674
IFT05	186.4	198.9	3.106	3.154	0.991	1.038	1.665	1.6	0.989	1.136
IFT07	232	246.5	3.221	3.135	0.906	0.905	1.339	1.428	2.147	1.764
IFT08	294.1	298.3	2.743	2.755	0.862	0.862	1.234	1.192	1.424	1.543
IFT10	236.1	221.6	2.283	2.254	0.792	0.849	0.943	0.983	1.206	0.928
IFT11	258.9	244.4	3.116	3.363	1.471	1.316	1.239	1.587	0.893	1.013
IFT12	269.3	244.4	3.296	3.604	0.883	0.862	1.942	2.108	1.036	1.395
IFT14	366.6	372.9	4.924	6.032	1.407	1.824	2.717	3.102	1.759	2.433
IFT15	261	275.5	3.376	3.669	1.047	1.156	1.838	1.998	1.08	1.132
IFT16	209.2	209.2	4.215	4.22	1.551	1.565	1.806	2.052	1.887	1.326
IFT17	263.1	248.6	2.688	3.082	1.312	1.41	1.059	1.277	0.698	0.869
IFT18	256.9	242.4	2.329	2.71	0.656	0.739	1.049	1.443	1.373	1.162
IFT19	219.6	393.6	4.946	4.619	1.666	1.654	2.897	2.509	0.842	1.004
IFT20	279.6	279.6	3.572	3.501	1.043	1.054	1.768	1.571	1.675	1.927
CET01	194.7	190.6	2.774	2.75	0.926	0.844	1.223	1.314	1.375	1.303
CET02	354.2	426.7	3.532	3.114	0.956	0.854	1.998	1.756	1.271	1.109
CET03	225.8	254.8	5.53	5.326	1.111	1.125	3.809	3.541	1.343	1.453
CET04	203	203	5.261	6.105	1.322	1.541	3.068	3.883	1.917	1.498
CET05	225.8	236.1	2.534	2.498	1.107	1.115	0.835	0.768	1.302	1.352
CET06	263.1	292.1	2.933	3.303	0.731	0.954	1.736	1.917	1.025	0.95
CET07	265.1	285.9	2.098	2.263	0.801	0.925	1.012	0.959	0.627	0.833
CET09	171.9	192.6	4.066	3.483	1.134	1.107	2.409	1.926	1.151	0.99
CET10	209.2	219.6	3.407	3.811	1.666	1.931	1.371	1.558	0.813	0.709
CET12	265.1	263.1	3.544	3.135	1.369	1.222	1.606	1.336	1.251	1.27
CET13	341.8	401.9	3.383	3.263	1.238	1.104	1.386	1.584	1.67	1.266
CET14	298.3	277.6	3.917	3.729	1.082	0.995	2.408	2.279	0.939	1.001
CET19	169.9	186.4	2.647	2.565	0.971	0.994	0.946	0.776	1.606	1.749

The resting indirect calorimetry data indicated a shift in whole-body energy metabolism over the study period. Although little change in pre to post-measurements of daily resting energy expenditure was observed (MD = -21 kcal $24hr^{-1}$, CI: -103 to 61), the agreement between measured and predicted values was improved after exercise training compared to baseline. Bland-Altman analysis of the percent difference between measured and predicted resting energy expenditure [100 * (measured – predicted) / average] revealed the bias and 95% confidence interval of the agreement to be 2.82 (CI: -22.72 to 28.38) and -2.19 (-19.02 to 14.64) at pre-and post-assessments, respectively. As displayed in Figure 3-4, the discrepancy between measured and predicted values decreased from pre to post measurements. This change was coupled with a shift in resting substrate partitioning toward increased reliance on carbohydrate energy substrates. As displayed in Figure 3-5, lipid oxidation rates decreased, and carbohydrate oxidation rates increased from pre to post resting metabolic rate measurements after IFT (Lipid: MD = -10.6 mg min^{-1} CI: -29.4 to 8.1; CHO: MD = 18.8 mg min^{-1} CI: -17.4 to 55.2) and CET (Lipid: MD = -12.5 mg min^{-1} CI: -22.5 to -2.5; CHO: MD = 34.0 mg min^{-1} CI: 4.2 to 63.8).

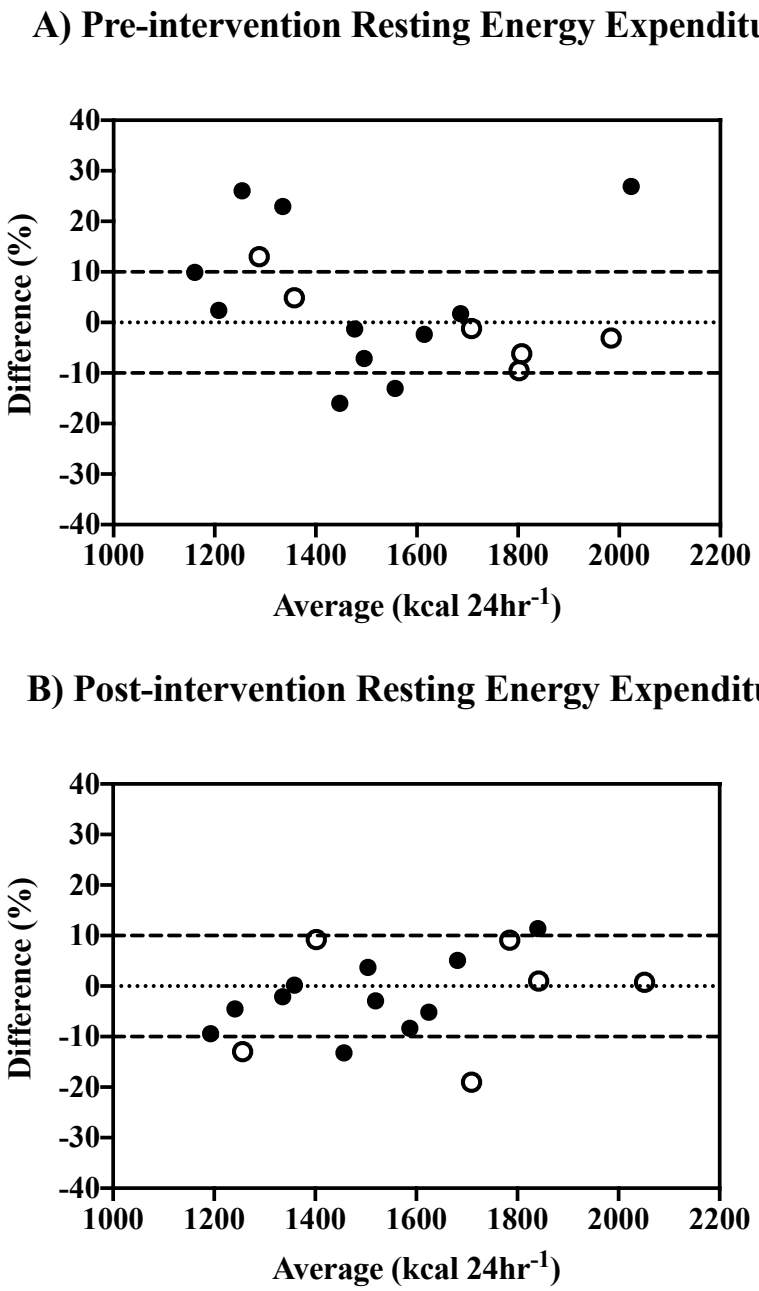


Figure 3-4: Bland-Altman analysis of agreement between measured resting energy expenditure via indirect calorimetry and predicted energy expenditure via the Mifflin-St Jeor equation during pre (A) and post (B). IFT (n= 11) closed circles; CET (n= 6) open circles.

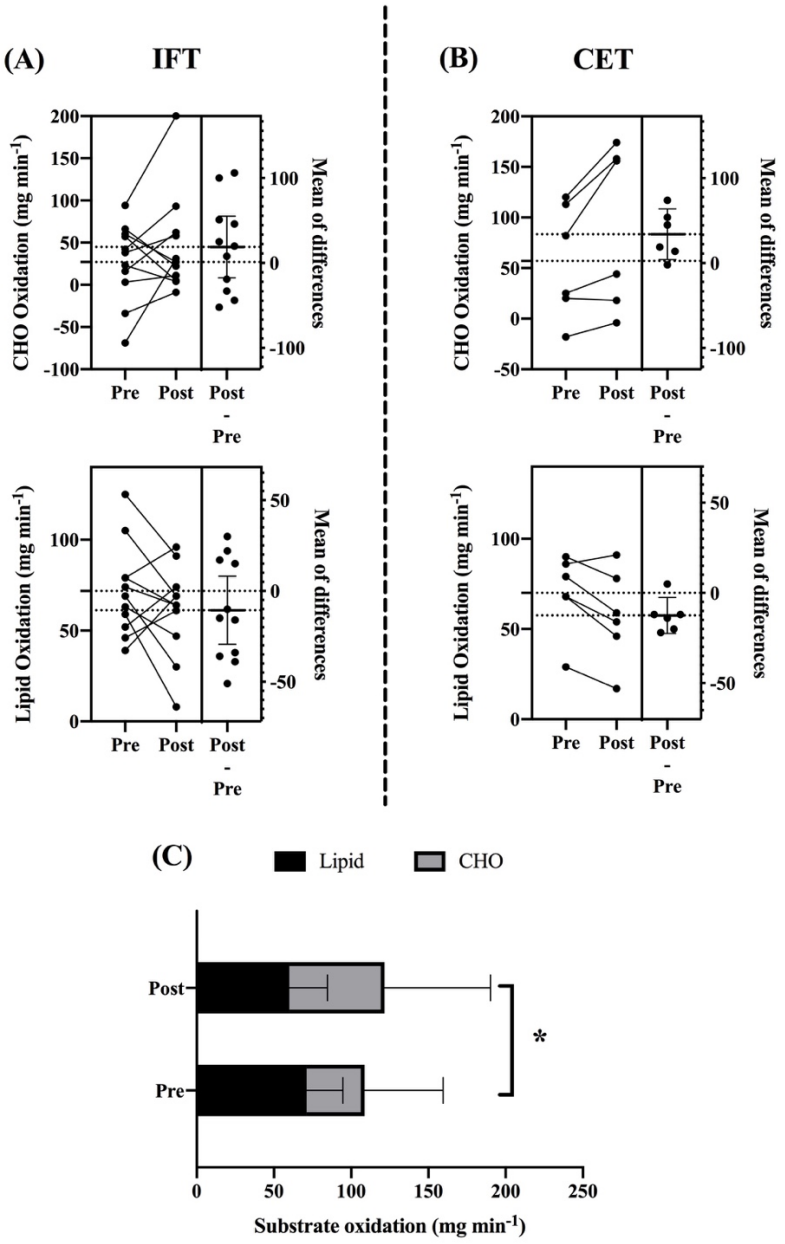


Figure 3-5: Resting Substrate Partitioning. Changes in rates of resting carbohydrate (CHO) and lipid oxidation over the intervention period. (A) Intermittent functional training (IFT), (B) constant-load ergometer training (CET), and (C) combined groups. Panels A and B display individual changes along with mean difference and 95% CI. Panel C displays pre to post changes in substrate partitioning across both groups, * $p < 0.05$.

