

SINGLE LIMB EXERCISE INFLUENCES CARDIOVASCULAR FUNCTION  
FOLLOWING STROKE: "A ONE-SIDED VIEW"

BY

Sandra Anne Billinger  
M.S. University of Kansas Medical Center, Physical Therapy  
B.S. Fort Hays State University, Physical Education

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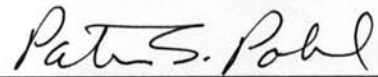
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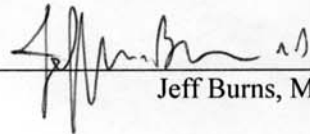
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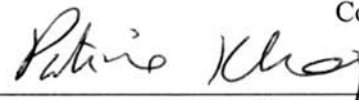
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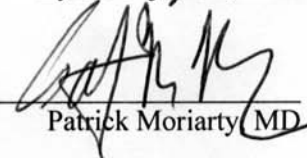
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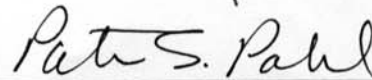
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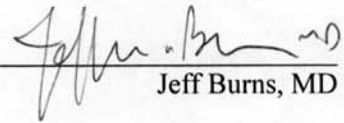
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Patrick Moriarty MD



Patricia Pohl, PT, Ph.D



Jeff Burns, MD

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## **Abstract**

Despite the recommendations of health care professionals, the research community and even pharmaceutical companies, exercise remains a neglected daily regimen for most individuals. Very simply, exercise is any activity that engages our muscles and increases oxygen delivery and uptake with the goal of improving cardiorespiratory health. As physical therapists, we prescribe and encourage exercise training for our patients. For those individuals with neurological deficits such as stroke, the complexity of exercise prescription and training becomes significantly more difficult. Many questions come to mind such as what modality will work with various neuromuscular deficits, will the exercise response be normal or abnormal, and what types of exercise training will improve cardiovascular control and cardiorespiratory fitness. This dissertation explores the central and peripheral cardiovascular responses of an exercise training program using the hemiparetic limb after stroke. Two primary questions guided this dissertation project. First, does single limb exercise (SLE) training improve femoral artery blood flow in the hemiparetic limb? Second, what is the effect of SLE on the central and peripheral cardiovascular system?

Before we could address these questions, we needed an exercise modality that would accommodate stroke-related deficits. Obtaining cardiorespiratory fitness values from a maximal effort graded exercise test has been challenging in the post-stroke population. Previous studies have reported that traditional modalities such as the cycle or treadmill prove difficult secondary to neuromuscular and balance deficits. To address these problems, we developed an exercise test for a total body recumbent stepper (TBRS) and assessed its validity and reliability in healthy individuals. Next, participants with stroke were recruited to examine the feasibility and validity of a modified version of this exercise test (mTBRS-XT). These individuals performed two exercise tests on separate days: one using the mTBRS-

XT and one on the cycle ergometer. We reported that individuals post-stroke with varying levels of lower extremity motor performance could perform the mTBRS-XT. In addition, cardiorespiratory fitness values were higher using the all-extremity exercise test, implying a more accurate description of peak oxygen uptake.

The cardiovascular system continually adjusts to changes in position and to meet the body's needs during dynamic movements and exercise. These vascular changes occur to maintain pressure and regulate blood flow based on the metabolic demands of the body (rest vs exercise). Previous literature suggests that decreased oxygen consumption combined with physical inactivity can alter the vascular composition and blood flow in the lower extremities. However, femoral artery adaptations such as reduced diameter, slower blood flow velocity and increased wall thickness in the hemiparetic limb in people post-stroke have not been previously investigated. Therefore, we sought to examine whether the hemiparetic lower extremity demonstrates vascular changes in the femoral artery when compared to the less affected side. To address this question, seventeen people with chronic stroke had Doppler ultrasound imaging to bilateral femoral arteries. Comparisons between the less affected and hemiparetic limb were interesting in that the femoral artery in the hemiparetic limb demonstrated vascular changes. This may be indicative of reduced oxygen consumption associated with decreased use.

Next, we focused on an exercise intervention as a method for improving femoral artery blood flow. Human research in both healthy and clinical populations has reported increased arterial blood flow and diameter in response to exercise. Twelve people with stroke participated in a 4-week single limb exercise (SLE) training intervention using the hemiparetic limb. After SLE, the hemiparetic limb increased both femoral artery diameter and blood flow. No significant changes were observed in the non-trained limb. These data

support previous literature that suggests an exercise intervention improves arterial blood flow.

Cardiorespiratory fitness can be evaluated during a maximal effort graded exercise test to obtain peak oxygen uptake ( $\text{VO}_2$  peak) or during submaximal exercise to assess oxygen uptake at a specific workload/workrate. Submaximal performance was evaluated during Days 1 and 12 during SLE.  $\text{VO}_2$  peak was obtained during an all-extremity maximal effort graded exercise test using the mTBRS-XT. For the 12 participants, SLE had a greater effect on oxygen uptake during submaximal work than  $\text{VO}_2$  peak. This finding illustrates the hemiparetic limb may have become more efficient (decreased energy expenditure) during exercise.

In conclusion, individuals with stroke with varying levels of lower extremity motor function and vast ranges in time post-stroke demonstrated femoral artery adaptations in the hemiparetic limb. A focused training intervention such as single limb exercise, which encourages use of the hemiparetic limb only, was beneficial for improving peripheral cardiovascular function.

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*“Optimism is the faith that leads to achievement.”- Helen Keller*

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## **Chapter 1**

### Introduction

## 1.1 Overview

Stroke is a leading cause of death and disability for older adults in the United States with approximately 700,000 new strokes occurring each year.(AHA, 2002; CDC, 1996) It is anticipated that the incidence of stroke will continue to rise as a result of an increasing elderly population and sedentary lifestyle.(Gordon et al., 2004) While current literature continues to support the benefits of exercise after stroke,(Gordon et al., 2004) the evidence regarding the most effective modalities and exercise prescription remains unclear.(Sibley, Tang, Brooks, Brown, & McIlroy, 2008) Despite rehabilitative efforts, most people after stroke will continue to experience deficits that can affect exercise performance.(Taub et al., 2006) These can include hemiparesis, decreased postural control, and neuromuscular incoordination of the limbs. Functional mobility and exercise training after stroke presents many challenges due to an asymmetrical gait pattern, decreased walking speed and increased energy expenditure during activity.(Macko, DeSouza et al., 1997; Macko et al., 2005; Silver, Macko, Forrester, Goldberg, & Smith, 2000) Ironically, most people post-stroke will try to compensate for these deficits by relying on the less affected limb.(Chen, Chen, Chen, Fu, & Wang, 2005; Landin, Hagenfeldt, Saltin, & Wahren, 1977; Sibley et al., 2008)

Despite the evidence that demonstrates increased use of the less affected limb, most therapeutic interventions consist of bilateral activities such as treadmill training (Duncan et al., 2003; Kelly, Kilbreath, Davis, Zeman, & Raymond, 2003; Macko, DeSouza et al., 1997; Macko et al., 2005; J. H. Rimmer, Braunschweig et al., 2000; J. H. Rimmer, Riley, Creviston, & Nicola, 2000; Silver et al., 2000; Teixeira da Cunha Filho et al., 2001) or cycle ergometry.(Duncan et al., 2003; Potempa et al., 1995; J. H. Rimmer, Braunschweig et al., 2000; J. H. Rimmer, Riley et al., 2000) These modalities are used to improve aerobic fitness despite the fact that most individuals post-stroke prefer to use their less affected limb, which



may contribute to the metabolic and muscular changes in the hemiparetic limb.(Landin et al., 1977) After stroke, bilateral aerobic exercise has been effective for improving overall central parameters of cardiorespiratory fitness such as maximal heart rate and peak oxygen consumption.(Duncan et al., 2003; Macko et al., 2001; Teixeira da Cunha Filho et al., 2001)

However, peripheral mechanisms may be impaired as evidenced by decreased leg blood flow in the affected limb during rest and exercise.(Ivey, Gardner, Dobrovolny, & Macko, 2004; Landin et al., 1977) Peripheral cardiovascular training effects that occur from exercise are uncertain. With the understanding that individuals post-stroke primarily use the less affected limb, an intervention using bilateral exercise may diminish the expected vascular outcomes associated with exercise training. Therefore, the primary purpose of the present work is to determine the impact of single limb exercise on cardiorespiratory fitness and central and peripheral cardiovascular adaptations in the hemiparetic limb in chronic stroke. As a result of this work, we hope to obtain a better understanding of how cardiovascular changes may affect their daily activity performance and provide a therapeutic framework for rehabilitation professionals.

## **1.2 Cardiorespiratory Fitness**

Cardiorespiratory fitness, or aerobic fitness, is a term used to describe the ability of the circulatory and respiratory systems to supply energy and oxygen to the working muscles during continuous physical activity. Since individuals with low levels of cardiorespiratory fitness have an increased risk for death,(Blair et al., 1996; Blair et al., 1995; Wei et al., 1999) the American College of Sports Medicine (ACSM) has set guidelines for exercise programs to improve cardiorespiratory fitness in healthy adults.(ACSM, 1998) ACSM recommends that healthy individuals participate in aerobic exercise 3-5 days per week, at 55-90% of maximal

heart rate, for 20-60 minutes. Cardiorespiratory fitness can be measured objectively by performing a maximal effort exercise test. The results provide quantifiable measures of cardiorespiratory fitness and can be used to guide exercise prescription as recommended by ACSM.

Although cardiorespiratory fitness decreases with age, evidence suggests that fitness levels can be favorably changed with endurance training and healthy, older participants in exercise programs can make similar gains in cardiorespiratory fitness as compared to healthy, young adults.(Barry et al., 1966; Hagberg et al., 1989) Several studies have observed that exercise training will increase cardiorespiratory fitness by either increasing central cardiovascular mechanisms such stroke volume or cardiac output or peripheral changes such as capillary density or the cross sectional area of Type I muscle fibers in older adults.(Binder et al., 2002; Coggan et al., 1992; Ehsani et al., 2003; Posner et al., 1992; Skinner et al., 2001; Wilmore et al., 2001a, 2001b) For example, the HERITAGE Family Study performed exercise training using a cycle ergometer. The results showed that all participants regardless of age demonstrated increases in  $VO_2$  peak values. For the older adults 50-65 years of age, baseline measures prior to training were  $26.2 \pm 6.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and then increased 17% to  $30.7 \pm 6.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  after the 20-week training period.(Skinner et al., 2001)

### **1.3 Cardiorespiratory Fitness and Stroke**

#### *1.3.1 Peak Oxygen Consumption ( $VO_2$ peak)*

For individuals post-stroke, obtaining values for cardiorespiratory fitness has been challenging using traditional modes of testing thus several modifications in testing protocols have been used. For treadmill testing, the use of 15% body weight support (Mackay-Lyons & Makrides, 2002) aids the individual with stroke in maintaining balance. Other treadmill

protocols have eliminated the increasing incline and chosen lower incremental ambulating speeds to accommodate neuromuscular deficits.(Macko, Katzel et al., 1997; Macko et al., 2001) A cycle ergometer has been a popular modality for exercise testing specifically to eliminate balance and ambulation deficits. However the cycle ergometer poses its own challenges: mounting the cycle ergometer, the cyclical motion, decreased lower extremity coordination, and trunk and leg weakness have all contributed to exclusion from studies.(Eng, Dawson, & Chu, 2004; Yates et al., 2004) Additionally, variability in workload at starting and for exercise progression can influence results by either increasing or decreasing exercise testing time.(Eng et al., 2004; Kelly et al., 2003; Pang, Eng, & Dawson, 2005; Potempa et al., 1995; Yates et al., 2004) Utilization of various protocols and modalities may be over or under-estimating cardiorespiratory fitness, which makes interpretation of results and exercise prescription difficult for researchers and clinicians. Taking this previous information into account, two recent studies have recommended using an all-extremity ergometer to assess cardiorespiratory fitness in order to eliminate lower extremity fatigue that may be experienced during walking or cycling.(S. A. Billinger, Tseng, B.Y., Kluding, P.M., 2008; Hill, Ethans, MacLeod, Harrison, & Matheson, 2005) We present the feasibility and validity of an exercise test to obtain  $VO_2$  peak using an all-extremity recumbent stepper for healthy adults (Chapter 2) and people post-stroke (Chapter 3).

For clinical exercise testing, ACSM lists the treadmill and cycle ergometer as the primary modalities used to assess individual tolerance to strenuous exercise.(ACSM, 2006) For these specific modalities, well-established exercise testing protocols exist for healthy adults and those with cardiopulmonary dysfunction. Unfortunately, individuals with neuromuscular disorders experience difficulty using “standard” equipment. ACSM recognized these challenges and has recommended alternative modalities including a

recumbent stepper.(Palmer-McLean, 2003) However, no information on exercise testing procedures or test progression is available for the recumbent stepper. Therefore, development of an exercise test using the recumbent stepper in healthy adults was conducted. The results suggest the exercise testing protocol (TBRS-XT) is a valid and reliable test for healthy adults (Chapter2). The TBRS-XT protocol used relatively large incremental increases in workloads. In consideration of decreased physical activity and aerobic capacity associated with people post-stroke, the protocol was modified (mTBRS-XT, see Chapter 3).

The American Heart Association issued a statement in 2004 encouraging physical activity post-stroke to reduce risk factors for heart disease and recurrent stroke, the #1 and #3 causes of death in the United States.(Gordon et al., 2004) It has been reported that individuals post-stroke have lower peak oxygen uptake ( $VO_2$  peak) values than age-matched sedentary controls.(Eng et al., 2004; Mackay-Lyons & Makrides, 2004; Macko et al., 2001) Declines in cardiorespiratory fitness can occur early after stroke. Within just 30 days post-stroke, a 30% decrease in  $VO_2$  peak has been observed.(Duncan et al., 2003; Kelly et al., 2003; Teixeira da Cunha Filho et al., 2001) Furthermore, several studies have reported  $VO_2$  peak values around 8 to 14  $ml \cdot kg^{-1} \cdot min^{-1}$ .(Duncan et al., 2003; J. H. Rimmer, Riley et al., 2000; Teixeira da Cunha Filho et al., 2001) which is less than the 15  $ml \cdot kg^{-1} \cdot min^{-1}$  needed to perform activities of daily living (ADL's).(Cunningham, Paterson, Himann, & Rechnitzer, 1993) With decreased  $VO_2$  peak values and trends toward a sedentary lifestyle, improving fitness levels in individuals with stroke would be highly advantageous.

### *1.3.2 Aerobic Exercise*

Healthy young and older adults can improve their cardiorespiratory fitness from aerobic exercise training. We have a clear understanding of the physiological mechanisms

behind the effects of aerobic exercise. Despite the known benefits of exercise, most therapists in the 1960's to late 1970's assumed that aerobic exercise would negatively affect the neuromuscular system through increasing muscle tone or decreased controlled, volitional movement in the hemiparetic limb. However, in the 1990's, researchers began to question this consensually valid framework in stroke rehabilitation. This led to an in-depth exploration regarding cardiorespiratory fitness and aerobic exercise training in people after stroke. From these studies, we find similarities in basic physiological responses to aerobic exercise when compared to sedentary older adults. People post-stroke can increase peak oxygen uptake ( $VO_2$  peak) and decrease heart rate and blood pressure after an exercise training period (Chu et al., 2004; Duncan et al., 2003; Kelly et al., 2003; Mackay-Lyons & Makrides, 2002; Macko et al., 2001) without abnormal responses in motor performance. (Badics, Wittmann, Rupp, Stabauer, & Zifko, 2002; Butefisch, Hummelsheim, Denzler, & Mauritz, 1995; Duncan et al., 2003; Patten, Dozono, Schmidt, Jue, & Lum, 2006)

Although improvements in cardiorespiratory fitness have been reported from several exercise training studies, the  $VO_2$  peak values are still below the  $15 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  needed to perform basic ADLs. For example, the study by Duncan and colleagues (2003) provided supervised exercise sessions 3 times per week for 12 weeks, which consisted of 20 minutes of walking or cycling, strengthening exercises using Theraband® and 15 minutes of balance exercises. While baseline  $VO_2$  peak values were reported at  $11.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , meager improvements (9.4%) were reported in the post-intervention mean  $VO_2$  peak scores, which were  $12.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .

One exercise training study chose treadmill walking for the 3-week intervention. Balance impairments, decreased lower extremity coordination, and muscle weakness of the hemiparetic limb can hinder exercise performance using a treadmill. Therefore, body weight

support (BWS) treadmill training was used to eliminate these challenges during treadmill walking. The results suggested that when unweighting the lower extremities and providing “a safety net,” a 35% increase in  $VO_2$  peak scores ( $8.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  to  $11.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) was feasible.(Teixeira da Cunha Filho et al., 2001) However, Macko and colleagues (2001) used treadmill training without BWS for a thrice weekly intervention lasting 6 months with only a 10% improvement in  $VO_2$  peak scores. With the exception of body-weight supported treadmill training, mounting evidence demonstrates that improvements in  $VO_2$  peak are minimal (3%-13% increase) with aerobic exercise training.(Carr & Jones, 2003; Duncan et al., 2003; Kluding & Billinger, 2005; Macko et al., 2001; Potempa et al., 1995) Clearly, further studies are needed to determine the role of exercise intensity and exercise performance by individuals post-stroke to elicit the greatest improvements in cardiorespiratory fitness.

### *1.3.3 Submaximal Exercise and Oxygen Uptake ( $VO_2$ )*

Submaximal exercise tests have been used to predict cardiorespiratory fitness in healthy individuals and patient populations.(ACSM, 2006) After an exercise intervention, a decline in oxygen uptake ( $VO_2$ ) or heart rate suggests a training effect has occurred.(Macko, DeSouza et al., 1997) Increased energy expenditure has been observed during exercise and ambulation because of the significant energy required to perform movement with the hemiparetic limb.(Brinkmann & Hoskins, 1979; Landin et al., 1977; Macko, DeSouza et al., 1997; Potempa et al., 1995) Landin and colleagues (1977) had individuals with stroke perform two separate exercise sessions using a 1-legged submaximal exercise protocol on a stationary bicycle. Participants exercised for 40 minutes with physiological measures taken at 10 and 40 minutes of exercise. Participants exhibited increased oxygen uptake and heart

rate during exercise using the hemiparetic limb with decreased femoral artery blood flow when compared to the less affected limb.  $\text{VO}_2$  was significantly higher at 10 minutes of submaximal exercise in the paretic limb versus less affected limb ( $12$  vs  $7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively). This paradigm suggests that compensatory patterns of movement, decreased efficiency of muscle motion and metabolic muscle changes in the hemiparetic limb affects physical performance.