3.5 Discussion

We undertook this study to evaluate chronic hemiparetic stroke survivors' ability to sustain moderate-intensity aerobic workloads during IFT over the 10-week study period and to investigate its preliminary effects on cardiorespiratory fitness and metabolic profile. Compared to best practice recommendations for ergometer-type aerobic exercise training, a similar proportion of participants randomized to IFT maintained the moderate-intensity aerobic exercise criteria over the 10-week study period. Accordingly, organizing task-oriented activities into 3-minute circuits that pair more metabolically demanding tasks with less demanding ones to increase HR 30 to 50 bpm above resting is a practical method to replicate the intensities of aerobic exercise imposed during ergometer-type training. The added value of such aerobic exercise strategies includes the fact that it does not require the use of specialized equipment, and task-oriented activities can be adapted to individuals' level of impairment, making IFT a practical tool to provide moderate-intensity aerobic exercise throughout the continuum of stroke recovery.

Previous studies have evaluated the effects of different functional exercise training paradigms among individuals recovering from a stroke (Marsden et al., 2016; Pang et al., 2005; Salbach et al., 2004; van de Port et al., 2012). However, the aerobic workloads maintained during prior investigations have not been well defined, and to date, no comparison has been made with traditional ergometer-type aerobic exercise training.

Among the ergometers appropriate for hemiparetic stroke survivors, the bodyweight-supported treadmill is perhaps the best choice for comparison with functional exercise because it incorporates both task practice and aerobic stress (M. Mackay-Lyons, McDonald, et al., 2013). Also, several randomized control trials have demonstrated the beneficial effects of treadmill aerobic exercise training on cardiorespiratory fitness and metabolic outcomes among stroke survivors during the subacute (M. Mackay-Lyons, McDonald, et al., 2013; Stoller et al., 2015) and more chronic phases of recovery (Globas et al., 2012; Ivey et al., 2007; Macko et al., 2005; Macko et al., 2001). However, in the current study, almost half of the participants randomized to CET failed to sustain the prescribed aerobic workloads. The extent to which this observation aligns with previous interventional studies is unclear because the authors often neglect to report the actual aerobic workloads maintained throughout the study period. However, it does align with previous feasibility studies that have identified stroke survivors' limited ability to sustain moderate-intensity workloads as barriers to implementing aerobic exercise guidelines during formalized rehabilitation (Biasin et al., 2014). Also, the within-group changes in cardiorespiratory fitness observed after CET are similar to those previously reported (Ivey et al., 2007; Macko et al., 2005; Macko et al., 2001). Therefore, the dose analysis likely reflects a true variability among chronic hemiparetic stroke survivors in their ability or willingness to sustain moderate-intensity aerobic workloads.

Although some participants (n = 6) randomized to IFT exceeded the *a priori* threshold for anticipated change in $\dot{V}O_{2max}$, CET was associated with more extensive effects on cardiorespiratory fitness. The blunted effect of IFT likely reflects a lower total energy expenditure of exercise compared to CET. Given that both interventions were matched for treatment time, the rest periods incorporated during the intermittent protocol and the time taken to switch between task-oriented activities reduced the total amount of time engaged in moderate-intensity aerobic exercise during IFT. Our cross-sectional study demonstrated that about 75 % of the IFT session is categorized as exercise time(L. P. Kelly et al., 2017). Although the aerobic workloads achieved during IFT are substantially higher than those observed during task-oriented therapies performed during contemporary stroke rehabilitation (Barrett et al., 2018; M. J. MacKay-Lyons & Makrides, 2002), they are not high enough to overcome the decreased energy demand during rest periods. Therefore, IFT session duration will likely need to be increased to match the energy expended during CET before a valid comparison between interventions can be made. In contrast, high-intensity interval training protocols have been used to achieve shorter exercise durations while matching for energy expenditure of exercise (Viana et al., 2018). The difference here is that high-intensity interval training interventions incorporate much higher relative workloads (e.g., 3-minutes at workloads > 80 % of $\dot{V}O_{2max}$) along with recovery intervals (e.g., 3-minutes at workloads < 60 % of $\dot{V}O_{2max}$) to match energy expenditure of exercise with constant-workload activities. The extent to which task-oriented activities can be used

to achieve high-intensity aerobic intervals in hemiparetic stroke survivors is beyond the current study's scope. However, the present data demonstrate that the moderate-intensity aerobic workloads sustained during IFT are sufficient to increase cardiorespiratory fitness for at least some stroke survivors.

Serum CRP was the most responsive blood marker to change in the current study. Elevated CRP levels are associated with an increased risk of future cardiovascular events (Blake, Rifai, Buring, & Ridker, 2003) and unfavorable long-term functional outcomes after ischemic stroke (VanGilder et al., 2014). Four participants in each group reduced their CRP levels into a lower risk category, and statistically, significant pre to post changes were observed across both groups. The observed changes in CRP align with the results of previous exercise interventions (Fedewa, Hathaway, & Ward-Ritacco, 2017) and highlight the value of including this biomarker of cardiovascular risk in future definitive trials among stroke survivors.

Fructosamine and serum lipids remained within normal and low-risk reference values throughout the study period. However, statistically significant within-group increases in average blood glucose levels and total cholesterol were observed after CET and IFT, respectively. The observed changes are in contrast with a recent meta-analysis on the topic, which reported decreases in fasting glucose and total cholesterol (D'Isabella et al., 2017). Similarly, the observed increase in carbohydrate oxidation during post-

intervention assessments of resting metabolic rate is inconsistent with the concept of improved metabolic fitness (Nordby, Saltin, & Helge, 2006). Given that dietary controls were not imposed in the current study, the increase in short-term glycemia and the shift toward increased oxidation of carbohydrate energy sources at rest could result from changes in eating behaviors over the study period. However, the ability to switch between energy substrates is depressed among deconditioned populations (Goodpaster & Sparks, 2017; Thyfault & Bergouignan, 2020), and the observed changes in substrate partitioning might reflect a positive acclimation to exercise training in this cohort. In fact, a small but statistically significant positive association was observed between changes in $\dot{V}O_{2max}$ and serum fructosamine levels. Also, the agreement between predicted and observed resting energy expenditure improved over the study period. More studies are needed to elucidate the dose-response effects of exercise on metabolic flexibility in clinical populations such as stroke survivors.

Among the limitations of the current study was that almost half of the study participants failed to achieve the *a priori* criteria for valid $\dot{V}O_{2max}$ measurement. This is a common observation in stroke rehabilitation trials, and because of this, many research groups describe the results of graded exercise testing as "peak oxygen uptake" rather than maximum (Letombe et al., 2010; M. Mackay-Lyons, McDonald, et al., 2013; Macko et al., 2005; Rimmer et al., 2000; Tang, Sibley, et al., 2009). However, without a valid assessment of $\dot{V}O_{2max}$, it is difficult to interpret the pre to post changes in graded exercise testing (Poole

& Jones, 2017). Therefore, new exercise testing protocols are needed to improve the validity of $\dot{V}O_{2max}$ measurements in clinical populations such as stroke survivors. As described above, the lack of dietary controls may have influenced outcomes, and future investigations should monitor changes in eating and physical activity behaviors over the study period. Finally, the current study was not powered to determine equivalence between the two interventions. Although the difference in proportions of participants achieving the threshold for the anticipated change in $\dot{V}O_{2max}$ did not reach the level of statistical significance, this data should be interpreted with caution.

3.6 Conclusions

Task-oriented circuit training can replicate the aerobic intensities sustained during traditional ergometer-type exercise training among chronic hemiparetic stroke survivors. However, relatively large proportions of participants in both exercise groups failed to achieve the moderate-intensity aerobic exercise criteria over the 10-week study period. Accordingly, more studies are needed to elucidate the individual variability in sustaining moderate-intensity aerobic workloads among participants with similar levels of impairment. Also, more work is needed to evaluate the extent to which task-oriented circuit training can be used to replicate the outcome observed after ergometer-type aerobic exercise.

Chapter 4: Normobaric hypoxia exposure during treadmill aerobic exercise after stroke: a safety and feasibility study

4.1 Abstract

Objective: To evaluate the safety and feasibility of performing treadmill aerobic exercise in moderate normobaric hypoxia among chronic hemiparetic stroke survivors.

Design: Observational study using convenience sampling.

Setting: Research laboratory in a tertiary rehabilitation hospital.

Participants: Chronic hemiparetic stroke survivors who could walk at least 10-meters with or without assistance and had no absolute contraindications to exercise testing.

Intervention: Participants (3 male and 4 female) were asked to complete three normobaric hypoxia exposure protocols within a single session. First, they were passively exposed to normobaric hypoxia through gradual reductions in the fraction of inspired oxygen (F_IO_2 = 20.9 %, 17.0 %, and 15.0 %) while seated (5-min at each level of F_IO_2). Participants were then exposed to the same reductions in F_IO_2 during constant-load exercise performed on a treadmill at 40% of heart rate reserve. Finally, participants completed 20-min of exercise while intermittently exposed to moderate normobaric hypoxia (5 x 2-min at FIO2= 15.0%) interspaced with 2-min normoxia intervals (F_IO_2= 20.9 %).