Submaximal exercise tests have been used as a method to measure energy expenditure during physical activity in people post-stroke.(Macko, Katzel et al., 1997; Potempa et al., 1995) As a result of aerobic exercise training, the cardiovascular system demonstrates a training effect though reductions in systolic blood pressure,(Potempa et al., 1995) heart rate (Brinkmann & Hoskins, 1979; Macko, DeSouza et al., 1997) and oxygen uptake ( $\text{VO}_2$ ).(Macko, DeSouza et al., 1997; Potempa et al., 1995) In the clinical or home setting, individuals post-stroke likely experience increased fatigue during submaximal efforts such as ADL's due to increased energy cost. Since individuals post-stroke can improve energy expenditure with exercise training, focusing on exercise interventions that decrease cardiovascular demands could result in astounding effects on functional activities such as ambulation in the home and community.

While not clearly understood, plausible explanations for improvements in energy expenditure after aerobic exercise training may be the result of efficiency of movement, physiological adaptations in either the peripheral or central cardiorespiratory system or all of the above.(Macko, DeSouza et al., 1997; Potempa et al., 1995) Chapter 6 addresses the effect of a 4-week single limb exercise protocol on both central and peripheral cardiorespiratory responses.

## 1.4 Physiology of Blood Flow

Blood flow is simultaneously regulated by changes in pressure, peripheral resistance and metabolic demand.(Mohrman & Heller, 2006) Differences in peripheral pressure allow blood to move through an artery to an arteriole and back through the venous system. As rehabilitation professionals, we observe how blood flow and pressure are intricately related when a patient experiences orthostatic hypotension. Immediately upon stance (or change in position), pressure decreases instead of increases and blood flows directly towards the pull of gravity.

The vasculature exhibits a certain amount of resistance as the blood flows through the vessel wall. For example, the arterioles have more resistance to flow than the arteries or capillaries. Additionally, as we age, the vessel walls become less compliant and resistance increases. It has been postulated that a rise in muscle sympathetic nerve activity drives increased vascular resistance.(Dinunno, Jones, Seals, & Tanaka, 1999) Furthermore, these effects are more profound in people with diabetes,(Bottini et al., 1995; Kingwell, Formosa, Muhlmann, Bradley, & McConell, 2003; Maiorana et al., 2001; Meyer et al., 2004) hypertension (Lind & Lithell, 1993) and cardiovascular disease.(Lind & Lithell, 1993)

Blood flow responds to metabolic demand. In some instances, blood flow must be sufficient for digestion while other times the working muscles require more blood flow. Immediately upon the onset of exercise, blood flow is increased and redirected from the organs (i.e. kidney, stomach) to the exercising muscle. As the muscles begin to work during exercise, the sympathetic nervous system (SNS) stimulates the nerves that innervate the heart via catecholamines such as epinephrine and norepinephrine.(Bottini et al., 1995) Heart rate increases to pump a greater volume of blood at a faster rate to meet the demands of the working muscles.(G. D. Thomas & Segal, 2004) This stimulation causes blood vessels in the



non-working muscles to vasoconstrict. This reduces the amount of blood flow to those specific regions until the metabolic demand shifts after exercise. Although the vessels in the working muscles also receive an identical command from the central nervous system, local factors such as metabolic byproducts produced within the muscle as a result of exercise override the command allowing a relaxation or vasodilation.(G. D. Thomas & Segal, 2004) Vasodilation of these vessels feeding the working muscles helps to further increase the delivery of oxygen-rich blood (Figure 1.1)

#### *1.4.1 Flow-Diameter Relationship*

Two components that influence blood flow delivery during exercise are an increase in the rate of flow (velocity) and arterial diameter enlargement (vasodilation). There is evidence that a peripheral “feedback mechanism” (Kamiya, Ando, Shibata, & Masuda, 1988) exists directly within the arterial vessel wall. This mechanism has been coined the flow-diameter relationship.(Ono, Ando, Kamiya, Kuboki, & Yasuda, 1991) It appears that changes (increase or decrease) in blood flow facilitate arterial diameter adaptations. It is important to note throughout the following discussion of the flow-diameter relationship that alterations aren't necessarily pathological but rather a response to change in the environment in an attempt to maintain homeostasis.

In animal models, blood flow through the carotid artery was surgically ligated to decrease blood flow by 60-70% for approximately 2 weeks.(Brownlee & Langille, 1991; Langille & O'Donnell, 1986) During this course of time, the sheer stress placed on the arterial wall by blood flowing through was diminished. After the two-week period, the diameter of the carotid artery was also reduced but once blood flow was restored to baseline values (100%) flow, arterial diameter also increased to pre-surgical values within just one week. In

order to test their hypothesis that the endothelial cells are responsible for detecting changes in blood flow, the endothelial lining of specific segments of the left carotid artery was destroyed (denuded) and then ligated to reduce blood flow by 70%. Langille and O'Donnell (1986) postulated that these results were related endothelium dependent factors within the arterial wall that respond to changes in blood flow secondary to increase/decrease in shear stress. Similar changes in diameter as a result of alterations in blood flow can be observed in humans. The work done in the animal model may be an example of peripheral adaptations of the cardiovascular system in response to exercise.

Parker and colleagues explored this idea of the flow-diameter relationship during an acute bout of exercise.(2007) They used Doppler ultrasound to quantify changes in femoral artery diameter and blood flow velocity during increasing workloads in men and women. Their results exemplified the relationship of increasing leg blood flow and diameter during an acute and immediate demand. Conversely, one study examined chronic changes that may occur in arterial blood flow and diameter after an 8-week exercise intervention.(Miyachi, Iemitsu, Okutsu, & Onodera, 1998) While the group that participated in normal, daily activities did not show any significant changes in the outcome measures, the exercise group improved with respect to blood flow and arterial diameter. Not only does the cardiovascular system respond to an acute metabolic demand but can modify this intimate relationship in response to chronic situations such as exercise.

Human studies in healthy individuals have demonstrated that blood flow must increase proportionately to the workload during exercise so that oxygen delivery meets the demands of the working muscles.(Mortensen et al., 2005) If femoral artery blood flow is reduced to the muscles of the lower extremity, then the limited oxygen delivery and uptake will no longer be sufficient to perform the work despite continued oxygen

extraction.(Mortensen et al., 2005) However, an interesting area to consider is the effect of decreased daily metabolic demand and whether or not these changes would directly oppose increased need for blood flow and oxygen delivery. To date, the literature suggests that a synergy exists between the flow-diameter relationship and metabolic demand. Indeed, in chronic patient populations, such as stroke (Ivey et al., 2004; Landin et al., 1977) or spinal cord injury (SCI), (de Groot, Bleeker, van Kuppevelt, van der Woude, & Hopman, 2006; Hopman, Groothuis, Flendrie, Gerrits, & Houtman, 2002; Thijssen, Ellenkamp, Smits, & Hopman, 2006) reductions in leg blood flow have been observed in the hemiparetic or paretic lower extremities. This is thought to occur based on decreased oxygen consumption and volitional muscle activity in the affected lower extremities. Of importance, healthy sedentary adults do not present with differences in between the lower extremities for femoral artery diameter (Bleeker, De Groot, Poelkens et al., 2005; Radegran & Saltin, 2000) and blood flow.(Bleeker, De Groot, Poelkens et al., 2005) Chapter 4 provides more in-depth information characterizing femoral artery adaptations (ie: arterial diameter and wall thickness) and blood flow velocity that can occur after stroke. These changes directly affect lower extremity blood flow. These components of blood flow were assessed in the hemiparetic and less affected limb in people with chronic stroke. Arterial adaptations and reductions in blood flow may potentially affect tissue perfusion and muscular performance during various stages of rehabilitation and certainly with exercise. Information presented in the next sections discusses peripheral vascular changes that occur from cardiovascular deconditioning and the response to an intervention.

## 1.5 Vascular Dysfunction

Peripheral vascular resistance is maintained through balance of the autonomic nervous system.(Hopman et al., 2002) Sympathetic neural fibers innervate the arterial vasculature and elicit varying degrees of vasoconstriction depending on the body's needs.(Mohrman & Heller, 2006) Hyperactivity in the firing rate of these sympathetic fibers can increase vascular resistance (via vasoconstriction), which can potentially decrease blood flow to the muscle fibers.(Mohrman & Heller, 2006) In contrast, Hopman and colleagues (Hopman et al., 2002) discussed the effects of decreased sympathetic activity on vascular resistance in a central nervous system lesion such as chronic SCI. Logically, it would be expected that vascular resistance would decrease below the lesion secondary to the decreased sympathetic input to the peripheral vascular system.(Hopman et al., 2002) However, they postulated that the lack of physical activity and deconditioning to the lower extremities may lead to a reduction in nitric oxide (NO) production/availability (in the endothelium) and synthesis of NO by endothelium nitric oxide synthase (eNOS). NO is a primary mediator in smooth muscle relaxation.(Mohrman & Heller, 2006) Therefore, interventions aimed at improving synthesis of NO and promoting increased vasodilatory responses would be advantageous. Increased NO production and synthesis via eNOS can be stimulated by greater shear stress either mechanically (Davis, Cai, Drummond, & Harrison, 2001) or physiologically through exercise.(Hambrecht et al., 2000; Koller, Huang, Sun, & Kaley, 1995; Miller & Vanhoutte, 1988; Sessa, Pritchard, Seyedi, Wang, & Hintze, 1994; Watts et al., 2004)

Several studies have suggested that aerobic exercise results in improved endothelial function and blood flow in humans with cardiovascular disease, (Hambrecht et al., 2000) diabetes (Maiorana et al., 2001; Watts et al., 2004) and SCI.(Gerrits, de Haan, Sargeant, van

Langen, & Hopman, 2001; Thijssen et al., 2006) One study suggested that endothelial dysfunction may be present in people after stroke.(Ivey et al., 2004) They used a hyperemic response to evaluate endothelial function between the hemiparetic and less affected limb. Their findings in the hemiparetic limb are similar to those with SCI where the physically inactive limbs have decreased blood flow and an abnormal response to hyperemia. While the present study did not use active hyperemia to assess endothelial function, we used ankle brachial index (ABI) to assess the response to an exercise intervention (Chapter 5).(Andreozzi, Leone, Laudani, Deinite, & Martini, 2007)

## **1.6 Blood Flow Responses to Exercise Interventions**

We have discussed the evidence that suggests physical activity levels play a primary role in blood flow regulation. However, little information is available regarding peripheral cardiovascular responses to exercise in neurologically impaired populations. For individuals with bilateral paralysis such as SCI, vascular adaptations and arterial remodeling can be observed within 3 weeks after the injury.(de Groot, Bleeker, van Kuppevelt et al., 2006) The reduction in blood flow to bilateral lower extremities is significantly different when compared to age-matched controls.(de Groot, Bleeker, & Hopman, 2006; de Groot, Poelkens, Kooijman, & Hopman, 2004; Taylor, Ewins, Fox, Grundy, & Swain, 1993; Ter Woerds, De Groot, van Kuppevelt, & Hopman, 2006) However, an exercise intervention using functional electrical stimulation (FES) aimed at increasing active muscle contraction has improved blood flow (De Groot et al., 2003; Hopman et al., 2002; Taylor et al., 1993; Thijssen et al., 2006) and arterial diameter (De Groot et al., 2003; Thijssen et al., 2006) in the femoral artery after SCI. Recently, a study by Thijssen (2006) used a repeated measures design to assess differences in blood flow at baseline, 2 weeks and 6 weeks after FES training and found that

the most significant improvements in blood flow occurred after 2 weeks of training. In contrast to the FES intervention, passive muscle movement to lower extremities in people with SCI did not improve blood flow.(Ter Woerds et al., 2006) Peripheral muscle metabolism associated with active muscle movement appears to have a greater influence on blood flow regulation and is an area of research that requires further exploration especially in clinical populations.

As mentioned previously, our work presented in Chapter 4 concurs with the available literature that suggests there are differences in blood flow between the hemiparetic and less affected limb at rest. To our knowledge, no research has attempted to assess both central and peripheral cardiovascular changes after a focused exercise intervention using the hemiparetic limb. Due to hemiparesis and decreased muscle coordination, individuals post-stroke prefer to use the less affected limb during exercise (Landin et al., 1977) and during activities requiring postural stability such as stance and ambulation.(Brunt, Vander Linden, & Behrman, 1995; Messier, Bourbonnais, Desrosiers, & Roy, 2005; Mizrahi, Solzi, Ring, & Nisell, 1989; Yavuzer, Eser, Karakus, Karaoglan, & Stam, 2006) Therefore, we sought to examine the effect of a 4-week single limb exercise training protocol with respect to improvements in femoral artery diameter and blood flow velocity in the hemiparetic limb post-stroke.

### **1.7 Single Limb Exercise**

A large body of literature suggests single-leg exercise (SLE) training promotes vascular remodeling and improves blood flow in the femoral artery. In healthy adults, SLE increases  $VO_2$  peak (Bell et al., 2001; Davies & Sargeant, 1975; Klausen, Secher, Clausen, Hartling, & Trap-Jensen, 1982; Miyachi et al., 2001; Saltin et al., 1976; Shoemaker, Hodge, & Hughson, 1994) and limb blood flow (Bell et al., 2001; Klausen et al., 1982; Miyachi et al.,

2001; Shoemaker et al., 1994) in the trained versus the untrained limb without increasing muscle mass.(Davies & Sargeant, 1975; Hardman, Williams, & Boobis, 1987) Two well-used modalities for SLE training are the cycle ergometer (Asanoi et al., 1992; Bell et al., 2001; Davies & Sargeant, 1975; Hardman et al., 1987; Klausen et al., 1982; Miyachi et al., 2001; Paterson, Kowalchuk, & Paterson, 2005; Radegran & Saltin, 2000; Saltin & Landin, 1975) and seated knee extension/flexion protocol using a Biodex™ or similar apparatus.(Flansbjerg, Holmback, Downham, & Lexell, 2005; Shoemaker et al., 1994; Shoemaker, Phillips, Green, & Hughson, 1996) In order to demonstrate that unilateral exercise increases blood flow only to the exercising limb, Asanoi et. al (1992) examined the changes in leg blood flow of the exercising and non-exercising (control) legs at rest and during single limb exercise. The study used thallium, a radioactive substance, which was injected into the bloodstream through the antecubital vein during rest. The distribution of blood flow between the two legs was not different at rest. However, during SLE a significant increase was observed at VO<sub>2</sub> peak in the exercising leg when compared to the control leg.

The majority of the research related to cardiovascular responses to SLE training has been in healthy adults. However, this may be an appropriate training method for a clinical population such as stroke. Landin suggested that bilateral exercise may pose some limitations for individuals with a hemiparetic limb.(1977) In their study, individuals with chronic stroke were incapable of equally distributing the work between both limbs despite verbal and visual feedback. In fact, the less affected limb performed approximately 66% more work than the hemiparetic limb. Since individuals post-stroke have a tendency to rely on the stronger limb during exercise, (Landin et al., 1977) bilateral training may not be an effective means of improving cardiovascular performance on the hemiparetic limb.

The literature in stroke rehabilitation research provides ample studies that suggest task specific, single limb activities may improve motor function in the hemiparetic upper extremity. A therapeutic intervention, constraint-induced movement therapy (CIMT) or modified CIMT (mCMIT), has been utilized as part of rehabilitation to “force” individuals to use their hemiparetic upper extremity. The goal of CIMT is to improve functional use of the hemiparetic limb. Results from these studies (Bowman et al., 2006; Butefisch et al., 1995; Page, Sisto, Levine, & McGrath, 2004; Ro et al., 2006; Taub et al., 2006; Wolf et al., 2006) indicate those receiving CIMT to the hemiparetic upper extremity had significant functional improvements when compared to those in the usual care group. Based on the premise that CIMT encourages use of the hemiparetic extremity, SLE is a training intervention designed to maximize use of the affected lower extremity during physical activity. SLE eliminates the issues related to unequal force production during bilateral activity.(Landin et al., 1977) Additionally, greater cardiovascular benefits are expected as a result of a focused training intervention.

## **1.8 Distinction of Experimental Design**

### *1.8.1 Assessment of Femoral Artery Characteristics*

Blood flow measures in the lower extremities after stroke have been performed using intravenous method (Landin et al., 1977) or strain-gauge plethysmography.(Ivey et al., 2004) The present research study used Doppler ultrasound to assess femoral artery diameter and blood flow velocity between the hemiparetic and less affected limbs. To this author’s knowledge, this body of work was the first to use Doppler ultrasound in people after stroke. This method was chosen based on the literature available for reliability (Chapter 4) (AbuRahma, Diethrich, & Reiling, 1980; Blackshear, Phillips, & Strandness, 1979; Gill,



1985; Shaalan, French-Sherry, Castilla, Lozanski, & Bassiouny, 2003; Sumner & Lambeth, 1979) and use in people with SCI.(De Groot et al., 2003; Olive, Dudley, & McCully, 2003; Thijssen et al., 2006) However, two key components (arterial diameter and blood flow velocity) are intricately related to muscle blood flow. Using Doppler ultrasound allowed precise assessment of both arterial diameter and flow velocity.

### *1.8.2 Single Limb Exercise*

The majority of exercise interventions reported in the literature for people post-stroke focus on bilateral activity such as treadmill walking or cycling. Consideration of the tendency to compensate with the less affected limb during exercise was paramount when determining the training intervention. Therefore, a unilateral intervention to maximize the effects of training to improve limb blood flow and cardiorespiratory fitness was selected. For this study, we used the Biodex and a knee extension/flexion protocol. The advantage of this novel exercise training protocol in chronic stroke was the encouraged use of the hemiparetic limb. Finally, this body of work presents findings related to both cardiorespiratory fitness and central and peripheral alterations in response to a unique exercise model.

## **1.9. Significance of the Presented Work**

Most individuals with stroke will require rehabilitation to help them achieve the best possible long-term outcome.(Gordon et al., 2004) Ambiguity exists in stroke rehabilitation regarding “best practice” for exercise prescription (intensity, frequency, duration) and cardiovascular outcome measures. Even more complex is the relationship between aerobic exercise and its effect on a dynamic multi-system “human machine” with varying levels of physical performance. Questions are raised about how stroke-related brain damage will affect

the cardiorespiratory system, muscular performance, and neurological function.

Rehabilitation scientists have suggested that “forced use” or constraint-induced therapy has a more profound effect on functional recovery of the hemiparetic upper extremity than those participating in usual care.(Page et al., 2004; Taub et al., 2006) Despite this knowledge, most therapeutic interventions consist of bilateral activities such as treadmill training (Duncan et al., 2003; Kelly et al., 2003; Macko, DeSouza et al., 1997; Macko et al., 2005; J. H. Rimmer, Braunschweig et al., 2000; J. H. Rimmer, Riley et al., 2000; Silver et al., 2000; Teixeira da Cunha Filho et al., 2001) or cycle ergometry (Duncan et al., 2003; Potempa et al., 1995; J. H. Rimmer, Braunschweig et al., 2000; J. H. Rimmer, Riley et al., 2000) to improve aerobic fitness despite the fact that most individuals post-stroke tend to primarily use their less affected limb.(Landin et al., 1977) The training protocol used in the present study encourages use of the hemiparetic limb during single limb exercise consisting of knee extension/flexion.