Outcome measures: The primary outcome was occurrence of adverse events, which included standardized criteria for terminating exercise testing, blood oxygen saturation (S*p*O2) < 80 %, or acute mountain sickness score > 2. The increased cardiovascular strain

imposed by normobaric hypoxia exposure at rest and during exercise, was evaluated by changes in SpO_2, heart rate (HR), blood pressure, and rating of perceived exertion (RPE).

Results: One participant reported mild symptoms of nausea during exercise in normobaric hypoxia and discontinued participation. No other adverse events were recorded. Intermittent normobaric hypoxia exposure was associated with reduced SpO_2 (MD = -7.4 %, CI: -9.8 to -5.0) and increased HR (MD = 8.2, CI: 4.6 to 11.7) compared to intervals while breathing typical room air throughout the 20-min constant-load exercise period. The increase in HR was associated with a 10 % increase in relative effort. However, reducing F_IO_2 had little effect on blood pressure and RPE measurements.

Conclusion: Moderate normobaric hypoxia appeared to be a safe and feasible method to increase the cardiovascular strain of submaximal exercise in chronic hemiparetic stroke survivors. Future studies evaluating the effects of pairing normobaric hypoxia exposure with existing therapies on secondary prevention and functional recovery are warranted.

4.2 Introduction

Poor cardiorespiratory fitness is characteristic of individuals experiencing the effects of stroke. Measurements taken during the first three months of recovery demonstrate that maximum oxygen uptake values range from 10 to 18 mL min^{-1} kg^{-1} (M. Mackay-Lyons, McDonald, et al., 2013; M. J. Mackay-Lyons & Makrides, 2004; Tang, Sibley, Thomas, McIlroy, & Brooks, 2006). Given the inverse association between cardiorespiratory fitness and future risk of stroke (Pandey et al., 2016) it is perhaps not surprising that these values correspond to the "very poor" category based on normative data (Riebe et al., 2018). However, it is striking that fitness levels among stroke survivors are less than 60% of that reported for age and sex-matched coronary heart disease patients upon completion of cardiac rehabilitation (Banks et al., 2019). Such differences in fitness could be explained by the fact that people with cerebrovascular disease are offered lower-intensity task-oriented rehabilitation compared to people having cardiovascular disease (Hebert et al., 2016). Although relevant to overcome functional limitations, task-oriented therapies offered during stroke rehabilitation provide insufficient cardiovascular stress (Barrett et al., 2018; M. J. MacKay-Lyons & Makrides, 2002)

Important advances are taking place in the field of stroke rehabilitation to enhance the provision of aerobic training (Biasin et al., 2014); specifically transitioning eligible patients with stroke to cardiac rehabilitation (Marzolini, 2018). Feasibility and preliminary

effectiveness of comprehensive cardiac rehabilitation programs has been confirmed among individuals who have experienced a transient ischemic attack or non-disabling minor stroke (Prior et al., 2011). The challenge, however, is adapting such programs for individuals with more severe stroke-related impairments (Tang, Closson, et al., 2009). Indeed, stroke survivors with mild-to-moderate levels of motor impairments can meet the minimal aerobic exercise targets (Marzolini, McIlroy, Oh, & Brooks, 2012) and achieve statistically significant increases in pre-to-post measures of cardiorespiratory fitness upon completion of adapted cardiac rehabilitation programs (Lennon et al., 2008; Marzolini et al., 2012; Marzolini et al., 2014; Tang et al., 2010). However, notably cardiorespiratory fitness remains in the "very poor" category upon completion of adapted cardiac rehabilitation and the training-induced improvements in cardiometabolic risk factors have been inconsistent (Lennon et al., 2008; Marzolini et al., 2014; Tang et al., 2010). Accordingly, new approaches are needed to enhance the effects of physical exercise interventions currently offered to stroke survivors.

Normobaric hypoxia conditioning has the potential to enhance the effects of exercise in stroke survivors. Normobaric hypoxia exposure involves reductions in the fraction of inspired oxygen (F_IO_2) from values recorded near sea-level (F_IO_2= 20.9%) to values that simulate the moderate levels of hypoxia experienced at elevations between 2000 and 3000 m above sea-level (F_IO_2= 17.0 to 15.0%) (Bartsch & Saltin, 2008). During normobaric hypoxia conditioning studies, participants perform submaximal exercise while

breathing the normobaric hypoxia gas mixture (Klug et al., 2018). Since maximum aerobic workloads decrease at a rate of about 7% for every 1000 m increase in altitude (≅ 2% decrease in F_IO_2) (Fulco et al., 1998), the absolute workloads performed in normobaric hypoxia must be reduced to be equivalent to the relative exercise intensity experienced under typical sea-level conditions (Bartsch & Saltin, 2008). In other words, training in normobaric hypoxia is a method to increase the cardiometabolic stress of submaximal exercise without an increase in biomechanical strain (Pramsohler et al., 2017). Interestingly, among overweight/obese participants, exercise completed in normobaric hypoxia conditions resulted in similar (Klug et al., 2018) or even enhanced (Netzer et al., 2008; Wiesner et al., 2010) benefits on cardiometabolic outcomes compared to aerobic workloads matched for relative intensity at sea-level. Clinically, the approximately 15% increase in relative effort during submaximal exercise performed in moderate normobaric hypoxia (Fulco et al., 1998) may provide a unique solution for stroke survivors with diminished ability to perform external work due to hemiparesis. Although preliminary evidence in other clinical populations suggests a synergistic effect of pairing exercise with normobaric hypoxia exposure on metabolic (Mackenzie, Maxwell, Castle, Brickley, & Watt, 2011; Mahler et al., 2018) and functional outcomes (Navarrete-Opazo, Alcayaga, Sepulveda, Rojas, et al., 2017; Navarrete-Opazo, Alcayaga, Sepulveda, & Varas, 2017), more work is needed to translate these findings to stroke survivors. Accordingly, the objective of the current preliminary study was to determine if exposing chronic hemiparetic

stroke survivors to moderate levels of normobaric hypoxia during treadmill aerobic exercise was safe and feasible.

4.3 Methods

4.3.1 Participants

Participants were recruited from a registry of chronic stroke survivors who completed inpatient/outpatient rehabilitation services and recently participated in a rehabilitation trial at our laboratory (NC1674790). Participants had to meet the following inclusion criteria to be considered for the current study: (1) age ≥18 years, (2) ischemic or hemorrhagic stroke >6 months before study enrollment, (3) ability to perform 2-step instruction, (4) and ambulatory with or without aid >10 m. Participants were excluded if they presented with any absolute contraindications for graded exercise testing as described elsewhere (Riebe et al., 2018) or reported a change in physical activity levels (increase or decrease) since their last graded exercise test. The study protocol was approved by the regional Health Research Ethics Board (2018.013) in accordance with the TCPS (II) guidelines (Canadian Institutes of Health Research, 2018) and the declaration of Helsinki (see Appendix B).

4.3.2 Physical Profile

Data collected during the follow-up period of the previous trial, including assessments of stroke severity (National Institute of Health Stroke Scale, and Chedoke McMaster stage of recovery for leg and foot) (Goldstein et al., 1989; Gowland et al., 1993), walking performance, and symptom-limited graded exercise testing, were used in the current study to describe participants' physical profile. As described elsewhere (Ploughman et al., 2019), self-selected walking speed was assessed on an instrumented gait analysis walkway (Zeno Walkway, Protokinetics LLC, PA, USA) and the average of two trials were recorded. Symptom-limited graded exercise tests were performed on either a motorized treadmill (Trackmaster TMX58, Full Vision Inc, KS, USA) with harness support (<10% of body weight, PneuWeight, Pneumex, ID, USA) or a total-body recumbent stepper (T4r, Nustep, LLC, MI, USA) as described previously (L. P. Kelly et al., 2017). Maximum heart rate (HR), maximum oxygen uptake ($\dot{V}O_{2max}$), and the HR corresponding to 40% of $\dot{V}O_{2max}$ were recorded for use in the current study.

4.3.3 Experimental Design

Given the preliminary objectives of this observational study, the aim was to recruit 8 participants (4 females). Study participants were asked to complete three different normobaric hypoxia exposure protocols within a single session. As illustrated in Figure 1., F_IO_2 was manipulated using a hypoxicator (GO2Altitude, Biomedtech Ltd, VIC, Australia)

that continuously pumped air (120 L min^{-1}) into two 120-liter Douglas bags. Gas concentration within the Douglas bags was monitored using an oxygen sensor (Rapidox O_2, Sensotec Ltd, Cambridge, UK), ensuring that the target F_IO_2 was maintained within ± 0.2%. Participants were interfaced with the hypoxicator using a two-way non-rebreathing valve (2700, Hans Rudolph, Kansas, USA) connected to an oro-nasal facemask (series 8900, Hans Rudolph, Kansas, USA), and tubing. Blood pressure (BP; systolic / diastolic), HR (using 12-lead electrocardiography; CardoCard, Nasiff Associates Inc., NY, USA), oxygen saturation (S_pO_2; Massimo SET, CA, USA), and rating of perceived exertion (RPE) (G. A. Borg, 1982) were monitored throughout the three normobaric hypoxia exposure protocols, which are described below. Also, symptoms of acute mountain sickness were recorded at the end of each exposure protocol and again the next morning over the telephone using the Lake Louise Acute Mountain Sickness Scale (Roach et al., 2018).

4.3.3.1 Passive Progressive Normobaric Hypoxia Exposure Protocol

During the first exposure protocol, participants were passively exposed to gradual reductions in F_IO_2 during seated rest. As illustrated in Figure 1A, participants first breathed a gas mixture consistent with typical room air (i.e., normoxia; F_IO_2 = 20.9%) for 5-min and then F_IO_2 was reduced to 17.0% for an additional 5-min and finally reduced to 15.0% for the last 5-min of the passive progressive normobaric hypoxia exposure protocol. Measures of HR, SpO_2, and BP were recorded during the last 30-sec of exposure at the

three levels of F_IO_2 studied. The facemask was removed between each 5-min exposure period to allow time (5-to 10-min) for the adjustment of F_IO_2 within the Douglas bags.