The present study contributes to the existing literature by increasing the understanding of vascular changes that may occur in the hemiparetic limb after an intensive exercise-training program using single limb exercise. These results may be used to improve stroke rehabilitation by targeting exercise programs or rehabilitation activities with an emphasis on improving blood flow to the hemiparetic limb and potentially avoid arterial remodeling that appears to occur after stroke. SLE using the hemiparetic leg may be a feasible therapeutic intervention to increase blood flow and improve muscular endurance during tasks such as independent activities of daily living (IADLs) that require increased energy expenditure. Very little information is available to clinicians and researchers concerning the effect of SLE training on femoral artery characteristics and cardiorespiratory fitness post-stroke.

This dissertation project will disseminate novel information to the scientific and clinical community regarding vascular alterations that occur in the hemiparetic femoral artery and a training protocol that encourages use of the hemiparetic leg as a method to reverse these adaptations. This line of work presented in the following chapters will contribute to a greater understanding of the impact that SLE has on central and peripheral cardiovascular mechanisms in people post-stroke.

### **1.10 Specific Aims and Statement of Hypotheses**

The foundation and expansion of this dissertation project stems from 3 preliminary research studies. First, a maximal effort graded exercise test using a total body recumbent stepper (TBRS) was designed specifically for healthy adults (TBRS-XT; Chapter 2) and clinical populations such as stroke (mTBRS-XT; Chapter 3). The mTBRS-XT protocol elicited higher cardiorespiratory fitness values than the cycle ergometer in people post-stroke. (Chapter 3) Based on these results we used this exercise test to assess cardiorespiratory fitness for our sample. Second, the vasculature was assessed in bilateral femoral arteries to determine if arterial remodeling occurs in the hemiparetic leg in people with chronic stroke. The results suggest that femoral artery blood flow, diameter and peak velocity are reduced in the hemiparetic leg. (Chapter 4) Therefore, the goal of this project was to characterize the effect of single limb exercise (SLE) on cardiorespiratory fitness and peripheral cardiovascular adaptations in the hemiparetic limb in people with chronic stroke. Two central aims guide this research:

**1. Characterize the effect of a 4-week SLE training protocol on the femoral artery vasculature in the hemiparetic leg. (Chapter 5)** If the endothelium in the femoral artery detects and responds to the increased blood flow during a lower extremity exercise

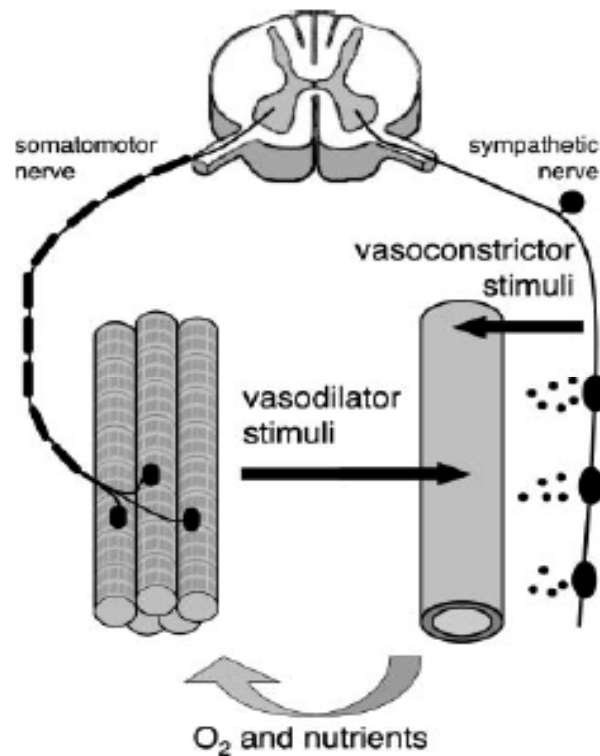
intervention, then arterial adaptations such as increased diameter (flow-diameter relationship) would be observed. It was hypothesized that after 4-weeks of SLE training using only the hemiparetic leg, femoral artery blood flow, diameter, flow velocity and ankle-brachial index (ABI) would improve. This would indicate that the vasculature in the hemiparetic leg could respond to the dynamic effects of chronic exercise. After the training intervention, it was found that femoral artery diameter and blood flow velocity increased. ABI values shifted either higher or lower towards the normal value of 1.0. No significant changes were found in the less affected, non-trained limb. The results suggest vascular remodeling may be driven by changes occurring in the periphery such as decreased oxygen demand rather than sympathetic tone.

**2. Determine whether a 4- week SLE intervention can improve central and peripheral cardiovascular mechanisms during maximal and submaximal exercise. (Chapter 6)** If an exercise training intervention is sufficient in intensity, duration and frequency, then central mechanisms such as cardiac output should increase to deliver adequate blood and oxygen to the working muscles. Additionally, enhanced capacity of the exercising muscles should allow for improved oxygen exchange (peripheral mechanism). It was hypothesized that after 4-weeks of SLE training,  $VO_2$  peak would significantly increase. The results demonstrated that participating in SLE three times per week for 4 weeks was insufficient at improving  $VO_2$  peak (central mechanisms). The second hypothesis focused on oxygen uptake ( $VO_2$ ) during submaximal single limb exercise. Results suggest that after the training intervention the exercising muscle decreased energy expenditure at a submaximal exercise and became more efficient at oxygen utilization (peripheral mechanism).

In summary, the research presented in this dissertation contributes to the existing body of literature through 4 separate and distinct manuscripts. These manuscripts consider

and attempt to address the unique and variable physical deficits related to stroke regarding: 1) modality selection for maximal effort exercise testing in healthy adults (Chapter 2, published *Journal of Strength and Conditioning Research*, 2008) and people post-stroke (Chapter 3, published in *Physical Therapy*, 2008); 2) differences in the arterial vasculature between the hemiparetic and less affected limb (Chapter 4, resubmitted to *Cerebrovascular Disease*); 3) the effect of a SLE training intervention on femoral artery adaptations that occur in the hemiparetic limb (to be submitted to *Archives of Physical Medicine and Rehabilitation*); (see appendix for single subject case study for vascular adaptations to SLE, and 4) changes in central and peripheral cardiovascular mechanisms after a 4- week SLE training protocol (to be submitted to *Stroke*).

Figure 1.1 Neural Control of Blood Flow to Skeletal Muscles.



This figure illustrates neural control of blood flow to the skeletal muscles during exercise. The somatomotor system increases signaling to recruit more skeletal muscle motor units for contraction to do work. However, vast amounts of vasodilator signals are generated by the contracting muscles, which cause vessel relaxation and allow greater blood flow. In order to regulate blood flow, the sympathetic nerve increases its extrinsic control over the blood vessels. The intimate coupling of neural control (somatomotor and sympathetic nerves) provides a balance between the amount of oxygen and blood flow delivered while attempting to meet the metabolic demands of the skeletal muscle. *Used with permission, Gail D. Thomas and Steven S. Segal, Invited Review, Neural control of muscle blood flow during exercise, J Appl Physiol 97: 731-738, 2004.*

## **Chapter 2 Preface**

Chapter 2 is the genesis of using the total body recumbent stepper (TBRS) for standardized exercise testing. This chapter sought to address the need for developing a valid and reliable maximal effort exercise test using the TBRS in healthy adults. The work presented in this chapter reflects many trials and tribulations but ultimately success in development of an exercise test (TBRS-XT) for the TBRS. The results suggest that the TBRS-XT is a valid and reliable exercise test to assess cardiorespiratory fitness. Further, the results presented in Chapter 2 were used as a guide for the development of a modified version of the TBRS-XT (mTBRS-XT) to use clinical populations such as stroke.

## Chapter 2

### Validity of a Total Body Recumbent Stepper Exercise Test (TBRS-XT) to Assess Cardiorespiratory Fitness

Billinger SA, Loudon, JK, Gagewski, BJ. Validity of a Total Body Recumbent Stepper Exercise Test (TBRS-XT) to Assess Cardiorespiratory Fitness, *Journal of Strength and Conditioning Research*. 2008; 22(5):1556-1562.



## 2.1 Abstract

Maximal oxygen consumption ( $\text{VO}_2 \text{ max}$ ) is the primary measure for cardiorespiratory fitness, and the  $\text{VO}_2 \text{ max}$  value achieved on the treadmill using the Bruce protocol is considered the gold standard. A novel exercise test using a total body recumbent stepper (TBRS) would be an alternative for measuring  $\text{VO}_2 \text{ max}$  in healthy individuals. Furthermore, the TBRS exercise test (TBRS-XT) may be beneficial for individuals such as those with stroke, who cannot tolerate a treadmill or cycle ergometer test due to hemiparesis, increased tone in the extremities or balance deficits. The purpose of the study was to assess the validity and reliability of the TBRS-XT in determining  $\text{VO}_2 \text{ max}$  in healthy adults. Twenty-two healthy adults (9 women, 13 men;  $26.9 \pm 6.1$  years of age) participated in two maximal exercise tests in random order. One exercise test was performed on the treadmill using the Bruce protocol and the other exercise test was the TBRS-XT. Statistical analysis of the data was conducted using simple linear regression where the response variable was the  $\text{VO}_2 \text{ max}$  from the Bruce protocol and the predictor variable was the  $\text{VO}_2 \text{ max}$  from the TBRS-XT. A 95% prediction interval (PI) was used to assess the strength of the prediction of  $\text{VO}_2$  from Bruce protocol with an R-squared of 0.851. Preliminary data suggests that the TBRS-XT may be a valid test to predict maximal oxygen consumption when treadmill testing is not feasible. This would allow clinicians an alternative method for exercise testing and prescription to promote healthy lifestyle interventions for a variety of patient populations.

## 2.2 Introduction

Data collected from a maximal exercise test can be used to assess an individual's level of aerobic fitness. A maximal exercise test with concomitant measurement of oxygen uptake ( $\text{VO}_2$ ) is one method used to guide exercise prescription. However, assessment of  $\text{VO}_2$  max using traditional modes of testing may prove to be difficult in a variety of populations such as elderly,(Siconolfi, Cullinane, Carleton, & Thompson, 1982) deconditioned individuals (Siconolfi et al., 1982) or those with brain injury such as stroke due to balance deficits, gait impairments, and decreased coordination.(Dobrovolny, Ivey, Rogers, Sorkin, & Macko, 2003) For these individuals, cycle ergometer (Dobrovolny et al., 2003; Ponchiatti-Mulcare, 1995) or use of combined arm and leg ergometer (Hagan, 1983; Loudon, Cagle, Figoni, Nau, & Klein, 1998) may be beneficial for exercise testing when treadmill testing is not feasible. However, appropriate exercise testing protocols should be used to obtain accurate values for cardiorespiratory fitness.

For example, Siconolfi and colleagues (1982) suggested that even for healthy individuals some testing protocols may not provide an accurate assessment of cardiorespiratory fitness. In their study, 13 out of 32 participants who were 39 years of age and older demonstrated difficulty performing two minutes of exercise during the Astrand-Rhyming cycle test. These 13 participants were unable to complete the test because pedaling against the resistance was too difficult, therefore the test values were underestimated for  $\text{VO}_2$  max in this sample. Arm ergometry is another viable option for exercise testing; however, arm cranking can produce peak  $\text{VO}_2$  values that are up to 30-35% less than treadmill testing. (J. Rimmer & Nicola, 2002) ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities recommends using a seated stepper to implement exercise prescription for individuals with neuromuscular disorders such as traumatic brain injury or

stroke.(Palmer-McLean, 2003) However, in order to allow for appropriate exercise programming using a seated stepper, a valid and reliable exercise test for the total body recumbent stepper (TBRS) would be valuable.

A seated stepper has been utilized within an exercise intervention in a variety of settings including rehabilitation, community fitness centers and retirement communities. The NuStep TRS 4000 (NuStep, Inc Ann Arbor, MI), (Figure 2.1), or TBRS consists of 10 settings (1-10) with Load 1 (50 watts) being the least amount of resistance. The TBRS utilizes reciprocal movements of both upper and lower extremities. Because the TBRS is a seated stepper, it is low impact, which is ideal for the elderly, individuals with arthritis or joint replacements of the lower extremities.(Loudon et al., 1998) Since the individual using the TBRS grasps the arm pole in a position halfway between wrist pronation and supination, this also accommodates those with limited ranges of motion.(Palmer-McLean, 2003) For individuals who experience difficulty maintaining proper foot placement during exercise, wide footplates with posterior and lateral borders support the feet and foot straps hold the foot securely in place.

No maximal exercise test exists for the TBRS. The purpose of this study was to assess the validity and reliability of the total body recumbent stepper exercise test (TBRS-XT) for maximal exercise testing in a healthy population. It was hypothesized that the maximal TBRS-XT would be a valid and reliable test for determining VO<sub>2</sub> max.

## **2.3 Methods**

### *Approach to the problem*

This was a within subject design to examine the validity and reliability of the TBRS-XT that terminated at VO<sub>2</sub> max or when the participant reached volitional fatigue. The

variables (maximal heart rate,  $\text{VO}_2$  max, respiratory exchange ratio (RER), and maximal exercise time) from TBRS-XT were compared to the Bruce protocol treadmill test.

### *Subjects*

Twenty-two healthy participants (13 men, 9 women) with a mean age of  $27.9 \pm 6.0$  years volunteered to participate in the study. Eighteen participants were tested for the validity of the TBRS-XT and 5 participants participated in reliability testing. All participants reported no neuromuscular, cardiopulmonary, metabolic or musculoskeletal impairments that would limit their performance. Participant responses from the non-exercise estimation of  $\text{VO}_2$  max placed 19 individuals in the high and 3 in the moderate physical exercise categories. (Foster, Thompson, & Bales, 1991) Institutionally approved informed consent was obtained in writing prior to participation in the study. Data collection was performed at the Georgia Holland Cardiopulmonary and Neuromuscular Lab at the University of Kansas Medical Center.

Eighteen participants performed two maximal graded exercise tests in random order on separate days to test validity of the TBRS-XT. Exercise testing sessions were separated by at least 48 hours but no more than 14 days apart and were controlled for time of day. Participant demographics are presented in Table 2.1. Reliability testing consisted of two paired test-retest sessions that were separated by no more than 5 days and were also controlled for time of day. Five participants including one that participated in the validity testing performed the two maximal graded exercise tests using the TBRS-XT for the purpose of assessing reliability. Participants were instructed not to eat food 2 hours prior to testing, but were allowed to hydrate with water ad libitum. Additionally, participants were asked to avoid caffeine and vigorous physical activity for at least 6 and 24 hours, respectively, prior to testing. Once informed consent was obtained, participants were asked to complete a non-

exercise estimation of  $\text{VO}_2$  max to place them in a fitness level based on the subject's exercise activity.(Foster et al., 1991)

### *Procedures*

#### *Treadmill Maximal Exercise Test.*

The Bruce protocol was used for treadmill testing. Participants' heart rate, RER, and  $\text{VO}_2$  were recorded continuously and calculation of expiratory gases was performed every 30 seconds throughout the test. The treadmill exercise test was considered maximal when the patient reached at least 2 of the 3 criteria: 1) maximal heart rate was within 10 beats of predicted maximum, 2) plateau of  $\text{VO}_2$  max (within  $0.57 \text{ L} \cdot \text{min}^{-1}$ ) and 3)  $\text{RER} \geq 1.10$  as suggested by Loudon and colleagues.(1998)

#### *TBRS Maximal Exercise Test*

Participants were acclimated to the TBRS prior to the exercise test. The seat was adjusted either forward or backward to allow for a slight bend in the knee with extension, which would prevent hyperextension or the knee from "locking" in full extension. Differences in arm lengths were accounted for by modifying the length of the adjustable arm poles. These values were recorded for reuse in subsequent testing sessions. Individualization allowed participants to adequately and appropriately extend and flex the elbow and the shoulder joints during the exercise session. The maximal TBRS-XT (Table 2.2) consisted of 2-minute stages and concomitant increases in resistance until the participant reached test termination criteria. Exercise testing began with a warm-up stage at Load 1 (50 watts). Preliminary study suggested that Loads 2 and 3 prolonged test duration greater than 16-18 minutes (data not shown). Therefore, participants exercised at loads 4-10, increasing in

resistance with test progression. At each load, participants were asked to maintain a stepping cadence of 115 steps\*minute<sup>-1</sup> but were allowed a range of 110-120 steps\*min<sup>-1</sup>. If participants were unable to maintain a stepping cadence at 110 steps\*min<sup>-1</sup> with verbal cues and encouragement for participation, the test was terminated. No tests were terminated based on this criterion. Test termination criteria for the TBRS exercise test utilized identical criteria mentioned above in the treadmill protocol.(Loudon et al., 1998)

Heart rate was continuously monitored throughout each exercise testing session using the Polar Vantage XL heart rate monitor (Polar Electro, Finland). The maximal treadmill graded exercise test was performed on a Quinton Q55 (Quinton Instrument Co, Seattle, WA) and the TBRS protocol was performed on the NuStep (Nustep, Ann Arbor, MI). To ensure reliability of the TBRS exercise test, the NuStep was calibrated during assembly using the Lode Portable Calibrator 2000 (Lode BV, Netherlands). A ParvoMedics TrueOne 2400 open circuit spirometry (ParvoMedics, Sandy, UT) was used for collection and analysis of expired gases continuously using a two-way rebreather valve (Hans Rudolph, Kansas City, MO) and a noseclip. The sampling technique was a 30 second averaging of the data. All equipment was calibrated according to the manufacturer's recommendations prior to testing procedures. Participants rated perceived exertion at each stage of exercise testing using Borg's 6-20 scale.

### *Statistical Analysis*

#### *Validity*

Statistical analyses of data was conducted using a simple linear regression where the response variable was the VO<sub>2</sub> max from the Bruce protocol and the prediction variable was the VO<sub>2</sub> max from the TBRS-XT. Since the Bruce protocol is considered gold standard, it

was chosen as the response variable in order to predict measures from the TBRS-XT (prediction variable). For the regression equation, a 95% prediction interval was used to assess the strength of the prediction of VO<sub>2</sub> max and maximal heart rate from Bruce protocol. A Pearson's Correlation Coefficient was used to assess the relationship between VO<sub>2</sub> max and maximal heart rate for the TBRS-XT and Bruce protocol. Paired student t-tests were conducted to determine if a significant difference existed between VO<sub>2</sub> max and maximal heart rate values for the TBRS-XT and Bruce protocol. One goal of this study was to assess the clinical predictability of TBRS-XT for the Bruce protocol. Therefore, using linear regression, we calculated a predicted Bruce protocol using a linear combination of slope and intercept for each TBRS-XT for both VO<sub>2</sub> max and maximal heart rate. Paired student's t-tests were conducted to determine if a significant difference between VO<sub>2</sub> max and maximal heart rate values for the predicted Bruce Protocol (using TBRS-XT) and Bruce protocol on the treadmill.