If no adverse events were recorded during passive progressive normobaric hypoxia exposure, participants moved onto the active phases of the study where normobaric hypoxia exposure was paired with constant-load exercise performed on the treadmill with bodyweight supported (~10%) at self-selected walking speed. To determine self-selected walking speed, participants were first familiarized with the treadmill and then asked to choose a speed that they could comfortably maintain for 20 minutes or more. Treadmill incline was then adjusted to achieve a target HR corresponding to 40% of participants heart rate reserve while breathing normoxia room air.

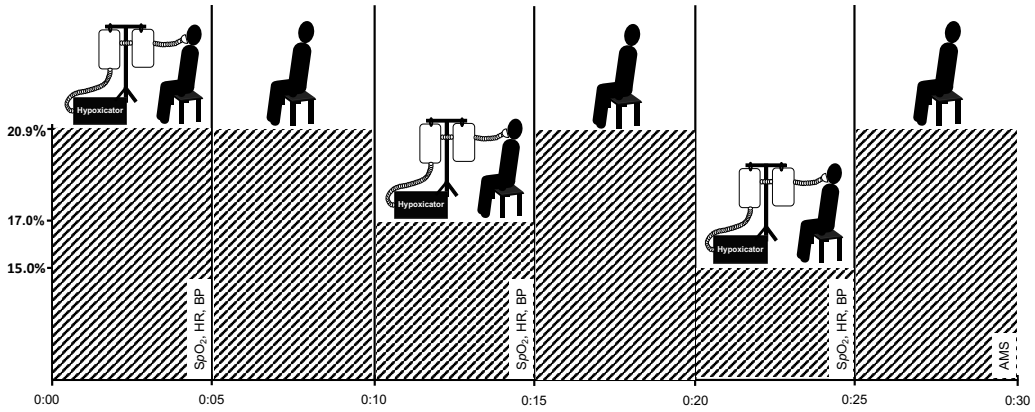
4.3.3.2 Active Progressive Normobaric Hypoxia Exposure Protocol

During the second exposure protocol, participants were exposed to gradual reductions in F_IO_2 while walking on the treadmill at the predetermined treadmill speed and incline. As illustrated in Figure 1B, the same protocol described above was used to progressively increase the level of normobaric hypoxia exposure during treadmill walking in 5-min epochs. Measures of HR, S_pO_2, BP, and RPE were recorded during the last 30-sec of exposure at the three levels of F_IO_2 studied. Again, if no adverse events were recorded, participants moved onto the final exposure protocol.

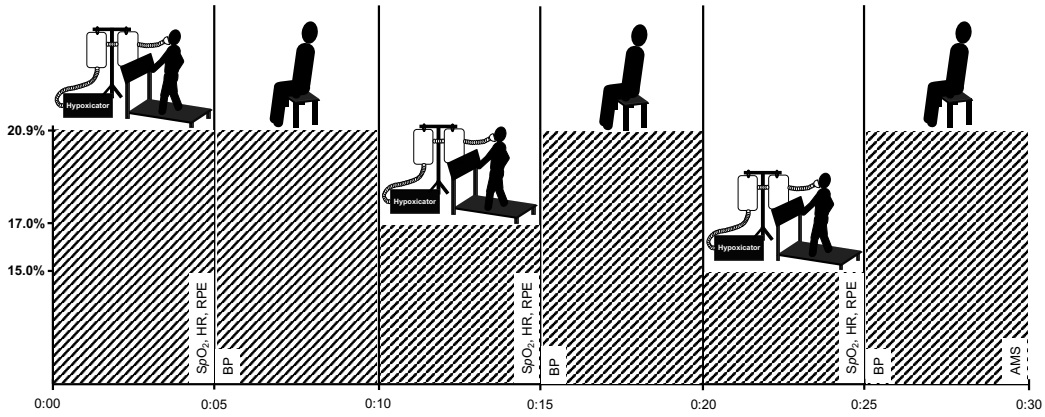
4.3.3.3 Active Intermittent Normobaric Hypoxia Exposure Protocol

During the third exposure protocol, participants walked on the treadmill at the predetermined speed and incline for 20-min while intermittently exposed to 5 x 2-min intervals at F_IO_2= 15% interspaced with 2-min intervals at F_IO_2= 20.9% (see Figure 1C). During active intermittent normobaric hypoxia exposure, gas concentration remained constant within the Douglas bags (i.e., 15.0 ± 0.2%) and a valve was used to switch between room air and moderate normobaric hypoxia every 2-min. Measures of HR and SpO_2 were recorded during the last 30-sec of each 2-min interval.

(A) Passive Progressive Normobaric Hypoxia Exposure



(B) Active Progressive Normobaric Hypoxia Exposure



(C) Active Intermittent Normobaric Hypoxia Exposure

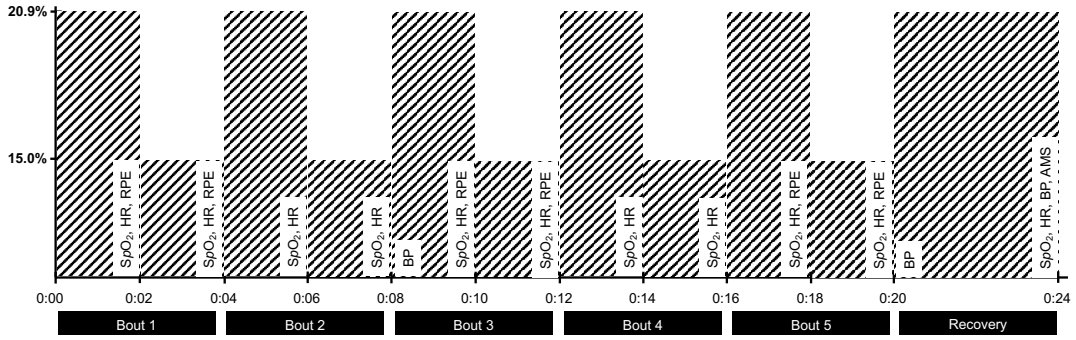


Figure 4-1: Experimental design**.** To evaluate the safety and feasibility of moderate normobaric hypoxia exposure, participants were exposed to gradual reductions in the fraction of inspired oxygen (F_IO_2) during sitting (panel A) and during constant-load treadmill walking (panel B). Then, participants completed 20-min of constant-load treadmill walking while intermittently exposed to normobaric hypoxia (5 x 2-min at F_IO_2= 15.0%) interspaced with intervals of typical room air (normoxia; 5 x 2-min at F_IO_2= 20.9%) (panel C). Each pair of normobaric hypoxia and normoxia intervals were defined as a bout (5-bouts in total). Measures of blood oxygen saturation (SpO_2), heart rate (HR), blood pressure (BP), rating of perceived exertion (RPE), and symptoms of acute mountain sickness (AMS) were monitored throughout the three exposure protocols and recorded at defined intervals as indicated in the figure. A hypoxicator using nitrogen filtration technique was used to manipulate fraction of inspired oxygen in two Douglas bags. Participants were interfaced with the bags using corrugated tubing, non-breathable valve, and an oro-nasal facemask.

4.3.4 Outcome Measures

The primary objective of the current study was to determine if exposing chronic hemiparetic stroke survivors to moderate levels of normobaric hypoxia during treadmill aerobic exercise was safe and feasible. Accordingly, having to stop the protocol due to occurrence of adverse events and circumstances for termination were of primary importance. The normobaric hypoxia exposure periods were terminated according to accepted indications for stopping an exercise test (Riebe et al., 2018) and evidence of acute mountain sickness (Roach et al., 2018). Specifically, the exercise was halted if there was a decrease in systolic blood pressure (< 10 mm Hg) below baseline values or a hypertensive response (systolic > 250 mm Hg or diastolic > 115 mm Hg), a significant change in the electrocardiography tracing (e.g., ST elevation/depression, ventricular tachycardia, premature ventricular contractions, etc.), onset of angina like symptoms, shortness of breath, signs of severe fatigue, or participant requested to stop. Given the anticipated effects of normobaric hypoxia exposure on S_pO_2, especially among individuals treated with beta blockers (Bilo et al., 2011), a cutoff score of 80% was set for exercise termination. Participants could only proceed from one exposure protocol to the next if there was absence of termination indicators. As described above, symptoms associated with acute mountain sickness were also recorded and scores >2 was suggestive of acute mountain sickness (Roach et al., 2018). In terms of feasibility, participants' ability to sustain constant

workloads under moderate normobaric hypoxia was evaluated along with changes in cardiovascular strain.

4.3.5 Statistical Analysis:

Effects of normobaric hypoxia exposure on HR, SpO_2, and BP were evaluated at the levels of F_IO_2 studied during seated and treadmill walking activities. The Shapiro-Wilk test was first performed to determine if the data came from an approximately normal distribution and log transformed if required. Repeated measures one-way ANOVA was used to test for differences at the three levels of F_IO_2 during the passive progressive normobaric hypoxia and active progressive normobaric hypoxia exposure protocols. Repeated measures two-way ANOVA was used to test for differences in HR and SpO_2 response between the 5-intervals of normoxia (F_IO_2= 20.9%) and normobaric hypoxia (F_IO_2= 15.0%) during the active intermittent exposure protocol. Changes in RPE were recorded during the active treatments only and evaluated using the Friedman test and Wilcoxon matched pairs signed rank test during the progressive and intermittent protocols, respectively. Ratio data are reported as mean difference (MD) and 95 % confidence interval (CI), unless otherwise indicated. Ordinal data are reported as the median and range. Statistical significance was set at $p< 0.05$. All statistic tests and figures were prepared using Prism 8 for MacOS (GraphPad Software, CA, USA).