### *Reliability*

To determine the reliability for each testing protocol, an Intraclass Correlation Coefficient (ICC) was calculated for the paired TBRS-XT and Bruce protocol. One-way ANOVA F-statistic was used to test for statistical significance ( $\alpha \leq 0.05$ ).

## **2.4 Results**

The individual scores for VO<sub>2</sub> max values ( $L \cdot \text{min}^{-1}$ ) and heart rate (bpm) for each test are located in chapter Appendix 2.1. For the VO<sub>2</sub> max prediction interval, the slope and intercept point estimates were 0.96 and 0.56 respectively with an R-squared of 0.851 and the standard error estimate (SEE) of 0.307. For the heart rate max prediction interval, the slope

and intercept point estimates were 16.25 and 0.95 respectively with an R-squared of 0.93 and the standard error estimate (SEE) of 3.48 (see Figures 2.2 and 2.3).

A Pearson's correlation for  $\text{VO}_2$  max and maximal heart rate ( $r = 0.92$  and  $0.96$ , respectively) between the Bruce protocol and TBRS-XT protocol indicates a strong relationship for the group. Data was then analyzed separately for men and women. Pearson's correlation coefficient also revealed a strong relationship for  $\text{VO}_2$  max (men:  $r = 0.88$ ; women:  $r = 0.96$ ) and max heart rate (men:  $r = 0.97$ ; women:  $r = 0.92$ ) between the Bruce protocol and TBRS-XT protocol.

Group mean  $\text{VO}_2$  max values were  $3.67 \pm 1.07$  ( $1.97$  to  $4.77 \text{ L} \cdot \text{min}^{-1}$ ) and  $3.13 \pm 0.80 \text{ L} \cdot \text{min}^{-1}$  ( $1.72$  to  $4.20 \text{ L} \cdot \text{min}^{-1}$ ) for the Bruce protocol and TBRS-XT, respectively. A statistically significant difference was observed between  $\text{VO}_2$  max values for the Bruce protocol and the TBRS-XT where  $p < 0.01$ . Group mean maximal heart rate for the Bruce protocol was  $188 \pm 13$  bpm while the TBRS-XT elicited  $181 \pm 13$  bpm with a statistically significant difference observed between values ( $p < 0.01$ ). Significant differences in  $\text{VO}_2$  max and maximal heart rate were seen for both men and women ( $p < 0.01$ ). Adjusted TBRS-XT data for both  $\text{VO}_2$  max and heart rate max values using the slope and intercept showed no significant differences ( $p = 0.40$ ) for either maximal heart rate or  $\text{VO}_2$  max. Table 2.3 shows  $\text{VO}_2$  max, heart rate, RER, and metabolic equivalent (METS)

The ICC for the Bruce protocol and TBRS-XT proved highly reliable, ( $r = 0.99$ ,  $p < 0.001$ ;  $r = 0.98$ ,  $p < 0.001$ , respectively). In a review article, Atkinson and Nevil suggest using 20-30 participants for assessing the reliability of variables.(1998) However, even with the sample size at 5 subjects, statistically significant values were obtained.



## 2.5 Discussion

In this study, we evaluated the validity and reliability of a novel maximal exercise test using the TBRS-XT. Our results indicate that the TBRS-XT is a valid, reliable and alternative exercise test for assessing cardiorespiratory fitness and predicting VO<sub>2</sub> max. The validity for group VO<sub>2</sub> max and heart rate ( $R^2 = 0.85, 0.93$ , respectively) between tests suggested a strong relationship. The current study had a higher VO<sub>2</sub> max in the Bruce protocol ( $3.67 \pm 1.07$ ) than the TBRS-XT ( $3.13 \pm 0.80 \text{ L} \cdot \text{min}^{-1}$ ). The lower values for VO<sub>2</sub> max and heart rate for the TBRS-XT may be attributed to the fact that participants' body weight was supported by the TBRS' seat in addition to localized fatigue of the upper and lower extremities, which according to ACSM guidelines may account for a 5-20% reduction in VO<sub>2</sub> max values.(ACSM, 2006) In this study, a 12% decrease in VO<sub>2</sub>max values existed between the Bruce protocol and TBRS-XT, which was statistically significant. Therefore, based on the inability to reach VO<sub>2</sub> max and maximal heart rate, the TBRS-XT may be used to assess and measure VO<sub>2</sub> peak rather than VO<sub>2</sub> max.

Pollock and colleagues found significant differences in VO<sub>2</sub> max measures among three different protocols (Bruce protocol and Balke for the treadmill) and a bike test.(1975) Maximal heart rates were significantly lower with the bike protocol ( $177 \pm 11 \text{ bpm}$ ) when compared to the two treadmill tests ( $181 \pm 9 \text{ bpm}$  and  $182 \pm 9 \text{ bpm}$  for the Bruce and Balke protocol, respectively.) No significant differences for heart rate existed between the Bruce and Balke treadmill tests. In addition, VO<sub>2</sub> max values for the group were significantly lower in the bike test when compared to the Bruce protocol. The bike test elicited a VO<sub>2</sub> max of  $36.6 \pm 4.9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  while values from the Bruce protocol were  $40.7 \pm 4.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The results found by Pollock et al. concur with our results that a seated modality elicits a lower maximal heart rate and VO<sub>2</sub>, which are similar to other studies for cycle and treadmill

testing.(Fernhall & Kohrt, 1990; Moody, Kollias, & Buskirk, 1969; Pannier, Vrijens, & Van Cauter, 1980; Pollock et al., 1975)

Hass and colleagues used the TBRS as a mode of exercise training in a randomized study measuring  $\text{VO}_2$  max.(2001) In Hass' study,  $\text{VO}_2$  max was measured using the Bruce (and modified Bruce) depending on their age to determine baseline  $\text{VO}_2$  max values then the TBRS max exercise test was performed. Participants were asked to maintain a step rate of  $120 \text{ steps} \cdot \text{min}^{-1}$  while the intensity increased every two minutes until participants reached exhaustion. In the present study, participants were asked to maintain  $115 \text{ steps} \cdot \text{min}^{-1}$  and the intensity progressed every two minutes. However, Loads 2 and 3 were eliminated from our protocol for two reasons: 1) The watts for Loads 1, 2, and 3 (50 W, 52W and 55W) were similar across the bandwidth of the TBRS and 2) this resulted in max exercise tests greater than 16 and 18 minutes in pilot testing. Hass and colleagues report the mean TBRS max exercise time for the exercise group (EX) at  $16.2 \pm 4.1$  vs. 10.9 minutes on the treadmill. In the present study, mean exercise duration for the TBRS-XT was not significantly different from the Bruce protocol (Table 2.3).

After baseline  $\text{VO}_2$  max testing, Hass and colleagues had participants begin a 12-week exercise training program using the TBRS.(2001) After the training period, a significant increase in  $\text{VO}_2$  max was observed with both the Bruce protocol and TBRS exercise tests. Hass and colleagues did not mention validation of the TBRS exercise test that was used and if any significant differences were observed between the Bruce protocol and TBRS maximal exercise test. For the exercise group, mean  $\text{VO}_2$  max values reported by Hass et al. were higher with the Bruce (or modified Bruce) protocol  $2.3 \pm 0.06 \text{ L} \cdot \text{min}^{-1}$  than on the TBRS  $2.1 \pm 0.5 \text{ L} \cdot \text{min}^{-1}$  for the exercise group, which is similar to the results presented in the current study.

Loudon and colleagues recruited 33 women of various ages and fitness levels to engage in a discontinuous “all-extremity maximal exercise test” and a maximal treadmill test using the Bruce protocol.(1998) The all-extremity device used by Loudon was a combined arm and leg cycle ergometer and is similar to the TBRS-XT, which is an all-extremity recumbent stepper. While both modes of exercise utilize the upper and lower extremities, Loudon found no significant difference in VO<sub>2</sub> max and heart rate values between the two modes of testing, which differs from the results of the present study. Loudon and colleagues suggested that use of an all-extremity device may be appropriate for assessing cardiorespiratory fitness in women with varying fitness levels.

The TBRS allows movement of bilateral upper and lower extremities, which may be beneficial to individuals who have limitations of motion secondary neuromuscular deficit.(Palmer-McLean, 2003) Recently, Hill and colleagues (2005) used an all-extremity device similar to the one used by Loudon et al. (1998) for exercise testing in individuals in the sub-acute phase of stroke recovery. Hill suggested that use of the all-extremity ergometer as an exercise modality would be appropriate to use in sub-acute post-stroke rehabilitation settings whereby increasing functional capacity and/or mobility skills would be beneficial. The authors of the current study agree that using a seated recumbent stepper that incorporates use of the upper and lower extremities such as the TBRS would be an appropriate mode of exercise testing for individuals with neuromuscular deficits.(S. A. Billinger, Tseng, & Kluding, 2008)

Limitations of this study are the small sample size and physical activity level. Most of the participants were actively engaging in regular, vigorous physical activity. A heterogenous sample for fitness levels would be desirable so the TBRS-XT could be applied to a variety of fitness levels. Also, maintaining a consistent stepping cadence of 115

steps\*min<sup>-1</sup> for the duration of the TBRS-XT was difficult, and the use of a metronome may have helped participants maintain a consistent cadence. Participants who are not accustomed to exercise on the TBRS may have experienced localized leg fatigue similar to that of cycle ergometry, which would cause them to reach volitional fatigue more quickly.(ACSM, 2006) However, if the lower extremities experience fatigue, the upper extremities can assist in performance and disperse the load across other muscle groups.

### *Practical Applications*

A strong correlation exists between the TBRS-XT and the Bruce protocol for maximal heart rate and VO<sub>2</sub> max. Therefore, the TBRS-XT may be a valid and reliable alternative method for assessing cardiorespiratory fitness in a young, healthy population. A future study to determine the percent difference between the Bruce protocol and the TBRS-XT would be advantageous for individuals using the TBRS-XT. Furthermore, comparing a seated modality such as cycle protocol to the TBRS-XT would be beneficial and recommended to determine whether or not any differences exist in VO<sub>2</sub> max or heart rate between the two modalities.

The results of this study may be applicable to those individuals who perform graded exercise tests where the TBRS-XT may be a valid and reliable alternative method for maximal effort exercise testing. For individuals who train or exercise on a recumbent stepper, VO<sub>2</sub> peak values obtained from the TBRS-XT may help guide exercise intensity during training. It is recommended that future studies using the TBRS-XT focus on other populations that would benefit from using a recumbent stepper for exercise testing or prescription.

## Chapter 2 Tables, Figures and Appendix

Table 2.1 Subject Characteristics of men (M) and Women (W) and Fitness Levels Determined From a Non-exercise Estimate of VO<sub>2</sub> max.

Subject #	Age (years)	Gender (M,W)	Fitness Level from Non-exercise Estimate*
1	23	W	High
2	24	W	High
3	25	M	High
4	25	W	High
5	39	M	High
6	26	W	Moderate
7	24	M	High
8	24	M	High
9	27	W	High
10	25	M	High
11	21	M	High
12	36	M	High
13	24	M	High
14	34	M	High
15	22	W	High
16	25	M	High
17	40	M	Moderate
18	20	M	High
19	36	W	High
20	34	W	High
21	30	W	High
22	29	M	Moderate

\*High = participates regularly in heavy physical exercise such as running, cycling, or swimming

\* Moderate = participates regularly in recreation or work requiring modest physical activity such as golf, bowling, weight lifting or yard work

Table 2.2 Flowchart of TBRS-XT testing protocol

Resistance	Watts	Stepping Cadence (steps*min <sup>-1</sup> )	Duration (min)
Load 1	50	115	2
Load 4	75	115	2
Load 5	100	115	2
Load 6	130	115	2
Load 7	160	115	2
Load 8	200	115	2
Load 9	240	115	2
Load 10	290	115	2

\*Loads 2 and 3 were omitted from the TBRS-XT due to minimal change in workload (W) and test duration exceeding 16 minutes.

Table 2.3 Data are Means  $\pm$  SD for Bruce protocol and TBRS-XT VO<sub>2</sub> max and Maximal Heart Rate for the Group (n = 18). \* Indicates Significant Difference Between-group

Activity	Variable	Mean $\pm$ SD	R <sup>2</sup>	p value
Bruce Protocol	VO <sub>2</sub> max (L* min <sup>-1</sup> )	3.67 $\pm$ 1.07	0.85	p < 0.01*
TBRS-XT	VO <sub>2</sub> max (L* min <sup>-1</sup> )	3.13 $\pm$ 0.80		
Bruce Protocol	Heart rate (beats*min <sup>-1</sup> )	188 $\pm$ 12.8	0.92	p < 0.01*
TBRS-XT	Heart rate (beats*min <sup>-1</sup> )	181 $\pm$ 12.9		

Difference for VO<sub>2</sub> max Values and Maximal Heart Rate, p < 0.01.



Figure 2.1 Participant Engaging in the TBRS-XT.



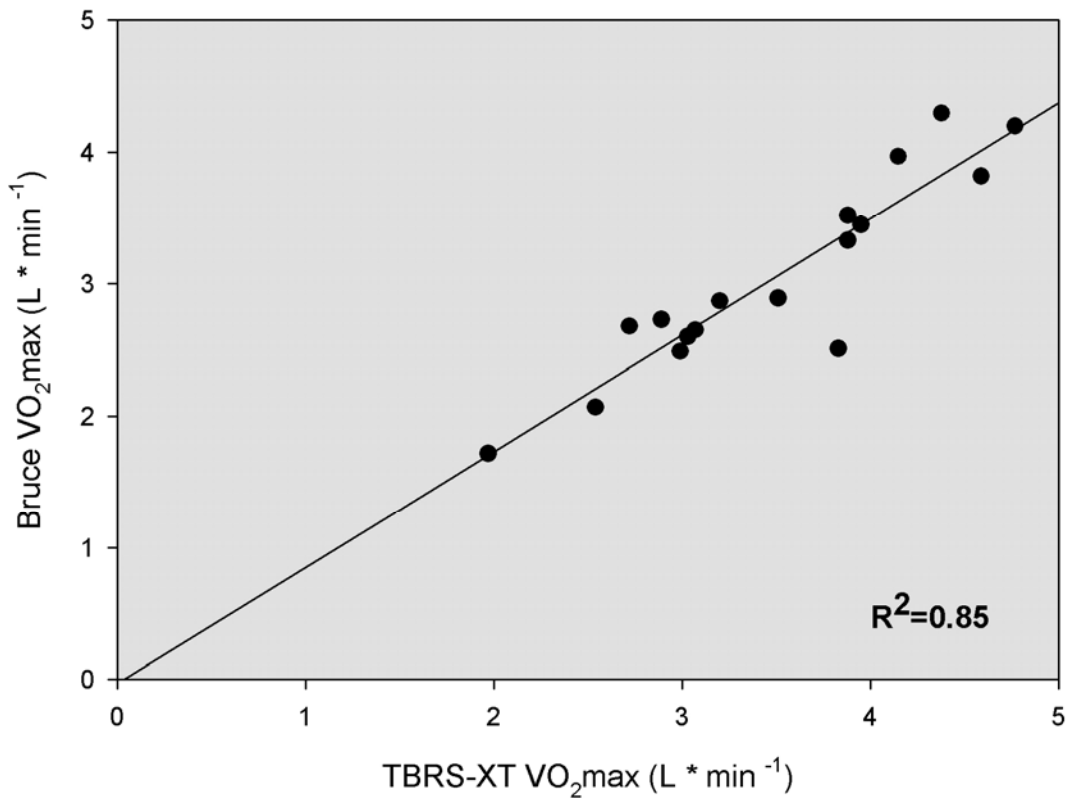


Figure 2.2 Scatter Plot of VO<sub>2</sub> max for the Bruce Protocol Versus TBRX-XT with an Overlay of the Regression Line.

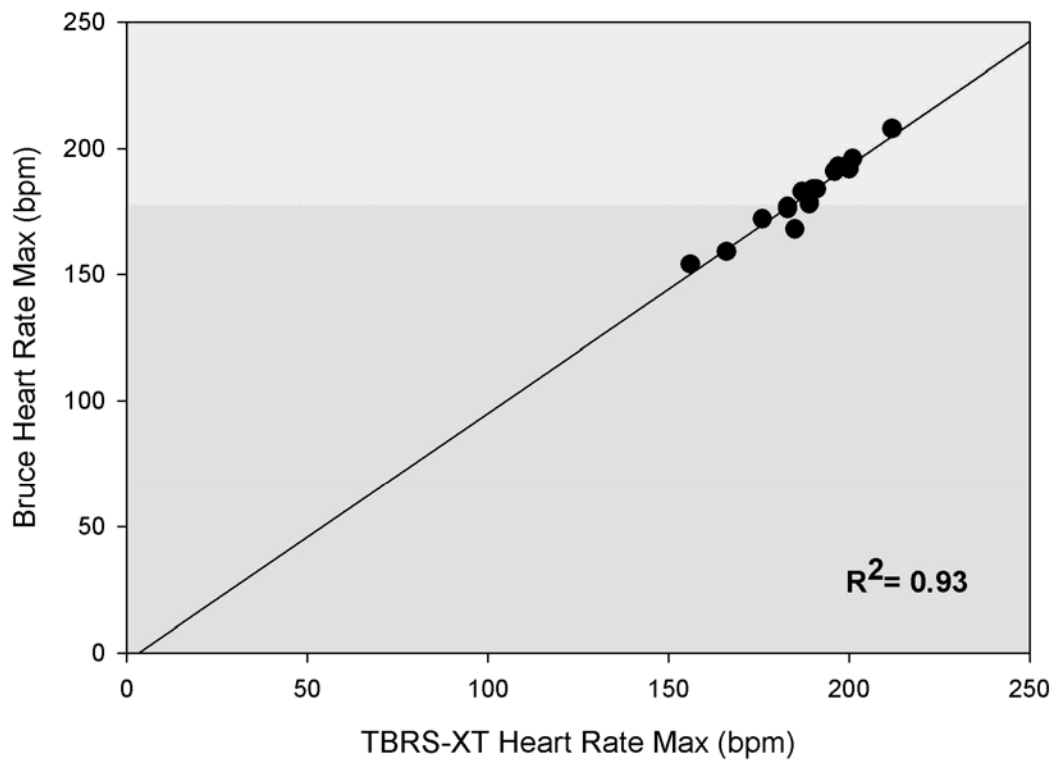


Figure 2.3 Scatter plot of Maximal Heart Rate for the Bruce protocol versus TBRS-XT with an overlay of the regression line.

Appendix 2.1 Subjects' Physiological Measurements During the Maximal Exercise Tests for the Bruce Protocol and TBR5-XT.

Ss	VO <sub>2</sub> max	VO <sub>2</sub> max	HR	HR	RER	RER	Exercise Time	Exercise Time	METS	METS
	Treadmill (L*min <sup>-1</sup> )	TBR5-XT (L*min <sup>-1</sup> )	(bpm)	Treadmill (bpm)	Treadmill	TBR5-XT	(min)	TBR5-XT (min)	Treadmill	TBR5-XT
1	2.72	2.68	187	183	1.18	1.20	13.94	12.49	15.5	15.3
2	3.07	2.65	200	192	1.26	1.32	12.47	11.93	14.1	11.9
3	3.20	2.87	185	168	1.14	1.36	13.02	10.85	13.3	11.9
4	2.99	2.49	183	176	1.32	1.42	15.03	13.02	15.7	13.1
5	3.03	2.60	176	172	1.28	1.37	12.13	14.05	12.6	10.8
6	1.97	1.72	189	178	1.46	1.34	9.09	12.08	9.5	8.3
7	4.15	3.97	187	183	1.29	1.12	15.95	18.00	16.7	16
8	6.73	4.57	191	184	1.31	1.25	14.07	16.00	20.6	21.1
9	3.83	2.51	196	191	1.33	1.22	13.78	10.78	17.9	11.7
10	3.88	3.52	190	184	1.29	1.22	12.99	12.80	13.3	12
11	3.95	3.45	201	196	1.19	1.30	14.08	12.07	10.9	12.4
12	2.89	2.73	190	184	1.38	1.25	9.82	9.02	9.3	8.8
13	3.88	3.33	197	193	1.24	1.25	12.20	12.76	14.3	12.3
14	4.59	3.82	166	159	1.19	1.23	14.03	12.20	15.2	12.6
15	2.54	2.07	189	179	1.27	1.21	11.14	8.28	12.0	9.8
16	4.77	4.20	183	177	1.28	1.19	15.15	14.80	16.0	14.1
17	3.51	2.89	156	154	1.19	1.09	9.18	9.08	9.2	7.6
18	4.38	4.30	212	208	1.20	1.22	16.02	14.02	18.8	18.5
Avg	3.67	3.13	187.67	181.17	1.27	1.25	13.01	12.46	14.16	12.68
SD	1.07	0.80	12.75	12.99	0.08	0.09	2.12	2.44	3.27	3.43
	RER =Respiratory Exchange Ratio(VCO <sub>2</sub> /VO <sub>2</sub> ); METS= Metabolic Equivalents									

### **Chapter 3 Preface**

The results from a maximal effort graded exercise test are commonly used to guide exercise prescription. However, in a clinical population such as stroke neuromuscular deficits can present many challenges for exercise testing. In Chapter 1, specifically section 1.3.1. we outlined these challenges related to stroke sequelae and discussed modifications that adaptations to exercise tests that are available in the current literature.

## Chapter 3

Modified Total Body Recumbent Stepper Exercise Test (mTBRS-XT) to Obtain VO<sub>2</sub> Peak in  
People With Chronic Stroke

Billinger, S. A., Tseng, B. Y. and Kluding, P. M. Modified Total Body Recumbent Stepper Exercise Test (mTBRS-XT) to Obtain VO<sub>2</sub> Peak in People With Chronic Stroke. *Physical Therapy*. 2008; 88(10): 1188-1195.

### 3.1 Abstract

Background: Assessment of peak oxygen consumption ( $\text{VO}_2$  peak) using traditional modes of testing such as treadmill or cycle ergometer can be difficult in individuals with stroke due to balance deficits, gait impairments, or decreased coordination. Objective: To quantitatively assess the validity and feasibility of a modified exercise test using a total body recumbent stepper (mTBRS-XT) in individuals post-stroke. Design: Sample of convenience, within subject design. Participants: Eleven participants completed the study: 40.1 (32.7) months post-stroke, 7 male; age of 60.9 (12.0) years and mild to severe lower extremity Fugl-Myer scores (range 13-34). Methods: Participants performed 2 maximal effort graded exercise tests on separate days using the mTBRS-XT and the cycle ergometer protocol to assess cardiorespiratory fitness. Peak oxygen uptake ( $\text{VO}_2$  peak), and peak heart rate (peak HR) were obtained from both tests. Results: A strong relationship exists between the mTBRS-XT and cycle ergometer exercise test for  $\text{VO}_2$  peak and peak HR ( $r = 0.91$  and  $0.89$ , respectively). Mean  $\text{VO}_2$  peak was significantly higher ( $p = 0.04$ ) between the mTBRS-XT ( $16.6 (4.5) \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and the cycle ergometer protocol ( $15.4 (4.5) \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). All participants performed the mTBRS-XT while one individual with severe stroke was unable to pedal the cycle ergometer. No significant adverse events occurred. Conclusion: The mTBRS-XT may be a safe, feasible and valid exercise test to obtain  $\text{VO}_2$  peak in people with stroke. Healthcare professionals may use the mTBRS-XT to prescribe aerobic exercise based on  $\text{VO}_2$  peak values for individuals post-stroke with mild to severe deficits.

### **3.2 Introduction**

Maximal effort exercise testing is performed to assess cardiorespiratory fitness. Information gathered from an exercise test such as oxygen uptake, heart rate and blood pressure is used to guide exercise prescription. Although safe and effective exercise guidelines are available,(Gordon et al., 2004; Palmer-McLean, 2003) fundamental questions regarding appropriate exercise test protocol selection and prescription for people post-stroke remain unclear.(Arsura, 2005; Eng et al., 2004; Tang, Sibley, Thomas, McIlroy, & Brooks, 2006) Although numerous protocols are available for the general population,(ACSM, 2006) these may not be feasible for people post-stroke due to balance deficits, poor postural control, or incoordination of the hemiparetic limb during cycling or ambulation. Therefore, in an attempt to improve exercise test performance in the post-stroke population, modifications to these protocols and/or modalities have been made. For treadmill testing, the use of 15% body weight support (Mackay-Lyons & Makrides, 2002) aids the individual with stroke in maintaining balance while other treadmill protocols use lower incremental ambulating speeds without concomitant changes in incline.(Macko, Katzel et al., 1997; Macko et al., 2001) Several studies (Chen et al., 2005; Pang et al., 2005; Potempa et al., 1995; J. H. Rimmer, Braunschweig et al., 2000; Yates et al., 2004) have chosen the cycle ergometer as the preferred modality for exercise testing post-stroke. However, to accommodate motor and postural deficits, modifications to the cycle ergometer such as using a seat with trunk support (Chen et al., 2005) or securing the hemiparetic limb to the pedals (Chen et al., 2005; Tang et al., 2006; Yates et al., 2004) have been used.

Despite modifications to the cycle ergometer, people with stroke may experience difficulty during exercise testing. In fact, a study by Yates (2004) reported that 11 of the 14 subjects excluded from the study could not perform the cyclical motion of the cycle

ergometer. In order to minimize the difficulties associated with exercise testing using a cycle ergometer, Tang and colleagues (2006) chose a semirecumbent cycle ergometer. This device provided posterior trunk support, and if needed, the hemiparetic limb was secured to the pedal. In their study using the semirecumbent cycle ergometer, only 1 subject was unable to complete the exercise test because the affected limb would not stay on the pedal.

One study incorporated both upper and lower extremities during exercise testing after stroke. Hill et al. (2005) postulated that an all-extremity exercise test would be beneficial to decrease early onset of limb fatigue in the lower extremities. Use of this modality allowed the participants to remain in their wheelchair while their hands grasped the hand bars and feet were placed in the foot pedals of the ergometer. The authors stated that use of the combined upper and lower cycle ergometer provided a better estimate of cardiorespiratory fitness secondary to incorporating more muscle mass, which may elicit a higher  $VO_2$  peak in people post-stroke.

Individuals post-stroke can experience decreased trunk control, impaired sitting or standing balance and lower extremity incoordination, making traditional exercise testing modalities inappropriate.(Palmer-McLean, 2003) These deficits in motor function can affect exercise performance and may compromise maximal effort testing as evidenced by previous studies.(Eng et al., 2004; Yates et al., 2004) Noting these challenges, the ACSM recommends the recumbent seated stepper (Figure 3.1) for both exercise testing and training in individuals after stroke.(Palmer-McLean, 2003) This modality accommodates many common motor function deficits by providing trunk and distal limb support.(Palmer-McLean, 2003) In addition, the total body recumbent stepper (TBRS) uses bilateral reciprocal movement of the arm coupled with the opposite leg, which allows for a push and pull motion.(Mendelsohn, Connelly, Overend, & Petrella, 2008)



In consideration of these recommendations we sought to establish a valid exercise testing protocol for individuals post-stroke using a TBRS. In previous work, we developed an exercise test protocol using the TBRS for healthy adults (see Chapter 2). (S. A. Billinger, Loudon, & Gajewski, 2008) In order to assess the validity and reliability of the TBRS exercise test (TBRS-XT), measures of peak oxygen consumption ( $VO_2$  peak) from the TBRS-XT were compared those values obtained from the Bruce protocol. Our previous results suggested that the TBRS-XT is a valid and reliable exercise test for obtaining  $VO_2$  peak in a healthy population. Therefore, the purpose of the current study was to assess the validity and feasibility of a modified exercise test using a total body recumbent stepper (mTBRS-XT) in individuals post-stroke. We anticipated that 1) a high correlation would be observed between  $VO_2$  peak for the mTBRS-XT and the cycle ergometer and 2)  $VO_2$  peak using the mTBRS-XT would be significantly higher than the cycle ergometer. A secondary goal was to assess whether the maximal effort exercise tests resulted in whole body fatigue or only leg fatigue.

### **3.3 Methods**

#### *Participants*

Thirteen participants were recruited to participate in this study. Data from two individuals were excluded from the study. One individual could not perform the cyclical movement of the cycle ergometer and another participant demonstrated ST segment elevation greater than 1 mm, which is an absolute indication for exercise test termination (n=1). (ACSM, 2006) Eleven participants (7 male, 4 female) with a mean age of 60.9 (12.0) years completed this within subject design study. Participant demographics are presented in Table 3.1.

Inclusion criteria included: 1) individuals could transfer from sitting to standing, 2) walk 30 feet independently with or without an orthotic or assistive device, and 3) had a score of  $\geq 24$  on the Mini Mental Status exam to screen for dementia and establish the ability to give informed consent for this study. Exclusion criteria consisted of the following: 1) hospitalization for myocardial infarction, heart surgery, or congestive heart failure during the preceding 3 months, 2) significant cardiac arrhythmia, hypertrophic cardiomyopathy, severe aortic stenosis, or pulmonary embolus, 3) recent symptoms of chest discomfort, 4) currently smoking or significant pulmonary pathology, and 5) musculoskeletal problems from conditions other than stroke that would limit the ability to exercise. Because the TBRS is a novel modality for assessing cardiorespiratory fitness in people post-stroke, we had no preliminary data on which to base a power analysis. Therefore, a precision argument was utilized to justify the sample size for this study. Based on the early data ( $n = 5$ ), the standard error of the mean (SEM) decreased drastically up to 10 participants beyond which there is a diminishing of return. This project set out to recruit 15 participants to buffer against drop out.

This study was approved by the Institutional Review Board at the University of Kansas Medical Center. Institutionally approved informed consent was obtained in writing prior to participation in the study. Stroke severity was assessed using the lower extremity section of the Fugl-Meyer (LEFM). (Daly et al., 2006; Duncan, Goldstein, Matchar, Divine, & Feussner, 1992) Data collection for the exercise tests was performed at the General Clinical Research Center (GCRC) at a medical center.

### *Exercise Testing*

Participants performed two maximal effort graded exercise tests in random order assignment. The exercise testing sessions were separated by at least 48 hours but no more

than 7 days and were controlled for time of day. Participants were instructed not to consume food, caffeine, or alcohol for 3 hours prior to exercise testing,(ACSM, 2006) but were allowed to hydrate with water ad libitum. On the day of testing, participants were familiarized with each testing protocol prior to the exercise test. The testing administrator explained Borg's rating of perceived exertion scale (RPE). Since the upper extremities were used during the mTBRS-XT, participants were instructed to nod "yes" or "no" when the test administrator asked, "Are you working harder than" the specific number on the RPE scale. The same procedure was used for the cycle ergometer exercise test. In addition, for individuals with Type 2 diabetes, blood glucose levels were assessed. If blood glucose levels were less than  $70 \text{ mg} \cdot \text{dL}^{-1}$  or higher than  $300 \text{ mg} \cdot \text{dL}^{-1}$ , the exercise test was rescheduled for another day.

The maximal effort cycle tests were performed on a cycle ergometer\* and the TBRS†. A ParvoMedics TrueOne 2400‡ for metabolic measurement was used to continuously collect and analyze expired gases using a two-way rebreather valve§. The metabolic cart produced a 30-second average of the data collected for the sampling technique during all exercise tests. Prior to testing, all equipment was calibrated according to the manufacturer's recommendations.

Baseline measures for height, weight, heart rate, and blood pressure were obtained prior to exercise testing. An exercise physiologist and physician continuously monitored heart

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\* Lode BV, Zernikepark 16, 9747 AN Groningen, Netherlands

† NuStep, Inc, 51111 Venture Dr., Ann Arbor, MI 48108

‡ Parvomedics, 8152 South 1715 East, Sandy, UT 84093

§ Hans Rudolph, Inc, 7200 Wyandotte St, Kansas City, MO 64114

rate and rhythm with a 12-lead electrocardiogram (ECG) throughout each exercise testing session. Thirty seconds prior to the end of each stage, blood pressure was taken and recorded and participants rated their perceived exertion using Borg's 6-20 scale.

#### *Cycle Ergometer Exercise Test*

Individuals were given physical assistance if they were unable to independently transfer onto the cycle ergometer. Once the participant was seated on the cycle, seat height was adjusted to allow for a slight bend in the knee while avoiding full knee extension during pedaling. If the individual experienced difficulty keeping the hemiparetic limb on the pedal, the foot was secured on the pedal with an ace wrap. Participants were instructed to pedal at 60 rpm for the duration of the test and verbal encouragement was given if cadence dropped below 55 rpm. The resistance was set at 0 watts for the first 3 minutes of the exercise test, and then was increased by 10 watts \* minute<sup>-1</sup> until test termination.(Yates et al., 2004) The exercise test was terminated using the following criteria: 1) participant reached volitional fatigue and requested to end the test, 2) the participant's VO<sub>2</sub> peak plateaued or decreased despite continuation of exercise, 3) the participant was unable to maintain the cadence, or 4) an adverse cardiovascular event or response to the exercise test was observed.

Once the exercise test was completed, participants were asked to verbally report their reason for terminating the exercise test. They were asked to identify 1 of 2 choices: 1) "generalized fatigue/whole body fatigue", or 2) "limb fatigue".

#### *mTBRS-Xt Exercise Test*

Once the participant was seated in the TBRS, necessary adjustments were made for leg and arm length according to methods used by Billinger and colleagues.(2008) The

protocol stages lasted 2-minutes with concomitant increases in resistance until the test was terminated (Table 3.2). Although the stepping cadence was modified from the original TBRS-XT protocol to 80 steps\*minute<sup>-1</sup>, exercise test progression was identical to our previous work.(S. A. Billinger, Loudon et al., 2008) If participants were unable to consistently maintain a stepping cadence at 80 steps\*min<sup>-1</sup> with verbal cues and encouragement for participation, the test was terminated. Test termination criteria for the mTBRS-XT used identical criteria mentioned above in the cycle ergometer protocol. Once the mTBRS-XT was completed, participants were asked for their reason for terminating the exercise test with criterion identical to the cycle ergometer test.

#### *Data Analysis*

Pearson's correlation coefficient was used to examine the relationship between the cycle ergometer exercise test and the mTBRS-XT for peak VO<sub>2</sub> and peak heart rate. Since the mTBRS-XT uses both the upper and lower extremities during the exercise test, and based on the article by Hill and colleagues,(2005) we hypothesized that VO<sub>2</sub> peak would be higher than the cycle. For physiological data (Table 3.3), a one-tailed paired student's t-test was conducted to determine if a significant difference existed between the cycle ergometer exercise test and the mTBRS-XT. Statistical significance was set at  $\alpha \leq 0.05$ . SPSS 15.0<sup>||</sup> was the software used for all data analysis.

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<sup>||</sup> SPSS, Inc, 233 S Wacker Dr., Chicago, Ill 60606

### 3.4 Results

Mean physiological values from the maximal effort graded exercise tests are presented in Table 3. At test termination (maximal effort), mean physiological values were higher using the mTBRS-XT than the cycle ergometer for  $\text{VO}_2$  peak ( $16.6$  vs  $15.4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), peak HR ( $132.9$  vs  $130.7$  bpm) and peak systolic blood pressure ( $144$  vs  $139$  mmHg). The correlation coefficient between the cycle ergometer exercise test and mTBRS-XT for  $\text{VO}_2$  peak ( $r = 0.91$ ,  $p < 0.001$ ; Figure 2), and peak heart rate ( $r = 0.89$ ,  $p < 0.001$ ) indicates a strong relationship between the two modalities for assessing cardiorespiratory fitness post-stroke. A paired t-test showed a statistically significant difference ( $p = 0.04$ ) between the cycle ergometer exercise test and the mTBRS-XT for mean  $\text{VO}_2$  peak ( $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) (Table 3.3). Seventy-three percent of the participants (8 of 11) reached 80% age-predicted heart rate (APHR) max using the mTBRS-XT, while 7 of 11 reached 80% APHR max using the cycle ergometer exercise test. Forty-five percent of the participants (5 of 11) using the mTBRS-XT reached 90% APHR max while 3 of 11 met the criteria for 90% ARHR max using the cycle ergometer exercise test. In this study, one individual presented with an ischemic ST segment change on the ECG. The physician terminated the exercise test prior to peak effort. During cool down, the ST segment returned to normal. During rest, this individual reported that he didn't want to mention to the staff that his medication was not taken at his usual time before the exercise test. No other adverse events occurred during exercise testing for either modalities.

Eight of 11 participants reported generalized/whole body fatigue while only 3 individuals stated leg fatigue was the reason for test termination using the TBRS. Results for the cycle ergometer were reversed. Leg fatigue on the cycle ergometer was the reason for test termination for 8 of the 11 participants while 3 reported generalized /whole body fatigue.

Baseline  $\text{VO}_2$  prior to starting the exercise test was significantly higher for the cycle ergometer than the TBRS (Table 3.3).