4.4 Results:

Thirteen potential participants were contacted; four declined to participate, one was excluded during the medical examination due to uncontrolled diabetes and peripheral neuropathy, and one participant dropped out prior to the intervention. Characteristics of the remaining seven participants are displayed in Table 1. Participants were on average 5.7 years (SD 0.8) since their first disabling stroke, most often due to ischemia. The cohort had mild to moderate stroke severity (National Institute of Health Stroke Scale; median = 2, range = 0 - 9) (Kwakkel et al., 2010) and incomplete sensori motor recovery of the lower-limb according to the Chedoke-McMaster Stroke Assessment (Gowland et al., 1993) (leg + foot / 14; median = 9.0, range = 4 - 13). Self-selected walking speed was below the 80 cm sec^{-1} threshold set for community ambulation in 3/7 subjects (Duncan et al., 2011; Perry, Garrett, Gronley, & Mulroy, 1995). All participants were receiving treatment for hypertension and most had at least one metabolic comorbidity. Average BMI was 28.5 kg m^{-2} (SD 6.9); corresponding to the overweight category (Riebe et al., 2018). Fitness levels were in the "very poor" to "poor" range (18.7 ml min^{-1} kg^{-1} (SD 5.0)) compared to age and sex matched normative data (Riebe et al., 2018). Maximum HR achieved during the prior symptom-limited graded exercise test was 149 bpm (SD 28), which was within 10% of age predicted values.

Table 4-1: Participant Characteristics

Participant #	1	2	3	4	5	6	7
Age (years)	83	63	57	65	53	73	48
Sex (Male / Female)	F	F	M	F	F	M	M
Weight (kg)	60.0	65.5	71.9	60.0	85.3	90.8	64.9
Stroke type	Ischemic	Hemorrhagic	Ischemic	Ischemic	Hemorrhagic	Ischemic	Ischemic
Time since stroke (years)	5.6	4.9	5.8	6.7	6.6	4.8	5.1
Stroke severity (NIHSS[1]; low 0 to 42 high)	0	2	9	2	5	1	7
Chedoke-McMaster Leg/Foot Impairment (low 7 to high 0)	6/6	5/4	5/3	5/5	5/4	7/6	3/1
Resting Heart Rate	52	55	63	71	88	72	88
Resting BP (mmHg)	130/80	110/60	142/90	110/70	140/80	134/66	90/60
Walking speed (cm sec^{-1})	66.8	103.7	46.7	75.4	83.5	116.3	89.9
$\dot{V}O_{2max}$ (mL min^{-1} kg^{-1})	14.2	25.1	15.0	16.6	14.0	20.3	25.7
Cardiorespiratory fitness category[2]	VP	P	VP	VP	VP	VP	VP
Maximum HR[3]	126	137	105	153	171	168	185
Age predicted Maximum HR	151	120	124	163	171	158	175
Dyslipidemia	Yes	No	Yes	Yes	No	Yes	Yes
Diabetes	No	No	No	Yes	No	Yes	Yes
Hypertension	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Betablocker (yes/no)	No	Yes	Yes	No	No	No	No
Osteoporosis / Osteopenia	Yes	Yes	Yes	Yes	No	No	No

[1]NIHSS= National Institute of Health Stroke Scale; [2]based on age and sex matched normative data published by the American College of Sports Medicine (Riebe et al., 2018), VP= very poor (< 20th percentile), P= poor (< 40th percentile); [3]maximum value recorded during a symptom-limited graded exercise test

All participants were able to complete the passive progressive normobaric hypoxia exposure period and no adverse events were reported. A gradual reduction in S*p*O_2 was observed at rest during exposure to moderate normobaric hypoxia compared to the normoxia condition. The mean difference and 95% confidence interval (CI) were 2.1% (0.9 to 3.4) and 4.6% (1.5 to 7.6) at F_IO_2 equal to 17.0 and 15.0%, respectively. A corresponding increase in resting HR was observed with reductions in F_IO_2 (MD= 4.1 bpm, CI: 1.4 to 6.9 and MD= 4.6 bpm CI: -0.1 to 9.3, respectively). Systolic and diastolic blood pressures remained relatively stable throughout the passive progressive normobaric hypoxia exposure protocol.

Participants were able to maintain constant-load treadmill walking at workloads corresponding to 40% of HRR in normoxia. One participant reported mild symptoms of nausea (acute mountain sickness score = 1) after initiation of exercise at F_IO_2= 17.0% and requested to stop. No adverse events were reported in the remaining participants. As displayed in Figure 2., dose response changes in S*p*O_2 were observed during exercise performed under normobaric hypoxia. Importantly, reductions in S*p*O_2 were above the cutoff score. Corresponding increases in HR were observed at the two levels of F_IO_2 studied. The increased cardiovascular strain imposed by moderate normobaric hypoxia exposure did not alter blood pressure responses to constant-workload exercise. Also, reducing F_IO_2 had little effect on participants RPE during exercise.

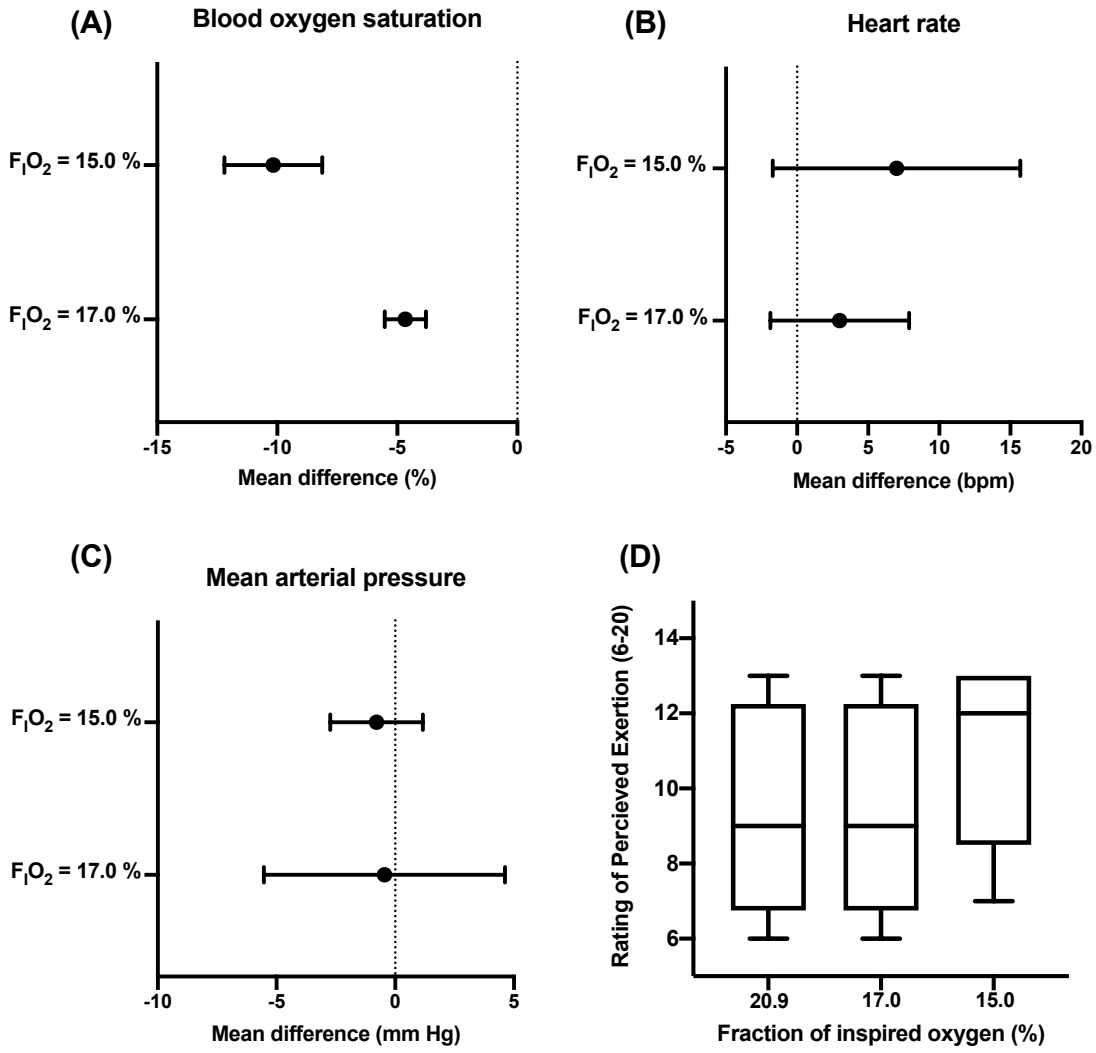


Figure 4-2: Active Progressive Normobaric Hypoxia Exposure. Effects of reducing F_IO_2 on blood oxygen saturation (panel A), heart rate (panel B), mean arterial blood pressure (panel C), and rating of perceived exertion (panel D) during constant workload exercise. Data reported as mean difference and 95% confidence interval for the difference between normoxia (F_IO_2= 20.9%) and the two levels of normobaric hypoxia (F_IO_2 = 17.0, and 15.0%). The box and whisker plots (panel D) report the median along with the 25th and 75th percentiles and range (min to max) at the three levels of F_IO_2 studied.

Participants (n = 6) were able to maintain 20-min of constant-load treadmill walking during intermittent (5-intervals of 2-min) exposure to moderate normobaric hypoxia (F_IO_2 = 15.0%) interspaced with 5-intervals of 2-min at F_IO_2 = 20.9%. No adverse events were reported during active intermittent normobaric hypoxia. As described in Figure 3., pairs of normobaric hypoxia and normoxia exposure were defined as bouts (i.e., 5-bouts in total). A significant group x time effect was observed for reductions in SpO$_2$ during normobaric hypoxia exposure compared to normoxia across the 5-bouts (p= 0.017). Correspondingly, group x time effects were observed for increases in HR during normobaric hypoxia exposure compared to normoxia across the 5-bouts (p= 0.003). Although two participants reported a slightly higher RPE during the first interval in normobaric hypoxia, scores were essentially the same by the final bout (see Figure 3.). No symptoms of headache, nausea, or dizziness/light-headedness were reported the next morning over the telephone.