### **3.5 Discussion**

Individuals with stroke experience many challenges to maximal effort exercise testing, including impaired sitting balance, inability to mount the cycle ergometer, and impaired coordination during the cyclical motion. We used a testing modality, the TBRS that accommodated these physical challenges. All individuals enrolled in this study were able to perform the mTBRS-XT despite the vast motor impairment differences (mild to severe stroke, LEFM range 13-34). This study provides important information to researchers and clinicians examining cardiorespiratory fitness in the chronic stroke population. Importantly, using this modality and exercise test allowed participants with stroke to engage in a maximal effort exercise test and eliminated the need for numerous test protocols based on motor performance. (Kelly et al., 2003; Pang et al., 2005)

The results from this study suggest that the mTBRS-XT is a valid, feasible and safe exercise test protocol to obtain  $\text{VO}_2$  peak in people with chronic stroke. We found the mTBRS-XT to have a strong relationship with the cycle ergometer exercise test for  $\text{VO}_2$  peak ( $r = 0.91$ ). While the cycle ergometer is a modality that is extensively used for exercise testing in the post-stroke population, the TBRS is a feasible alternative for assessing cardiorespiratory fitness. In addition, significantly higher ( $p = 0.04$ ) group  $\text{VO}_2$  peak values were found between the mTBRS-XT and the cycle ergometer. Our results agree with Hill and colleagues (2005) that the combined efforts of the upper and lower extremities may increase exercise capacity.

As evidenced in the current literature, numerous exercise test protocols for the cycle ergometer have been used for people post-stroke. For example, a recent study by Pang and colleagues (2005) used 2 different cycle protocols that varied in initial workload and intensity progression secondary to varying levels of motor performance. Potempa et al. (1995) and Kelly et al. (2003) chose a cycle protocol that started at 50rpm at 0W and then increased by 10 watts \* minute<sup>-1</sup> until volitional fatigue while Yates (2004) chose 60 rpm at 0W for 3 minutes and then progressed at 10 watts \* minute<sup>-1</sup> until test termination. Another study (Chu et al., 2004) chose a cycle protocol that began at a pedaling cadence between 50-70 rpm with a workload at 20 watts \* minute<sup>-1</sup>, but then increased the resistance by 20 watts \* minute<sup>-1</sup> throughout the exercise test where as Eng and colleagues (2004) had the participants pedal at a rate of 50-70 rpm but began at 0W and then progressed at 20 watts \* minute<sup>-1</sup> until test termination. As demonstrated by the variety of cycle protocols used for people post-stroke, interpretation of exercise test results can be difficult for both researchers and clinicians. We addressed this issue by modifying an existing protocol (TBRS-XT) that demonstrated reliability and validity in a healthy population (S. A. Billinger, Loudon et al., 2008) while using the identical exercise test progression for people with stroke. In doing so, we eliminate uncertainty and maintain consistency when using the TBRS for exercise testing.

Eng and colleagues (2004) suggested the need for alternative exercise testing methods for people post-stroke because of the challenges associated with cycle ergometry. In their study, 27 individuals met the initial screening criteria. Of the 15 excluded from the study, 10 with severe stroke were unable to pedal the cycle ergometer due to decreased coordination, muscle weakness or an inability to maintain appropriate leg position. The reasons for eliminating individuals from exercise testing participation are identical to Yates' study (2004) where 21% of the individuals excluded from their study could not perform the



cycle ergometer exercise test. Contrary to the studies by Eng and Yates,(2004; Yates et al., 2004) the results from our study demonstrate that people post-stroke with varying levels of lower extremity function (LEFM scores 13-34) can participate in the mTBRS-XT to assess cardiorespiratory fitness. In our study, all participants were able to perform the maximal effort graded exercise test using the TBRS without difficulty from balance deficits or motor impairments of the lower extremities. In addition, one participant with a LEFM score less than 19, which indicates a severe stroke (Daly et al., 2006) was unable to pedal the cycle ergometer to perform the exercise test but was able to use the TBRS.

We found that 8 the 11 participants using the mTBRS-XT reached a peak HR expressed at 80% of their age predicted heart rate (APHR) max while 5 of 11 participants reached a peak HR at 90% APHR max. Our results for APHR max are higher than those previously reported in the literature for a seated modality.(Hill et al., 2005; Kelly et al., 2003; Moldover, Daum, & Downey, 1984; Yates et al., 2004) Nine individuals were taking beta-blockers, which can lower maximal heart rate during an exercise test. Since we did not have access to information on these individual prior to beta-blocker therapy, it is difficult to gauge the true effect of the beta-blocker on maximal heart rate for each individual. Interestingly, a previous study reported individuals receiving beta-blocker therapy increased their maximal heart rate by 36% after an exercise intervention.(Vanhees, Fagard, & Amery, 1982) Although not directly assessed in the study by Vanhees and colleagues,(1982) participants in their study reached 80% of APHR max during a graded exercise test. Therefore, it is plausible that the participants in our study were able to reach this heart rate intensity despite the influence of beta-blockers. It reasonable to suggest that a combined upper and lower extremity modality such as the TBRS may be a feasible and accurate method for assessing cardiorespiratory fitness and guiding exercise prescription in people with chronic stroke.

Another potential benefit incorporating bilateral upper and lower extremity involvement may be a reduction in leg fatigue therefore eliminating early test termination by participants. Anecdotally, individuals post-stroke that use the combined efforts of the upper and lower extremities during a maximal effort exercise test report less leg fatigue than when a cycle ergometer is used.(Hill et al., 2005; Kelly et al., 2003) Results from our study indicated that 8 of 11 participants reported generalized fatigue while leg fatigue was the primary reason for test termination in 3 of 11 individuals using the TBRS. However, 8 of 11 participants reported leg fatigue on the cycle ergometer versus 3 of 11 for generalized fatigue, which may limit exercise test performance. One interesting and unexpected finding from this study was that mean baseline  $VO_2$  values were higher on the cycle ergometer than for the TBRS. One potential explanation may be related to the difficulty some individuals experienced mounting the cycle ergometer. Since increased energy expenditure ( $VO_2$ ) was observed prior to the start of the exercise test for the cycle ergometer, this could affect exercise test performance.

While we believe the present study included a wide variety of functional performance levels, the sample size ( $n = 11$ ) was small and may limit the ability to generalize the results to a stroke population. One disadvantage of the TBRS is that blood pressure measurements are difficult to obtain since all extremities are simultaneously moving during the exercise test. We had the participants release their grasp on one of the arm poles and relax it at their side during blood pressure measurements. Maintaining a constant stepping cadence of 80  $\text{steps} \cdot \text{min}^{-1}$  during the mTBRS-XT was difficult for some individuals, and required verbal cues to maintain the appropriate stepping rate. Finally, future research studies comparing cardiorespiratory fitness values between the mTBRS-XT and a protocol using a combined arm and leg ergometer,(Hill et al., 2005) may be advantageous since both modalities use all extremities.

### **3.6 Conclusion**

Based on the results of this study, the data suggest that the mTBRS-XT is a valid, feasible and safe exercise test protocol to assess cardiorespiratory fitness for most individuals post-stroke. In addition, lower scores from the LEFM did not exclude individuals post-stroke from participating in the mTBRS-XT. This is important because individuals post-stroke with various levels of lower extremity performance should be able to participate in exercise training programs and gain the cardiorespiratory benefits associated with aerobic exercise training.

While the cycle ergometer is a frequently used modality for exercise testing post-stroke, the mTBRS-XT demonstrated higher  $VO_2$  peak values than the cycle ergometer. The physiological values from the mTBRS-XT may be more representative of cardiorespiratory fitness since all extremities are engaged during the exercise test. The results from exercise tests using this protocol may be used to prescribe exercise intensity for exercise training in individuals post-stroke.

### Chapter 3 Tables and Figures

Table 3.1 Participant Demographics

Characteristics n = 11	Mean (SD)	Range
Men/women	7/4	
Age (years)	60.9 (12.0)	31-76
Type of stroke: ischemic/hemorrhagic	10/1	
Hemiparetic side: right/left	6/5	
Time (months) post-stroke	40.1 (32.7)	7-119
Lower Extremity Fugl-Meyer score	25.7 (6.4)	13-34
Beta-blockers	9	
Pacemakers	2	
Type 2 Diabetes mellitus	5	

Table 3.2 Flowchart of mTBRS-XT Protocol

Stage	Resistance (Watts)	Stepping Cadence (steps*min <sup>-1</sup> )	Duration (min)
Load 1	25	80	2
Load 4	40	80	2
Load 5	55	80	2
Load 6	70	80	2
Load 7	85	80	2
Load 8	100	80	2
Load 9	115	80	2
Load 10	130	80	2

\*Loads 2 and 3 were omitted from the mTBRS-XT, which is identical to the original TBRS-XT protocol. (S. A. Billinger, Loudon et al., 2008)

Table 3.3 Results From Maximal Effort Graded Exercise Test Performance Using the mTBRS-XT and Cycle Ergometer (n = 11)

Variable	mTBRS-XT	Cycle Ergometer
Baseline VO <sub>2</sub> (ml*kg <sup>-1</sup> *min <sup>-1</sup> )	3.2 (1.0)*	4.2 (1.2)
VO <sub>2</sub> peak (ml*kg <sup>-1</sup> *min <sup>-1</sup> )	16.6 (4.9)*	15.4 (4.5)
Resting heart rate (beats per min)	81.4 (11.8)	81.7 (9.7)
Peak heart rate (beats per min)	132.9 (21.0)	130.7 (19.2)
RPE (peak exercise)	17 (1.3)	15 (2.4)
SBP (mmHg) at rest	123 (22.7)	125 (26.4)
DBP (mmHg) at rest	73 (10.9)	77 (13.2)
Peak SBP (mmHg)	144 (19.8)	139 (15.0)
Peak DBP (mmHg)	78.0 (6.7)	79.0 (13.0)
RER	1.1 (0.1)	1.1 (0.1)
Exercise test time (min)	12.4 (3.0)	10.7 (4.4)

NOTE: Data are means (SD)

Abbreviations: VO<sub>2</sub>, oxygen uptake; RPE, rating of perceived exertion; RER, respiratory exchange ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Data analysis was performed using a one-tailed paired t-test. Significant differences are denoted by \*, where  $p < 0.05$ .



Figure 3.1 Participant Performing a Maximal Effort Exercise Test Using the mTBRs-XT.

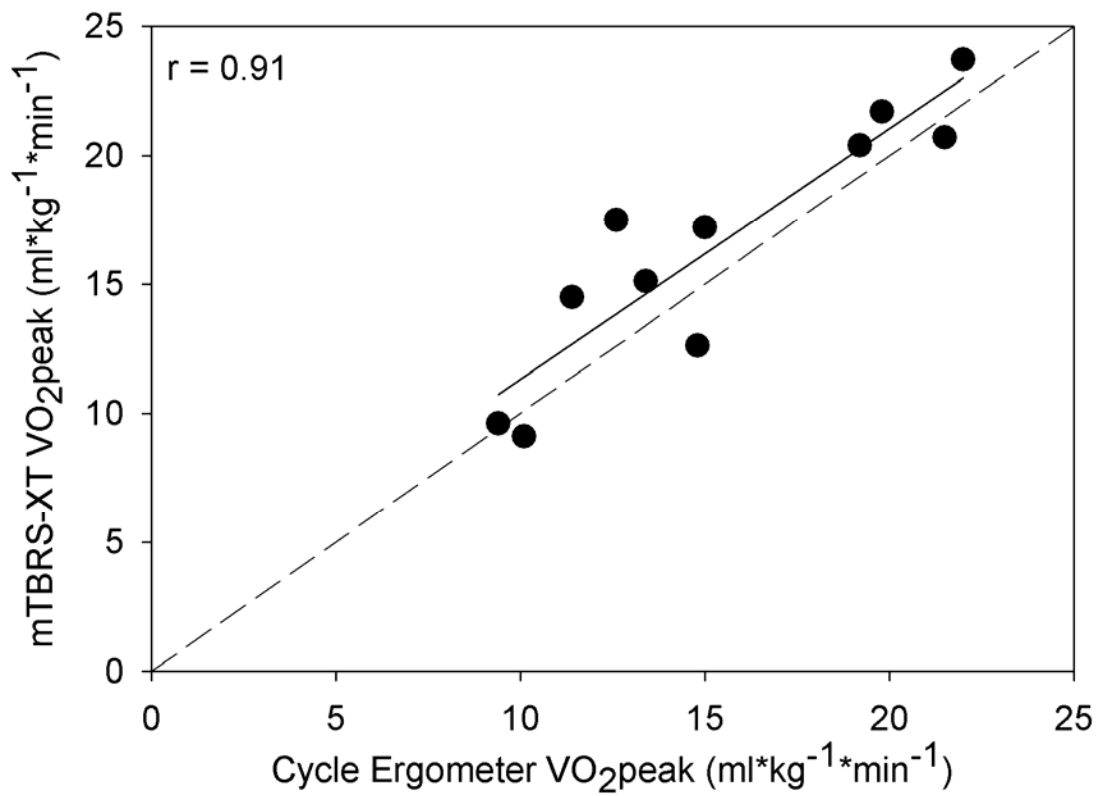


Figure 3.2 Relationship Between the mTBRS-XT and Cycle Ergometer Exercise Test for Peak Oxygen Uptake (ml\* kg<sup>-1</sup>\*min<sup>-1</sup>) Expressed as a Solid Line. Dotted line represents identity line.



## **Chapter 4 Preface**

In order to perform functional activities, adequate blood flow and oxygen exchange must be present for the muscles to perform work. From the available literature, we find that healthy young and older adults have similar femoral artery diameter and blood flow.

Interestingly, two previous studies suggest blood flow differences exist between the two lower extremities in people post-stroke.(Ivey et al., 2004; Landin et al., 1977) Chapter 4 not only explores the possibility that differences in femoral artery blood flow do exist between the hemiparetic and less affected limb but delves deeper into the vascular components of blood flow (arterial diameter and blood flow velocity).

Doppler ultrasound, a non-invasive technique, was used to assess resting bilateral femoral artery diameter and blood flow velocity in seventeen people with chronic stroke. This dissociation of blood flow into diameter and velocity provides a better understanding of the vascular alterations that occur in the hemiparetic limb after stroke. In addition, the adventitia of the femoral artery was assessed to determine vessel wall thickness, which may be related to arterial stiffness. The findings in Chapter 4 lead to interesting topics for consideration regarding the mechanisms responsible for the arterial adaptations in the hemiparetic limb after stroke.

## Chapter 4

### Use of Doppler Ultrasound to Assess Femoral Artery Adaptations in the Hemiparetic Limb in Chronic Stroke

Billinger, S. A., Kluding, P. M. Use of Doppler Ultrasound to Assess Femoral Artery Adaptations in the Hemiparetic Limb in People with Stroke. (revised and resubmitted, *Cerebrovascular Disease*, November, 2008).

#### **4.1 Abstract**

**Objective:** A reduction in physical activity combined with decreased demand for leg oxygen consumption may affect blood flow to the hemiparetic lower extremity after stroke. The purpose of this study was to characterize femoral artery adaptations that occur in the hemiparetic leg in chronic stroke. A secondary goal was to examine intra-rater reliability using Doppler ultrasound in people with hemiparesis after stroke.

**Design:** Descriptive study using a sample of convenience

**Setting:** University medical center research laboratory

**Participants:** Seventeen individuals ( $68.1 \pm 3.9$  years of age; 15 male) with chronic stroke ( $5.9 \pm 1.1$  years post-stroke; 12 with right-side hemiparesis) participated in the study.

**Intervention:** None

**Main Outcome Measures:** Femoral artery blood flow, diameter, velocity and vessel wall thickness in bilateral lower extremities with chronic stroke. Intra-rater reliability was determined for femoral artery diameter and blood flow velocity.

**Results:** Femoral artery blood flow, arterial diameter, and blood flow velocity were significantly lower ( $p < 0.0001$ ) in the hemiparetic limb when compared to the less affected limb. Femoral artery vessel wall thickness was significantly greater ( $p = 0.002$ ) in the hemiparetic limb. Doppler ultrasound intra-rater reliability was strong and significant ( $ICC_{3,1} > 0.94$ ;  $p < 0.0001$ ) for femoral artery diameter and blood flow velocity measures.

**Conclusion:** These data suggest that individuals with chronic stroke demonstrate vascular changes in the femoral artery of the hemiparetic limb.

## 4.2 Introduction

Reductions in blood flow specifically to the lower extremities have been reported during periods of bed rest,(Bleeker, De Groot, Poelkens et al., 2005) and after neurological injury such as chronic stroke (Ivey et al., 2004; Landin et al., 1977) and spinal cord injury.(De Groot et al., 2003; Hopman et al., 2002; Thijssen et al., 2006) The literature suggests these vascular adaptations occur secondary to decreased levels of physical activity,(Bleeker, De Groot, Poelkens et al., 2005; Dinunno et al., 1999) which can affect blood flow velocity, arterial diameter, and endothelial function. As demonstrated by both animal (Brownlee & Langille, 1991; Langille & O'Donnell, 1986) and human research,(Brownlee & Langille, 1991; Ivey et al., 2004; Landin et al., 1977; Thijssen et al., 2006) when arterial blood flow is reduced, changes in vessel diameter can occur. For individuals with bilateral paralysis such as spinal cord injury (SCI), vascular adaptations and arterial remodeling can be observed within 3 weeks after the injury.(de Groot, Bleeker, van Kuppevelt et al., 2006) Furthermore, blood flow in the femoral artery is significantly lower after SCI when compared to age-matched controls.(De Groot et al., 2003) These differences may result from decreased muscle use (Ivey et al., 2004; Landin et al., 1977) and reduced demand for leg oxygen consumption,(Dinunno et al., 1999) which may be responsible for reductions in blood flow. Similar findings have been reported in the stroke literature. Only two studies suggest that resting blood flow is significantly reduced in the hemiparetic lower extremity when compared to the non-hemiparetic limb in people post-stroke.(Ivey et al., 2004; Landin et al., 1977) However, to our knowledge, no information is available regarding the components of blood flow in the hemiparetic limb such as femoral artery diameter or blood flow velocity. Interestingly, unilateral differences in the lower extremity are not found

in healthy young and older adults regarding femoral artery diameter (Bleeker, De Groot, Poelkens et al., 2005) and blood flow velocity.(Bleeker, De Groot, Rongen et al., 2005)

The result of deconditioning and lower demand for oxygen consumption in the hemiparetic limb may also affect vascular resistance. Again, it may be postulated that increased vascular resistance may occur as a result from decreased physical activity similar to the findings from studies related to bed rest (Hughson et al., 2007) and after SCI.(Hopman et al., 2002) Increased artery wall thickness or hypertrophy (Ueno, Kanellakis, Agrotis, & Bobik, 2000) can occur after reductions in blood flow, which could have implications related to vascular conductance (Hopman et al., 2002) or compliance. However, in people after stroke, these mechanisms related to arterial adaptations in the hemiparetic limb are not understood.

Doppler ultrasound has been used to quantify both arterial diameter and blood flow velocity in humans.(Kooijman et al., 2008; Newcomer, Leuenberger, Hogeman, Handly, & Proctor, 2004; Newcomer, Leuenberger, Hogeman, & Proctor, 2005) The literature reports that in healthy adults Doppler ultrasound is a reliable tool for assessing arterial characteristics and blood flow.(Gill, 1985) However, people with stroke can present with limited in range of motion in the hemiparetic leg due to increased or lack of muscle tone. Positioning after stroke can be cumbersome and difficult to maintain for a period of time. This may potentially affect the ability to obtain accurate measurements in the hemiparetic limb. Therefore, we sought to examine the feasibility and reliability of obtaining femoral artery measures in people post-stroke.