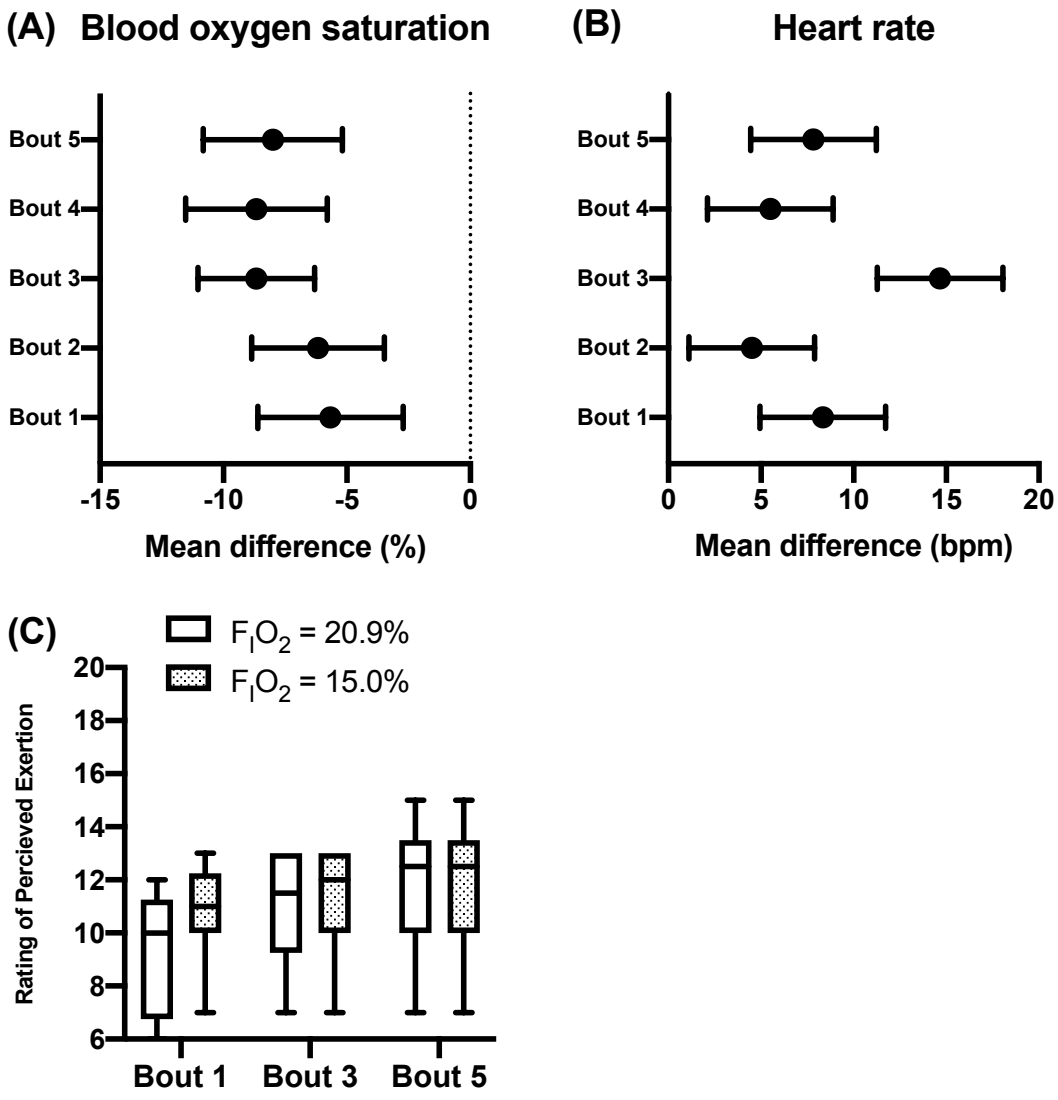


Figure 4-3: Effects of intermittent normobaric hypoxia exposure (F_IO_2= 15.0%) on blood oxygen saturation (panel A), heart rate (panel B), and rating of perceived exertion (panel C) during constant workload exercise. Data reported as mean difference and 95% confidence interval for the difference between 2-min intervals of normoxia (F_IO_2= 20.9%) and normobaric hypoxia (F_IO_2= 20.9%). Each pair of normobaric hypoxia and normoxia intervals were defined as a bout (5-bouts in total). The box and whisker plots (panel C) report the median along with the 25th and 75th percentiles and range (min to max) for rating of perceived exertion during constant workload exercise at the two levels of F_IO_2 studied during bouts 1, 3, and 5.

4.5 Discussion:

The current observational study was undertaken to examine the preliminary safety and feasibility of performing treadmill aerobic exercise under conditions of moderate normobaric hypoxia among chronic hemiparetic stroke survivors. Other than one participant reporting mild symptoms of nausea upon reducing F_IO_2 during exercise, no adverse events were observed during normobaric hypoxia exposure or the morning after. As anticipated, the addition of moderate normobaric hypoxia to constant workload exercise was associated with reductions in SpO_2 and corresponding increases in HR. However, the increased cardiovascular strain had little effect on BP measurements and participants did not perceive the efforts as more demanding, as indicated by RPE scores. The current study provides initial evidence that supports the use of normobaric hypoxia exposure to increase the cardiovascular demands of submaximal exercise in chronic stroke survivors with walking impairments.

Several research reports have evaluated the safety of exposure to environments with reduced oxygen availability, such as terrestrial high altitudes (i.e., hypobaric hypoxia), in older adults with preexisting cardiovascular conditions (Bartsch & Gibbs, 2007; B. D. Levine, 2015; Parati et al., 2018). It is generally accepted that individuals with asymptomatic coronary heart disease who have a sufficiently high exercise capacity (i.e. >6 metabolic equivalents or 21 mL min^{-1} kg^{-1}) are at minimal increased risk during high

altitude trekking (Bartsch & Gibbs, 2007). However, as reflected in the current data, the majority of stroke survivors have cardiorespiratory fitness levels below this threshold (Saunders et al., 2020; Smith et al., 2012). Also, hemiparetic gait is associated with a 1.5 to 2-fold increased energy demand (S. Kramer et al., 2016). The net effect of low cardiorespiratory fitness and increased energy cost of ambulatory activities is a diminished capacity to accommodate changes in aerobic demand. With the goal of developing normobaric hypoxia conditioning protocols appropriate for stroke rehabilitation, we investigated whether chronic hemiparetic stroke survivors could tolerate treadmill walking while progressively and intermittently exposed to reductions in F_IO_2. Arterial oxygen saturation, electrocardiography, blood pressure, and rating of perceived exertion were recorded during constant-load exercise to monitor for signs of excessive cardiovascular stress. Unremarkable changes in blood pressure and electrocardiography tracings were recorded during normobaric hypoxia exposure. These outcomes are consistent with data collected in a relatively large cohort (N=97) of older adults upon initial ascent to high altitude (Erdmann, Sun, Masar, & Niederhauser, 1998). As anticipated, normobaric hypoxia exposure reduced SpO_2 both at rest and during constant workload exercise. However, SpO_2 values remained above the cutoff score in all participants, including those prescribed beta blockers, which has previously been identified as a potential risk among individuals receiving antihypertensive treatment (Bilo et al., 2011). Mild symptoms of nausea were reported by one participant, which dissipated shortly after stopping the

exercise protocol. As reported in the Supplementary Table 1 (see Appendix C), this participant (#5) selected a treadmill speed above the target workload, and it is unclear if the symptoms of nausea were a result of normobaric hypoxia itself or the high-intensity nature of such workloads when paired with normobaric hypoxia. No symptoms of headache, nausea, or dizziness/light-headedness were reported in the remaining participants. Collectively, findings from this preliminary study support that performing submaximal exercise under conditions of moderate normobaric hypoxia provides no additional risk beyond that of exercise in typical environments among chronic hemiparetic stroke survivors.

With respect to feasibility, participants were able to sustain 20-min of constant workload exercise while intermittently exposed to moderate normobaric hypoxia. Although the treadmill speed and incline were maintained throughout active intermittent normobaric hypoxia, average HR was 7.8 bpm higher during the five 2-min intervals of normobaric hypoxia exposure. This corresponded to a 10% increase in relative effort based on participants' HRR. Although lower than the anticipated 15% increase in relative effort for the level of F_IO_2 studied (Fulco et al., 1998), the change in relative effort is likely underestimated given that HRR is diminished under conditions of reduced oxygen availability (Bartsch & Gibbs, 2007). It is equally important to point out that HR and $Sp O_2$ began to recover between intervals, which suggest that participants were able to accommodate the increased cardiovascular stain of moderate normobaric hypoxia exposure

during submaximal exercise. Furthermore, participants did not perceive the workloads as more demanding when performed at reduced F_IO_2. The lack of effect on RPE is consistent with the results of a previous placebo-controlled trial that reported participants were unable to accurately predict whether or not they performed submaximal exercise in normobaric hypoxia or under typical sea level conditions (Netzer et al., 2008). Accordingly, normobaric hypoxia exposure appears to be a feasible method of increasing the cardiovascular strain of submaximal exercise in chronic hemiparetic stroke survivors.

The focus of the current study was on using normobaric hypoxia exposure to increase the cardiovascular strain of submaximal exercise among chronic hemiparetic stroke survivors. However, normobaric hypoxia exposure may enhance the effects of submaximal exercise independent of changes in relative exercise intensity. For instance, in a recent randomized trial among overweight/obese females, metabolic benefits were enhanced when normobaric hypoxia was combined with 12-weeks of high-intensity interval training (Camacho-Cardenosa et al., 2018). This is consistent with normobaric hypoxia conditioning studies that report similar (Klug et al., 2018) or enhanced (Netzer et al., 2008; Wiesner et al., 2010) effects on cardiometabolic outcomes at lower absolute workloads. Furthermore, intermittent normobaric hypoxia exposure enhanced the effects of locomotor training on walking speed, endurance, and dynamic balance among individuals with incomplete spinal cord injury (Navarrete-Opazo, Alcayaga, Sepulveda, Rojas, et al., 2017; Navarrete-Opazo, Alcayaga, Sepulveda, & Varas, 2017). The latter

studies incorporated more severe levels of normobaric hypoxia (F_IO_2= 9.0%) immediately prior to bodyweight supported treadmill training, which suggests a priming effect of normobaric hypoxia exposure. Although mechanisms underlying the synergistic effects of pairing normobaric hypoxia exposure with exercise are yet to be elucidated, both acute physiological responses and more prolonged acclamatory processes are likely involved (Hochachka, Rupert, & Monge, 1999). For example, during constant workload exercise performed in hypoxia there is an increased mobilization of carbohydrate and lipid energy substrates compared to exercise performed in normoxia at the same absolute and relative workloads (F Peronnet et al., 2006). Despite the fact that increased mobilization of both energy substrates is characteristic of hypoxia exposure, substrate partitioning is shifted toward carbohydrate energy sources during exercise in hypoxia and lipid oxidation is enhanced during the post exercise recovery period under normoxic conditions (L.P. Kelly & Basset, 2017). Such metabolic perturbations during and in-between individual bouts of exercise may help to explain the similar or enhanced effects of normobaric hypoxia exposure on adiposity and metabolic profile among sedentary overweight adults at a lower total energy expenditure of exercise (Haufe et al., 2008; Netzer et al., 2008; Wiesner et al., 2010). Further, hypoxia-induced increases in the expression of transcriptional factors including hypoxia-inducible factor-1alpha (HIF-1 alpha) and proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1 alpha) have been linked to improvements in insulin sensitivity and skeletal muscle lipid metabolism after normobaric hypoxia

conditioning, respectively (Haufe et al., 2008; Wiesner et al., 2010). Normobaric hypoxia exposure also increases expression of brain derived neurotrophic factor and its receptor tyrosine kinase receptor-B (TrkB)(Dale, Ben Mabrouk, & Mitchell, 2014), which is reasoned to explain the beneficial effects of intermittent hypoxia on ambulatory function among individuals with incomplete spinal cord injury(Navarrete-Opazo, Alcayaga, Sepulveda, Rojas, et al., 2017). Given the benefits reported in other clinical populations and the multiple potential mechanisms underlying acute and more prolonged physiological responses, studies investigating the dose response effects of pairing normobaric hypoxia with task-oriented activity after stroke are warranted.