The primary purpose of this study was to characterize femoral artery diameter, blood flow velocity and vessel wall thickness in people post-stroke. We hypothesized that femoral artery 1) diameter would be smaller, 2) blood flow velocity would be reduced, and 3) wall

thickness would be greater in the hemiparetic limb when compared to the non-hemiparetic limb. Finally, a secondary goal was assess intra-rater reliability to obtain femoral artery measures in people after stroke using Doppler ultrasound.

### **4.3 Materials and Methods**

#### *Participants*

Eighteen men and women ( $68.4 \pm 2.7$  years,  $5.7 \pm 1.1$  years post-stroke, means  $\pm$  SE; Table 1) were recruited to participate in the study. Individuals were recruited for this multi-site study from two local stroke support groups and the ASTRA (Advancing Stroke Treatment through Research Alliances) participant database. Participants reported their weekly physical activity levels using the physical activity record (PAR) and the type of assistive device used for mobility. Predicted  $VO_2$  max was calculated from a non-exercise estimation of  $VO_2$  max prediction equation using the PAR.(Jackson et al., 1990) Inclusion criteria for this study was: 1) a diagnosis of stroke  $\geq$  6 months, 2) the ability to rise from sitting to standing and transfer to a mat with or without physical assistance and 3) a score of  $\geq$  24 on the Mini Mental Status exam to establish the ability to give informed consent for this study. Exclusion criteria were as follows: 1) Type 1 or 2 diabetes; 2) recent cardiovascular event, 3) currently smoking or pulmonary pathology, 4) active involvement in unilateral exercise using the hemiparetic limb to avoid the effects of exercise on blood flow or 5) currently receiving skilled physical therapy focused on the hemiparetic leg. The Human Subjects Committee at both universities approved the study. Institutionally approved informed consent was obtained in writing prior to participation in the study.

### *Experimental Design*

This study was a sample of convenience to: 1) characterize femoral artery diameter, blood flow velocity and vessel wall thickness in people post-stroke and 2) determine intra-rater reliability of femoral artery measures (diameter and blood flow velocity) using MicroMaxx\* Doppler ultrasound.

### *Procedure*

Individuals were asked to lie supine on a therapy mat quietly for 30 minutes prior to data collection. Pillows or towel rolls were placed under the knees or arms for comfort, if needed. For all participants, the right femoral artery was scanned first and then the left. (Ivey et al., 2004) Food and drink intake was restricted 30 minutes prior to all ultrasound scans. (Peiffer, Abbiss, Laursen, & NoSaka, 2007) Duplicate measures were taken on each leg for femoral artery diameter and blood flow velocity. The average of the two measures was used for comparison between the hemiparetic and non-hemiparetic limb. For assessing Doppler ultrasound reliability (n = 17), the same investigator used identical testing procedures for Doppler ultrasound measurements on 2 consecutive days (Day 1 and Day 2) at the approximately the same time. Participants were instructed to perform normal daily activities between Day 1 and Day 2 of testing.

### *Femoral Artery Measurements*

To measure diameter, the femoral artery was scanned and identified first in a cross-sectional view just above the bifurcation of the common femoral artery at peak systole and end diastole using pulsed Doppler signal. Once the image was obtained and frozen on the

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\* Sonosite, Inc., 21919 30th Drive SE Bothell, WA 98021-3904 USA

screen, arterial diameter (cm) measurements were taken from the superior medial border to the inferior medial border. For femoral artery blood flow velocity ( $\text{cm}\cdot\text{sec}^{-1}$ ), a longitudinal view of the vessel was used. First, the bifurcation of the vessel was identified and the area of interest was determined, which was 1 cm from the bifurcation of the femoral artery.(Newcomer et al., 2005) This reduces variability of the measurement and avoids turbulent flow at the femoral artery bifurcation site. The angle of inclination was maintained at  $60^\circ$  (Newcomer et al., 2004) and the velocity gate was set wide open to obtain peak systolic blood flow velocity across the entire arterial wall.(Newcomer et al., 2004; Osada, 2004; Parker et al., 2007; Radegran, 1997) Blood flow was then calculated using the equation:  $\text{blood flow (BF)} = ((\pi) * (\text{femoral artery peak systolic radius})^2 * (\text{mean blood flow velocity}) * (60))$ .(Anton et al., 2006) Mean blood flow velocity was averaged from 3 cardiac cycles.(Hopman et al., 2002) All reported values for arterial diameter and velocity measurements are the average of Day 1 and 2.

Measurements for arterial wall thickness ( $n=15$ ) were obtained in duplicate from the “far wall” (Wendelhag, Gustavsson, Suurkula, Berglund, & Wikstrand, 1991) of the femoral artery Doppler ultrasound scans. The bitmap images from the scans were magnified and pixel intensity was calculated (Beletsky, Kelley, Fowler, & Phifer, 1996) using Adobe Photoshop<sup>†</sup>. Due to software technical difficulties, one individual’s images were deleted. Mean blood flow velocity and arterial wall thickness could not be measured.

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<sup>†</sup> Adobe Systems, 345 Park Ave. San Jose, CA 95110-2704



### *Statistical Analysis*

#### *Femoral Artery Measurements*

Two-tailed paired t-tests were performed to assess differences in femoral artery diameter, blood flow velocity and vessel wall thickness between the hemiparetic and non-hemiparetic limb. To determine if a relationship existed between predicted VO<sub>2</sub> max and interlimb blood flow differences, Pearson's correlation coefficient was used.

#### *Intra-rater Reliability*

To determine intra-rater reliability, an Intraclass Correlation Coefficient (ICC<sub>3,1</sub>) was calculated for the repeated measures [days 1 and 2] and a one-way ANOVA F-statistic was used to test for statistical significance for both artery diameter and blood flow velocity in the hemiparetic limb and then for the non-hemiparetic limb. To adjust for multiple comparisons, statistical significance was set at  $\alpha \leq 0.01$  for data analysis. SPSS 15.0<sup>‡</sup> statistical software was used to perform all statistical analysis.

## **4.4 Results**

### *Femoral Artery Diameter, Blood Flow Velocity, and Vessel Wall Thickness*

Data was collected from eighteen individuals post-stroke to characterize differences in femoral artery diameter and blood flow velocity between the hemiparetic and less involved lower extremity (Table 4.1). One individual's data was excluded from the data set because femoral artery blood flow velocity values in the hemiparetic limb were above 300 cm\*sec<sup>-1</sup>. This individual's blood flow velocity was above the Doppler ultrasound's limits and accurate measures could not be obtained.

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<sup>‡</sup> SPSS, Inc; 233 S. Wacker Drive 11th Floor Chicago, IL 60606

For the 17 participants, femoral artery blood flow in the hemiparetic limb was 30.0% less than the non-hemiparetic limb, which was statistically significant ( $p < 0.001$ ) (Table 2). Mean arterial diameter and peak blood flow velocity between the two limbs was significantly different ( $p < 0.001$ ; Figure 4.1 and 4.2). Femoral artery wall thickness on the hemiparetic limb was significantly greater ( $p = 0.002$ ) than the non-hemiparetic limb (Table 4.2).

A non-significant relationship was found using Pearson's correlation coefficient for predicted  $\text{VO}_2$  max and interlimb blood flow differences ( $r = -0.090$ ;  $p = 0.73$ ).

#### *Intra-rater Reliability Testing*

Intra-rater reliability for Doppler ultrasound measurements of the femoral artery diameter and blood flow velocity was strong. The ICC values for femoral artery diameter for the hemiparetic limb were 0.99 ( $F = 678.09$ ,  $p < 0.0001$ ) while the non-hemiparetic limb ICC values were 0.96 ( $F = 54.14$ ,  $p < 0.0001$ ). The ICC values for femoral artery blood flow velocity for the hemiparetic and non-hemiparetic limb were 0.96 ( $F = 60.12$ ,  $p < 0.0001$ ) and 0.98 ( $F = 97.79$ ,  $p < 0.0001$ ), respectively.

## **4.5 Discussion**

### *Femoral Artery Blood Flow, Diameter, Velocity and Vessel Wall Thickness*

Our results are consistent with previous research (Ivey et al., 2004; Landin et al., 1977) that have demonstrated reduced blood flow in the hemiparetic leg when compared to the less affected leg in individuals after stroke. We observed a 30.0% reduction in mean femoral artery blood flow, which is similar to the literature reporting mean differences at -30% (Ivey et al., 2004) and -40%, (Landin et al., 1977) respectively when comparing the hemiparetic leg to the less affected side. In addition, our findings extend previous research

suggesting that decreased femoral artery blood flow in the hemiparetic limb results from chronic arterial adaptations such as 1) smaller arterial diameter and 2) diminished blood flow velocity. Arterial diameter adaptations that occur the hemiparetic leg may be similar to those reported after unilateral limb suspension.(Bleeker, De Groot, Poelkens et al., 2005) In this unique model of reduced physical inactivity, the leg avoids weight-bearing activities to mimic deconditioning from disuse.(Bleeker, De Groot, Poelkens et al., 2005; Bleeker, Kooijman, Rongen, Hopman, & Smits, 2005) For individuals after a SCI, limited or complete cessation of active muscle contraction occurs below the level of the lesion. In this chronic model whereby physical inactivity and bilateral lower extremity deconditioning occur, femoral artery diameter is significantly smaller post-SCI than in healthy age-matched controls.(de Groot, Bleeker, van Kuppevelt et al., 2006) Since no research studies were found that assessed femoral artery diameter changes in the hemiparetic leg post-stroke, we sought to examine whether vascular remodeling would parallel results from other studies such as unilateral limb suspension and spinal cord injury. Using Doppler ultrasound, we reported a statistically significant smaller arterial diameter in the hemiparetic limb when compared to the less affected side.

Our results suggest that people with stroke demonstrate reduced femoral artery blood flow velocity in the hemiparetic leg. Although research citing blood flow velocity changes in the hemiparetic leg are scarce, our results demonstrate differences between the two limbs do exist. While individuals post-stroke tend to lead a sedentary lifestyle,(Gordon et al., 2004) individuals in this study were primarily ambulatory (see Table 4.1) which is in contrast to individuals after SCI who used a wheelchair for mobility. This may suggest that the amount of volitional muscle movement may influence the magnitude of arterial remodeling that

occurs in the lower extremities in certain clinical populations. Certainly, this is an avenue of research that requires further exploration.

Our findings suggest that the femoral artery in the hemiparetic limb adapts to a change in arterial wall shear stress to maintain a constant rate of blood flow. This relationship between arterial diameter and blood flow velocity (flow-diameter relationship) (Ono et al., 1991) results as the endothelial cells react to either an increase or decrease in vessel wall shear stress.(Brownlee & Langille, 1991; de Groot, Bleeker, van Kuppevelt et al., 2006; Kamiya et al., 1988; Langille & O'Donnell, 1986) The flow-diameter relationship (Ono et al., 1991) has been reported in the literature related to sedentary individuals,(Bleeker, De Groot, Poelkens et al., 2005) older populations (DeSouza et al., 2000; Newcomer et al., 2005; Singh, Prasad, Singer, & MacAllister, 2002) and post-SCI.(de Groot, Bleeker, van Kuppevelt et al., 2006; Kooijman et al., 2008; Thijssen et al., 2006) Interestingly, healthy young and older adults have reported no significant differences for femoral artery diameter (Bleeker, De Groot, Poelkens et al., 2005; Radegran & Saltin, 2000) and blood flow velocity (Bleeker, De Groot, Poelkens et al., 2005; Thijssen, Rongen, van Dijk, Smits, & Hopman, 2007) when comparing the two limbs, which is contrary to our findings in these individuals post-stroke. We believe that our findings lead to interesting topics for consideration regarding the mechanisms responsible for the arterial adaptations in the hemiparetic limb.

Doppler ultrasound has been used to assess wall thickness in the carotid artery (Wendelhag et al., 1991) and femoral artery.(Anton et al., 2006) We chose to examine the vessel wall tissue density, which may be influence arterial stiffness or compliance if vessel wall thickness increases.(Glasser et al., 1998) We did observe increased vessel wall thickness in the femoral artery in the hemiparetic limb when compared to the non-hemiparetic limb. The clear differences in blood flow velocity and vessel diameter in the femoral artery of the

hemiparetic side and the less involved leg after stroke is certainly interesting. However, the more important question may be why these changes are occurring. The mechanisms involved in the changes in blood flow may be related to increased stiffness values of the vessel.(Glasser et al., 1998) If stiffness is greater in the hemiparetic limb, there are two plausible causes; 1) changes in vascular smooth muscle cell tone due to brain injury with the stroke and, 2) changes in the passive properties of the tissue likely due to fibrosis in the vessel adventitia. The experiments described in this study were not designed to evaluate smooth muscle tone, but give some hints as to changes in the passive structure of the vessel. Increased density in the outer region of the vessel point to a change in the adventitia that would negatively affect vessel compliance; something that future studies must examine. Ivey and colleagues (2004) reported a significant decrease in leg blood flow to the hemiparetic limb after ischemic hyperemia. While not directly assessed by Ivey, this may be due to increased stiffness in the artery and an impaired vasodilation response in the hemiparetic limb. Finally, individuals in Ivey's study did not exhibit peripheral artery disease (PAD) defined by ankle brachial index (ABI)  $\leq 0.90$ .(McDermott, Ferrucci et al., 2002; McDermott, Greenland et al., 2002) Contrary to the findings by Ivey, we report low ABI values (ABI = 0.88) on the hemiparetic side for a subset (n=6) participants. Low ABI post-stroke may be indicative of increased peripheral resistance and atherosclerotic-induced changes.(Nakano, Ohkuma, & Suzuki, 2004) Although heart disease and recurrent stroke are the primary causes of mortality after stroke, (Gordon et al., 2004) peripheral vascular changes such as PAD can influence the occurrence of stroke (Rother et al., 2008) and lower extremity function.(McDermott, Ferrucci et al., 2002; McDermott, Greenland et al., 2002) Since a paucity of information exists regarding overall vascular changes in the hemiparetic limb post-stroke, future research should emphasize the role of these regulatory mechanisms, time

course in which these adaptations begin, and determine any effects of an intervention strategy.

Decreased levels of physical activity and a lower demand for oxygen consumption have been plausible explanations driving these vascular adaptations especially in clinical populations.(Bleeker, De Groot, Poelkens et al., 2005; Dinunno et al., 1999; Posner et al., 1992) However, we found that predicted  $\text{VO}_2$  peak was not significantly related interlimb differences in femoral artery blood flow. One plausible explanation may be related to the accuracy of the non-exercise estimation of  $\text{VO}_2$  max. Although Jackson and colleagues (1990) reported the non-exercise estimation of  $\text{VO}_2$  max was valid for adults, they noted the prediction model was most accurate for individuals with a peak  $\text{VO}_2$  between  $36\text{-}55 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . Previous studies report mean  $\text{VO}_2$  peak values for people post-stroke under  $25 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ .(Mackay-Lyons & Makrides, 2002; Yates et al., 2004) Rather, objective measures obtained from a maximal effort graded exercise test may have provided a better representation for cardiorespiratory fitness. Therefore, a stronger relationship may have been observed between  $\text{VO}_2$  peak and femoral artery blood flow.

#### **4.6 Conclusion**

In summary, results from this study suggest that vascular remodeling in the femoral artery occurs in the hemiparetic limb after stroke. We found that resting femoral artery diameter and blood flow velocity were significantly lower in the hemiparetic limb when compared to the less affected side. Significant changes in the arterial vasculature post-stroke may be indicative of maintaining the flow-diameter relationship. Furthermore, we assessed one potential mechanism that may affect vascular resistance, which was vessel wall thickness. We found femoral artery wall thickness to be significantly greater in the

hemiparetic limb. Future studies investigating the other possible mechanisms regulating these changes and overall vascular function in people post-stroke would be advantageous. Finally, we found Doppler ultrasound to be a feasible and reliable tool for assessing resting femoral artery characteristics in people post-stroke.

## Chapter 4 Tables and Figures

Table 4.1 Participant Characteristics (n = 18). Values are means  $\pm$  SE.

<i>Characteristics</i>	<i>Values</i>
Men/women	15/3
Hemiparetic side: right/left	12/6
Age (years)	68.4 $\pm$ 3.7
Time post-stroke (years)	5.7 $\pm$ 1.1
Hypertensive Medications	13
Ankle-Brachial Index (n =6)	0.88 $\pm$ 0.03
Mobility	
Independent	10
Walker	3
Wheelchair	1
Cane	4



Table 4.2 Femoral Artery Characteristics and Predicted VO<sub>2</sub> max (n = 17 unless indicated otherwise) Values are means ± SE.

	<i>Values</i>
Non-exercise estimated VO <sub>2</sub> Max (ml*kg <sup>-1</sup> * min <sup>-1</sup> )	13.3 ± 1.4
HP Femoral Artery Blood Flow (ml * min <sup>-1</sup> )	510.32 ± 178.00*
NHP Femoral Artery Blood Flow (ml * min <sup>-1</sup> )	744.76 ± 188.44
HP Femoral Artery Wall Thickness <sup>†</sup>	107.5 ± 6.9*
NHP Femoral Artery Wall Thickness <sup>†</sup>	84.2 ± 4.9

\* p <0.01; † n= 15

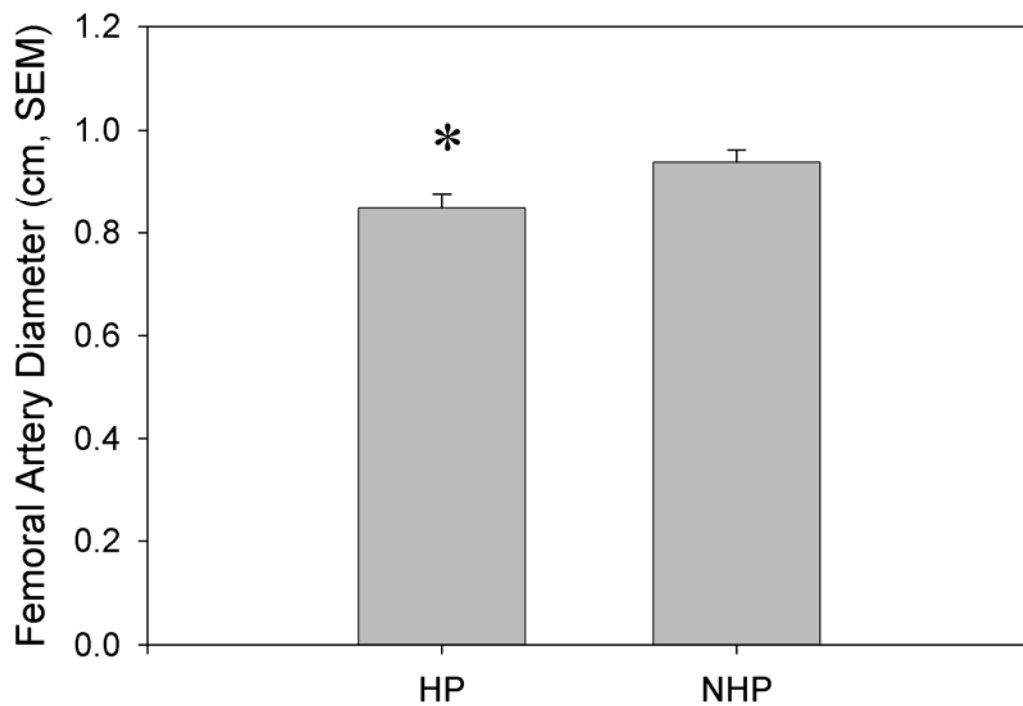


Figure 4.1 Differences in Femoral Artery Diameter in the Hemiparetic (HP) Versus Less Affected Limb (NHP) (n = 17); \*p=0.001.