There are several methodological considerations that must be discussed. Firstly, the current study was conducted in a small convenience sample of chronic stroke survivors. This cohort was chosen because of their previous experience with aerobic exercise and the fact that they were able to achieve moderate intensity workloads without adverse events in a previous trial. In order to prepare for future studies, we needed to demonstrate that the additional risk associated with normobaric hypoxia exposure was proportional to its potential benefits. Secondly, we exposed participants to a narrow range of normobaric hypoxia both at rest and during a single constant workload. This dose of normobaric hypoxia exposure was chosen because of previous intervention studies conducted in sedentary populations that demonstrated favorable outcomes when submaximal aerobic exercise was paired with similar reductions in F_IO_2 (Camacho-Cardenosa et al., 2018;

Fernandez Menendez et al., 2018; Haufe et al., 2008; Wiesner et al., 2010). Given the range of HR and SpO_2 responses observed and the fact that perception of effort was not influenced by normobaric hypoxia exposure, this cohort likely could have tolerated even further decreases in F_IO_2 and/or increases in absolute workload. Also, decreases in SpO_2 during exercise performed in normobaric hypoxia were highly variable between participants and individual adjustments in F_IO_2 may be required to ensure similar levels of cardiovascular and metabolic stress between participants (Lee & Thake, 2018).

4.5.1 Conclusion:

The current preliminary study provides initial evidence that moderate normobaric hypoxia exposure is a safe and feasible method to increase the cardiovascular strain of submaximal exercise after stroke. Scientific evidence collected over the last three decades indicates that stroke survivors can respond positively to aerobic exercise training (Saunders et al., 2020). However, the doses of aerobic exercise studied thus far are insufficient to enhance cardiorespiratory fitness to more normal and low risk levels. Stroke-related impairments and comorbid health conditions are significant barriers to sustaining workloads associated with moderate intensity aerobic exercise in this population (Biasin et al., 2014; Moncion et al., 2020). Accordingly, normobaric hypoxia exposure may be an effective strategy to enhance the effects of aerobic exercise training on cardiorespiratory fitness, secondary prevention, and functional recovery after stroke. Future studies are

needed to confirm the results of the current study and to determine the most appropriate protocols for pairing normobaric hypoxia exposure with physical exercise in large representative samples of stroke survivors at different stages of recovery.

Chapter 5: Summary

5.1 Introduction

Physical inactivity is a significant threat to individuals' health and quality of life in our modern societies. Population health directives focused on decreasing sedentary behaviors and promoting active communities form the foundation of our fight against the increasing prevalence of non-communicable diseases. However, for clinical populations such as stroke survivors, targeted solutions are likely required to reverse the consequences of previous physical inactivity. The "very poor" levels of cardiorespiratory fitness observed among stroke survivors across the continuum of recovery is a direct reflection of previous and ongoing physical inactivity. With the intent of developing aerobic exercise interventions appropriate for use during stroke rehabilitation, the current thesis had four aims: 1) design a task-oriented circuit training protocol that imposed at least moderate-intensity aerobic workloads over a 30-min exercise session without the use of ergometers or other specialized equipment, 2) evaluate the feasibility of sustaining moderate-intensity aerobic workloads over a 10-week intervention period using the task-oriented circuit-training protocol, 3) investigate the preliminary effects of our task-oriented circuit-training protocol on cardiorespiratory fitness and metabolic profile among chronic hemiparetic stroke survivors, and 4) evaluate the safety and feasibility of pairing moderate normobaric hypoxia exposure with treadmill aerobic exercise as a means to increase the cardiovascular

strain of submaximal exercise. A summary of the primary research findings and resulting conclusions are presented first. Then, recommendations for future research and contributions to knowledge are discussed.

5.2 Research Objectives

The first study, presented in Chapter 2, demonstrated that organizing task-oriented activities into 3-min circuits that paired more metabolically demanding tasks with less demanding ones was an effective method to sustain moderate-intensity aerobic workloads over a single 30-min session. The protocol was described as intermittent functional training because participants switched between functional tasks within each circuit, and rest periods were incorporated throughout the exercise session. The goal was to achieve a target heart rate of 30 to 50 beats per minute above resting while engaging in task-oriented activities typically employed during formalized stroke rehabilitation. The advantages of such exercise modalities include that specialized equipment is not required, tasks are individualized to impairments, and progression can be achieved by increasing difficulty of movement rather than only increasing the target HR.

The second and third research objectives were evaluated through parallel groups randomized comparative study design that recruited 40 chronic hemiparetic stroke survivors. Participants were randomized to complete 30-sessions of intermittent functional training or treadmill aerobic exercise training at workloads associated with 40 to 60% of

heart rate reserve. Similar proportions of participants in both groups sustained workloads related to moderate-intensity aerobic exercise over the 10-week study period. Accordingly, the intermittent functional training protocol was a feasible method to provide moderate-intensity aerobic exercise training among chronic hemiparetic stroke survivors. Its effects on cardiorespiratory fitness and metabolic profile were less clear and will require future investigation. Differences in proportions of participants achieving the *a priori* threshold for meaningful change in cardiorespiratory fitness did not reach the level of statistical significance. However, within-group improvements in fitness were demonstrated for the treadmill group only. In either case, the workloads sustained during both exercise interventions were insufficient to cause a categorical shift in cardiorespiratory fitness based on normative data (i.e., from "very poor" to "poor" or even "good") (Riebe et al., 2018). Similarly, small changes in systemic inflammation (C-reactive protein), lipid profile, short-term glycemia (fructosamine), and resting whole-body energy metabolism were observed over the study period. Based on the above outcomes, much higher dosages of aerobic exercise over more extended periods may be required to restore cardiorespiratory fitness to more normal and low-risk levels among individuals recovering from a stroke.

The final study was designed to evaluate the safety and feasibility of performing submaximal exercise under conditions of moderate normobaric hypoxia among chronic hemiparetic stroke survivors. Concerning safety, participants were continuously monitored for adverse events during normobaric hypoxia exposure, which included standard exercise

termination criteria and symptoms associated with acute mountain sickness. One participant reported mild symptoms of nausea (i.e., not indicative of acute mountain sickness) during exercise in moderate normobaric hypoxia and discontinued the protocol. Symptoms dissipated shortly after stopping the activity, and no adverse events were observed in the remaining participants. In terms of feasibility, participants maintained the constant absolute workload (i.e., same treadmill speed and incline) under conditions of normoxia and moderate normobaric hypoxia. Pairing moderate normobaric hypoxia with the submaximal exercise caused an 8.2 bpm (CI: 4.6 to 11.7) increase in heart rate, which was associated with a 10% increase in relative effort. The increased cardiovascular strain had little effect on arterial blood pressure measurements, and participants did not perceive the workloads as more difficult in normobaric hypoxia according to the rating of perceived exertion data. Collectively, this data suggests that moderate normobaric hypoxia was a safe and feasible method to increase the cardiovascular strain of submaximal exercise among chronic hemiparetic stroke survivors.

5.3 Recommendations

As an initial step, we designed the intermittent functional training protocol and evaluated its feasibility and preliminary effectiveness among chronic hemiparetic stroke survivors. However, the longer-term objective was to create a moderate-intensity aerobic exercise protocol that could be employed during subacute rehabilitation and continue to be

used once patients transitioned into the community after discharge from formalized care. Accordingly, the intermittent functional training protocol incorporated real-world task-oriented activities typically employed during inpatient/outpatient stroke rehabilitation. The difference between task-oriented activities offered during usual stroke care and how they are included during intermittent functional training is a shift of focus from quality to quantity of movement. For instance, when completing a task such as moving from sitting to standing, the intermittent functional training emphasized repetition to elevate heart rate and focused less on symmetry and precision of joint movement. Future studies are needed to determine at what point during subacute rehabilitation it is appropriate to initiate such task-oriented circuit training protocols. Also, more studies are required to evaluate the dose-response effects of intermittent functional training and the extent to which it could be used to replicate the effects of more traditional ergometer-type aerobic exercise. Finally, future studies are warranted to investigate the feasibility and effectiveness of such task-oriented circuit training protocols when implemented as part of a home-based exercise program or telerehabilitation service.

Pairing normobaric hypoxia exposure with submaximal exercise can enhance multiple outcomes important for secondary prevention and functional recovery after stroke. However, more work is needed before the results presented in Chapter 4 can be applied to the broader stroke population. Firstly, studies that include larger sample sizes of participants with less experience in aerobic exercise and are at earlier stages of recovery

are required. Secondly, studies should investigate the effects of normobaric hypoxia exposure at rest (i.e., passive) and in combination with exercise before, during, and after exposure compared to standard care. Finally, more studies are needed to determine the most appropriate types of activity (i.e., task-oriented, ergometers, whole-body, etc.) to pair with normobaric hypoxia and how the type of activity could influence outcomes.

5.4 Contributions to Knowledge

Among the first studies to investigate the effects of moderate-intensity aerobic exercise training on cardiorespiratory fitness after stroke was published nearly three decades ago by Potempa et al. (1995). The authors reported relatively large treatment effects on cardiorespiratory fitness and provided initial data linking increases in aerobic capacity with improvements in sensorimotor recovery among chronic hemiparetic stroke survivors. Since then, numerous studies have reproduced the effects of aerobic exercise training on cardiorespiratory fitness among stroke survivors in the subacute (Letombe et al., 2010; M. Mackay-Lyons, McDonald, et al., 2013; Stoller et al., 2015; Tang, Sibley, et al., 2009) and more chronic (Chu et al., 2004; Globas et al., 2012; Ivey et al., 2007; Ivey et al., 2015; Jin et al., 2013; Macko et al., 2005; Munari et al., 2018; Pang et al., 2005; Rimmer et al., 2009; Rimmer et al., 2000; Tang et al., 2014) phases of recovery. However, the challenge has been translating these findings into clinical practice where stroke survivors remain very sedentary (Barrett et al., 2018; Bernhardt et al., 2004). Among the barriers to

incorporating aerobic exercise during inpatient/outpatient rehabilitation services is a lack of access to ergometers and the adaptive equipment needed to accommodate stroke-related impairments (Biasin et al., 2014). The intermittent functional training protocol, described in chapters two and three, provides a framework for organizing task-oriented activities routinely offered during formalized rehabilitation in such a way to achieve moderate-intensity aerobic workloads. Although more work is needed to determine the optimal dose of intermittent functional training and investigate its effects on stroke survivors at earlier stages of recovery, such task-oriented protocols provide a practical tool to make moderate-intensity aerobic exercise accessible across the continuum of stroke recovery.

Although not an anticipated outcome, half of chronic hemiparetic stroke survivors randomized to treadmill aerobic exercise training failed to sustain the moderate-intensity criteria over the intervention period (Chapter 3). This outcome is consistent with the challenges reported among subacute stroke survivors during inpatient rehabilitation in their ability to reach prescribed aerobic exercise targets (Biasin et al., 2014). Nevertheless, we observed within-group changes in cardiorespiratory fitness after treadmill aerobic exercise training comparable to previous reports (Ivey, Macko, Ryan, & Hafer-Macko, 2005; Ivey et al., 2007; Macko et al., 2005; Macko et al., 2001). A deeper inspection of the results reveals that the statistically significant pre-to-post chances in cardiorespiratory fitness were unlikely to have a meaningful impact on cardiometabolic risk profile as fitness levels remain in the "very poor" category. Accordingly, much higher amounts of physical exercise

may be required to restore more normal and low-risk levels of cardiorespiratory fitness among stroke survivors.

To date, normobaric hypoxia conditioning studies have incorporated lower absolute workloads under simulated altitude conditions to match relative exercise intensities in typical sea-level states. Studies employing these methods have reported similar (Klug et al., 2018) or enhanced (Netzer et al., 2008; Wiesner et al., 2010) effects of moderate normobaric hypoxia exposure on cardiometabolic outcomes in overweight/obese subjects. Given the inconsistent results, it has been argued that normobaric hypoxia exposure provides little benefit beyond the effects of the exercise itself (Klug et al., 2018). However, we must acknowledge that the reduced absolute workloads imposed during normobaric hypoxia exposure result in a lower total energy expenditure of exercise. Accordingly, a lack of difference between groups is suggestive of a positive outcome. For clinical populations such as hemiparetic stroke survivors, normobaric hypoxia exposure offers the means to amplify the cardiometabolic stress of submaximal exercise without increasing the external workload. As reported in Chapter 4, chronic hemiparetic stroke survivors tolerated constant-load treadmill walking in moderate normobaric hypoxia, which was associated with a 10% increase in relative intensity compared to the same activity performed under typical sea-level conditions. Notably, the increased cardiovascular strain was not associated with adverse events, and participants did not perceive the workloads as more

demanding. This study was among the first to pair normobaric hypoxia exposure with submaximal exercise among stroke survivors.

While the intermittent functional training and normobaric hypoxia conditioning protocols are novel methods to provide aerobic exercise training after stroke, they are intended to be incorporated into a progressive rehabilitative strategy rather than stand-alone solutions. As presented in the literature review of Chapter 1, current aerobic exercise recommendations after stroke are not sufficient to increase cardiorespiratory fitness to more normal and low-risk levels. In fact, the simple linear regression model provided estimates that current recommendations will need to be multiplied by a factor of 10 in order to increase fitness enough to reduce cardiovascular risk. Recent evidence indicates that dedicated rehabilitation units are making progress on incorporating current best practice guidelines for aerobic exercise after stroke (Nathoo et al., 2018). However, it is questionable that a single exercise prescription of 150 minutes of moderate-intensity physical activity weekly will be sufficient to optimize functional outcomes and have a meaningful effect on secondary prevention after stroke. Accordingly, models for progressing the volume and intensity of activity according to individuals' phase of recovery are needed to realize the true potential of aerobic exercise training after stroke. Using periodization methodologies typically employed to prepare elite athletes for competition, we developed a model for progressing the volume and intensity of aerobic exercise throughout the first three months of stroke recovery (Ploughman & Kelly, 2016). Although

this model needs to be validated and extended to include stroke survivors in more chronic phases of recovery, it provides a starting point to create solutions that can significantly impact individual health and quality of life.

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Appendix A: Ethics Clearance for Studies Presented in Chapters 2 and 3

HREB

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

August 07, 2018

Dear Mr. Kelly:

Researcher Portal File # 20190137
Reference # 2018.082

RE: "Effects of Aerobic Exercise Training on Cerebral/ Cardiovascular Risk in Chronic Stroke Survivors "

Your application was reviewed by a sub-committee of the Health Research Ethics Board (HREB) via a delegated review process. **Ethics approval** of this research study has been granted for one year effective August 7, 2018. This ethics approval will be reported to the HREB at the next scheduled meeting.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Research proposal, approved
- Excel Record Sheet version 1 April 26, approved
- Letter to data custodian, approved
- Budget, approved

MARK THE DATE

This ethics approval will lapse on August 8, 2019. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event Form.

If you do not submit the completed Ethics Renewal form prior to date of renewal:

- **You will no longer have ethics approval**
- You will be required to stop research activity immediately
- You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again
- Lapse in ethics approval **may result in interruption or termination of funding**.

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; to **Research Grant and Contract Services** should your research depend on funding administered through that office.

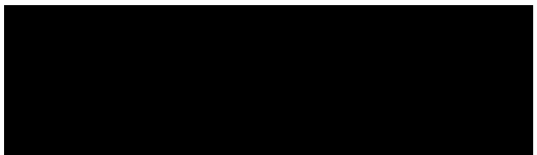
Modifications of the protocol/consent are not permitted without prior approval from the HREB. **Implementing changes in the protocol/consent without HREB approval may result in your ethics approval being revoked, meaning your research must stop.** Request for modification to the protocol/consent must be outlined on an amendment form available on the Researcher Portal website as an Event Form and submitted to the HREB for review. Please refer to the attached guidance document regarding on-going reporting requirements to the HREB.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval of the HREB.

We wish you every success with your study.

Sincerely,



Dr. Elizabeth Dicks (Co-Chair, Non-Clinical Trials Health Research Ethics Board)

CC: Dr. Michelle Ploughman

Appendix B: Ethics Clearance for the Study Presented in Chapters 4

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

April 11, 2018

Dear Mr. Kelly:

Researcher Portal File # 20181597
Reference # 2018.013

RE: "Altitude training to break through the recovery plateau after stroke: Phase I pilot study"

This will acknowledge receipt of your correspondence.

This correspondence has been reviewed by the Chair under the direction of the Health Research Ethics Board (HREB). ***Full board approval*** of this research study is granted for one year effective **March 1, 2018**.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Research proposal, approved
- Telephone script, version 3, approved
- List of variables, approved
- List of variables (Secondary data from HREB 13.218),approved
- Letter of request, approved
- Budget, approved
- Physical Activity Readiness Medical Examination, approved
- Record sheet, approved
- Lake Louise Score, approved

MARK THE DATE

This approval will lapse on March 1, 2019 . It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event form.

If you do not return the completed Ethics Renewal form prior to date of renewal:

- ***You will no longer have ethics approval***
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*
- *Lapse in ethics approval* ***may result in interruption or termination of funding***

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; **to Research Grant and Contract Services** should your research depend on funding administered through that office.

Modifications of the protocol/consent are not permitted without prior approval from the HREB. Implementing changes without HREB approval may result in your ethics approval being revoked, meaning your research must stop. Request for modification to the protocol/consent must be outlined on an amendment form (available on the Researcher Portal website as an Event form) and submitted to the HREB for review.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval of the HREB.

We wish you every success with your study.

Sincerely,

[redacted]

Ms. Patricia Grainger (Chair, Non-Clinical Trials Health Research Ethics Board)
Dr. Joy Maddigan (Vice-Chair, Non-Clinical Trials Health Research Ethics Board)

CC: Dr. Michelle Ploughman

Appendix C: Supplementary Table 1.

Table 5-1: Constant workload exercise and heart rate responses at the three levels of fraction of inspired oxygen studied during active progressive normobaric hypoxia exposure

Participant #	**1**	**2**	**3**	**4**	**5**	**7**	**8**
Self-selected treadmill speed (km hr^{-1})	2.3	2.3	1.9	1.3	1.6	4.8	2.9
Treadmill incline (%)	4	0	0	0	0	0	5
Target HR GXT (bpm)[1]	82	88	80	104	121	110	127
Target HR Age (bpm)[2]	92	81	87	108	121	106	123
Average HR at F_IO_2 = 20.9% (bpm)	84	82	81	112	145	121	118
Average HR at F_IO_2 = 17.0% (bpm)	84	88	81	112	-	132	120
Average HR at F_IO_2 = 15.0% (bpm)	89	90	81	116	-	144	120

[1]40 % of maximal HR recorded during graded exercise test; [2]40 % of age predicted maximal HR; F_IO_2 = fraction of inspired oxygen