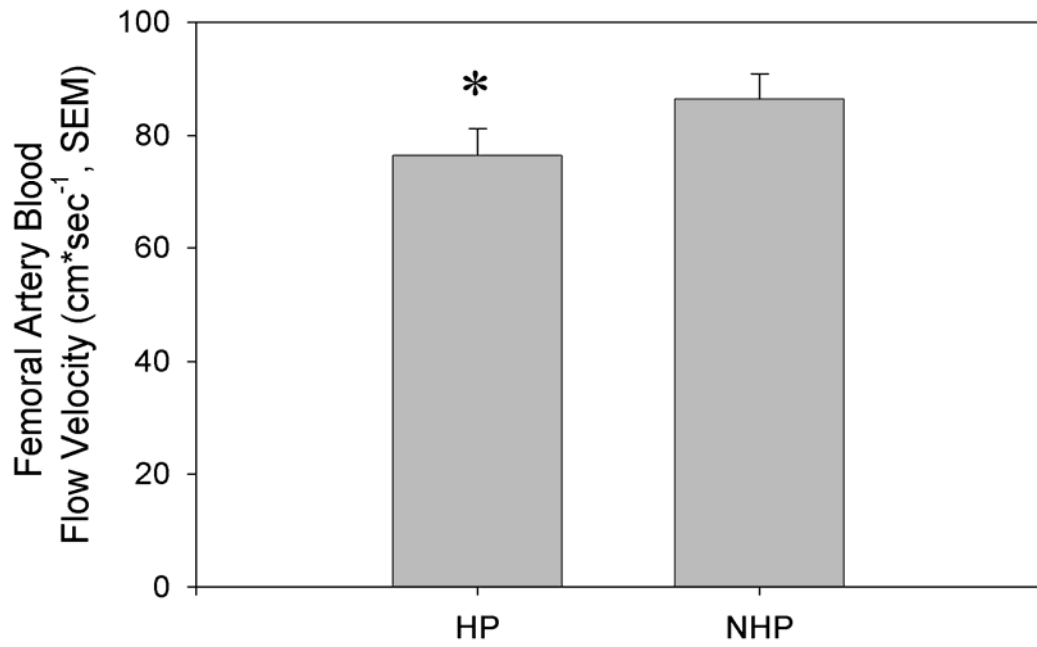


Figure 4.2 Differences in Femoral Artery Blood Flow Velocity in the Hemiparetic (HP) Versus Less Affected Limb (NHP) (n = 17); \*p = 0.005

## **Chapter 5 Preface**

Chapter 4 highlights the vascular adaptations that occur in the hemiparetic limb in people with stroke. We found that regardless of the time post-stroke or self-reported physical activity level, femoral artery diameter and blood flow velocity are reduced in the hemiparetic limb.

In Chapter 5, we describe the effect of a single limb exercise (SLE) protocol to encourage use of the hemiparetic limb. The guiding principle behind SLE is to increase physical activity and oxygen consumption by the exercising muscle in order to stimulate greater blood flow delivery and increase arterial diameter. Outcome measures (femoral artery blood flow, diameter and velocity) were assessed in both limbs at baseline, after 6 exercise sessions and post-intervention.

## Chapter 5

Single Limb Exercise Induces Femoral Artery Remodeling and Improves Blood Flow in the  
Hemiparetic Leg Post-Stroke

To be submitted for publication to *Stroke*, December, 2009

## 5.1 Abstract

**Background and Purpose:** After stroke, individuals may experience decreased blood flow in the femoral artery in the hemiparetic leg. This may be due to lower levels of muscle oxygen consumption in the hemiparetic leg. The purpose of this study was to determine the effect of single limb exercise (SLE) on femoral artery blood flow, diameter and peak flow velocity in the hemiparetic leg after stroke. **Methods:** Twelve individuals ( $60.6 \pm 14.5$  years of age; 5 male) with chronic stroke ( $69.1 \pm 82.2$  months; 5 with right-side hemiparesis) participated in the study. The intervention consisted of a SLE knee extension/flexion protocol three times per week for 4 weeks. Using Doppler ultrasound, bilateral femoral artery blood flow, diameter and peak flow velocity was assessed at baseline, after 2 weeks (T1) and after 4 weeks (post) of SLE. **Results:** Femoral artery blood flow, arterial diameter, and blood flow velocity in the hemiparetic limb were significantly improved ( $p < 0.0001$ ) after the SLE. No significant changes occurred in the non-trained limb for any outcome measures. **Conclusions:** These data suggest that a 4-week SLE training program using the hemiparetic limb improves femoral artery blood flow, diameter, peak velocity. SLE may be an important training strategy in stroke rehabilitation to minimize the vascular changes that occur post-stroke due to decreased activity of the hemiparetic limb.

## 5.2 Introduction

Blood flow distribution is governed by central cardiovascular command (parasympathetic/sympathetic activity)(Williamson, Fadel, & Mitchell, 2006) and peripheral mechanisms such as metabolic demand, peripheral resistance and alterations in pressure.(Gerrits et al., 2001; Mohrman & Heller, 2006) Exercise is a potent stimulus that promulgates adaptive responses to meet the metabolic demands of the working muscles.(Bottini et al., 1995; Mortensen et al., 2005; G. D. Thomas & Segal, 2004) One example would be the concerted response between arterial vasodilation and increased blood flow. At the onset of exercise, there is an immediate rise in vasoactive metabolites that facilitates vasodilation of the arterial vasculature and increases blood flow to the contracting skeletal muscles.(Asanoi et al., 1992; Segal, 2005; G. D. Thomas & Segal, 2004) Muscle oxygen demand is the primary regulator of blood flow in the skeletal muscle.(Mohrman & Heller, 2006)

Aging (Dinenno et al., 1999; Olive, DeVan, & McCully, 2002; Schmidt-Trucksass et al., 1999) and disease-induced changes (De Groot et al., 2003; Hopman et al., 2002; Ivey et al., 2004; Kingwell et al., 2003; Landin et al., 1977; Lind & Lithell, 1993; Maiorana et al., 2001; Meyer et al., 2004; Olive et al., 2003) can alter physiological function and demonstrate increased vascular resistance, decreased oxygen demand, and arterial remodeling.

Specifically, people after stroke often present with decreased cardiorespiratory fitness (Mackay-Lyons & Makrides, 2002; Macko, DeSouza et al., 1997) and peripheral vascular adaptations (i.e. reduced blood flow, decreased arterial diameter and endothelial dysfunction) in the hemiparetic leg as demonstrated in Chapter 4 and by others.(Ivey et al., 2004; Landin et al., 1977) These vascular changes in the hemiparetic limb increase the risk for mortality related to a cardiovascular event.(Gordon et al., 2004; Ivey et al., 2004; Roth, 1993) However, participation in regular physical activity such as aerobic exercise can alter these

pathological vascular changes in people with obesity,(Watts et al., 2004) Type 2 diabetes,(Maiorana et al., 2001) spinal cord injury,(Gerrits et al., 2001; Hopman et al., 2002; Zbogar et al., 2008) and coronary artery disease.(Hambrecht et al., 2000)

Most exercise interventions for people post-stroke focus on bilateral activity such as treadmill walking or cycling. However, evidence in the literature has suggested a reduced work effort by the hemiparetic limb during bilateral exercise than the less affected limb.(Chen et al., 2005; Landin et al., 1977; Sibley et al., 2008) This indicates a need to identify an exercise training strategy that would primarily focus on the hemiparetic limb to maximize work effort.

In healthy adults, single limb exercise (SLE) has been performed using a knee extension/flexion protocol or unilateral cycling.(Asanoi et al., 1992; Bell et al., 2001; Davies & Sargeant, 1975; Hardman et al., 1987; Klausen et al., 1982; Miyachi et al., 2001; Paterson et al., 2005; Radegran & Saltin, 2000; Saltin et al., 1976; Shoemaker et al., 1994; Wernbom, Augustsson, & Thomee, 2006) The evidence overwhelmingly implies SLE training can be a useful intervention to increase both arterial diameter and blood flow in the trained leg.(Bell et al., 2001; Davies & Sargeant, 1975; Klausen et al., 1982; Miyachi et al., 2001; Saltin et al., 1976; Shoemaker et al., 1994) Therefore, we chose to use SLE as a novel aerobic training intervention to modify femoral artery adaptations that can occur after stroke. For this study, we used the Biodex and a knee extension/flexion protocol. The advantage of this novel exercise training protocol in chronic stroke was the focused and encouraged use of the hemiparetic limb. Initially, we completed pilot data assessing the feasibility of a focused SLE knee extension/flexion protocol in one person post-stroke. This individual completed the thrice weekly training sessions for 3 weeks without any adverse events.



The purpose of the present study was to characterize the effects of a 4-week SLE training intervention on cardiovascular function in the hemiparetic limb in people post-stroke. We hypothesized that after the SLE training intervention significant improvements in femoral artery: 1) blood flow, 2) diameter, 3) peak blood flow velocity and 4) conductance would be observed after the training period when compared to baseline measures. Lastly, to determine if systemic vascular function would improve after SLE, we hypothesized that ABI would improve to the normal ranges of  $0.90 \geq 1.40$  as defined by Resnick and colleagues.(2004)

Tissue composition using a dual emission x-ray absorptiometry (DEXA) assessed lean tissue in both the hemiparetic and less affected limbs at baseline and post-training. This allowed for within and between-limb lean tissue comparison at the respective timepoints. The rationale for observing lean tissue changes was to ensure that improved blood flow was not the result of increased lean tissue.

### **5.3 Methods**

#### *Participants*

Thirty-three individuals were recruited to participate in this study. Twenty-two individuals were unable to participate for the following reasons: 1) did not meet the inclusion criteria (n = 15) and travel expenses (n = 7). Twelve participants with chronic stroke completed this within subject design study (Table 5.1). Inclusion criteria included: 1) a diagnosis of hemiparesis from a stroke at least 6 months ago confirmed by clinical assessment using criteria defined by the World Health Organization (WHO, 2004); 2) the ability to transfer from a sitting to standing position with minimal assist; 3) walking 10 meters independently with or without an orthotic or assistive device, 4) mild to moderate stroke deficits defined by a lower extremity Fugl-Meyer (LEFM) score from 20 to 33/34

(Daly et al., 2006); 5) 35 degrees of active knee extension/flexion with movement against gravity and 6) medical clearance from primary care physician for exercise testing and prescription. Exclusion criteria consisted of the following: 1) recent hospitalization; 2) new diagnosis or severe cardiopulmonary conditions; 3) currently smoking, 4) type 1 or 2 diabetes; (5) current participation in single limb exercise or physical therapy; (6) peripheral vascular disease (ABI < 0.40) or known stenosis of the lower extremity vessels (7) prescribed medications that improve vasodilation and (8) a difference  $\leq 2\%$  between the hemiparetic and less affected limbs for arterial diameter and blood flow velocity.

Institutionally approved informed consent was obtained in writing prior to enrollment in the research study.

### *Experimental Design*

This study was a sample of convenience to determine the effect of a single limb exercise (SLE) program on: 1) femoral artery blood flow, diameter, peak blood flow velocity, vascular conductance and 2) ankle-brachial index (ABI) in the hemiparetic and less affected limb in people post-stroke. Dual emission x-ray absorptiometry (DEXA) was used at baseline and post-intervention to assess any changes in lean tissue mass.

### *General Testing Procedures*

Individuals were asked to lie supine on a therapy mat quietly for 30 minutes prior to data collection. Pillows or towel rolls were placed under the knees or arms for comfort, if needed. For measurements, the right side was assessed first and then the left. (Ivey et al., 2004) Doppler ultrasound measures were taken in duplicate for femoral artery diameter (at peak systole) and blood flow velocity. A research assistant performed the second

measurement while the image was frozen on the screen. This individual was blinded to limb at the time of assessment. The average of the two measures was used in data analysis for both the hemiparetic and less affected limb. Food and drink intake was restricted 30 minutes prior to all ultrasound scans.(Peiffer et al., 2007) All femoral artery measures were taken at least 24 hours (range 24-48 hours) after SLE to avoid the effects of an acute bout of exercise.(Anton et al., 2006)

### *Femoral Artery Measurements*

The femoral artery was scanned and identified in a cross-sectional view just above the bifurcation of the common femoral artery. With the image frozen on the screen, femoral artery diameter was obtained at peak systole. The R-wave from an electrocardiogram (ECG) was used to determine the location at which peak systole occurred (Figure 5.1). Arterial diameter (cm) measurements were taken from the superior medial border to the inferior medial border. For each limb, two ultrasound images were taken. The average of the two measures were calculated and recorded.

To assess femoral artery blood flow velocity ( $\text{cm}\cdot\text{sec}^{-1}$ ), a longitudinal view of the vessel was used. First, the bifurcation of the vessel was identified and the area of interest was determined. Measurements were taken at 1 cm from the bifurcation of the femoral artery (Newcomer et al., 2005; Osada, 2004) to avoid turbulent flow. The angle of inclination was maintained at  $60^\circ$  (Newcomer et al., 2004; Olive et al., 2003; Parker et al., 2007; Radegran, 1997) and the velocity gate was positioned across the width of the vessel wall to obtain peak systolic blood flow velocity.(Newcomer et al., 2004; Olive et al., 2003; Osada, 2004; Parker et al., 2007; Radegran, 1997) Peak blood flow velocity was recorded as the highest speed at which blood flowed through the vessel. Five cardiac cycles were assessed for each of the two

images. The highest peak blood flow velocities for the two images were averaged and recorded. (Figure 5.2)

Blood flow was calculated using the equation: blood flow (BF) = (( $\pi$ ) \* (femoral artery radius)<sup>2</sup> \* (mean blood flow velocity ( $V_{mean}$ )) \* (60)).(Anton et al., 2006)  $V_{mean}$  is the average blood flow velocity (see equation 1) of the Doppler waveform for one cardiac cycle.(Gerrits et al., 2001) (Figure 5.3) Two images with 3 cardiac cycles each were used to calculate  $V_{mean}$ . Cardiac cycle waveforms were traced by a single investigator. The average of the 6 cycles was used for data analysis.

$$\text{Equation \#4.1: } V_{mean} = ((V_{max} + V_{min} + V_{dias})/3))^{\S}$$

Vascular conductance (Newcomer et al., 2004; Parker et al., 2007; Radegran & Saltin, 2000) was calculated using the following equation:

$$\text{Equation \# 4.2: } \text{Vascular conductance} = \text{BF}/\text{MAP}(\text{mean arterial pressure})$$

$$\text{Equation \#4.2a: } \text{MAP}(\text{Thijssen et al., 2007}) = ((2/3)*(DBP)) + ((0.333)*(SBP-DBP))^{**}$$

#### *Ankle Brachial Index (ABI)*

To perform the ABI test, the participant was resting for at least 10 minutes (McDermott, Ferrucci et al., 2002) in a supine position. An appropriately sized blood pressure (BP) cuff was placed above the antecubital space at the brachial artery for each arm and then above each malleolus to assess the tibialis posterior and dorsalis pedis arteries. For each systolic BP measurement, the cuff was inflated 20 mmHg above the last audible heart rate sound.(McDermott, Ferrucci et al., 2002) The BP cuff was slowly deflated by 2-4

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<sup>\S</sup>  $V_{max}$  = highest velocity measured;  $V_{min}$  = lowest velocity measured;  $V_{dias}$  = velocity at end diastole in one cardiac cycle. Values are determined from the Doppler waveform spectrum.

<sup>\*\*</sup> SBP= Systolic Blood Pressure(mmHg); DBP = Diastolic Blood Pressure(mmHg)

mmHg. Using a portable 5Mhz LifeDop<sup>††</sup> hand-held Doppler probe, we measured systolic blood pressure similar to the methods by McDermott and colleagues (McDermott, Ferrucci et al., 2002) regarding sequence.

First, the right brachial artery was assessed then the posterior tibialis followed by the dorsalis pedis. For left-side systolic BP, these were performed in the reverse order: dorsalis pedis, posterior tibialis and finally brachial artery. ABI was calculated by dividing the highest systolic arm BP by the highest right-side lower extremity BP measurement and then repeated for the left side. The lowest value of the two calculations was recorded as the participant's ABI. (Lefebvre, 2006; McDermott, Ferrucci et al., 2002) Since the hemiparetic side was an area of interest, ABI was assessed in the affected limbs. Therefore, using the limbs on the stroke-affected side, we used the systolic BP reading from the arm and divided the value by the highest lower extremity reading ( $ABI_{\text{hemi}}$ ).

#### *Dual Emission X-ray Absorptiometry (DEXA)*

Lean tissue and fat mass for bilateral lower extremities (greater trochanter to the foot) was assessed at baseline and post-intervention using DEXA<sup>||</sup> scans. Participants avoided food or water consumption 3 hours prior to the scan. The participants were asked to lie in the supine position while the DEXA scan was performed.

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<sup>††</sup> SummitDoppler, 4620 Technology Dr. Unit 100, Golden CO 80403

<sup>||</sup> GE Lunar, 726 Heartland Trail, Madison, WI 53717

### *Single Limb Exercise Training Protocol*

Single limb exercise (SLE) involved isokinetic movement on the Biodex System 3<sup>\*\*</sup> using only the hemiparetic limb. During the initial training session, participants were positioned comfortably in the seat and parameters set for leg length, chair height, and trunk support. These values were recorded and used for consistency with positioning during exercise sessions. Once positioning was completed, the participant was secured in place using the trunk support straps, the hip stabilization strap and leg strap. This prevented any compensatory movements from the hip or trunk in an effort to assist the hemiparetic leg.

No studies are available to suggest a valid protocol as an exercise intervention using SLE in individuals post-stroke. Several studies (Eng, Kim, & Macintyre, 2002; Flansbjerg et al., 2005; Pohl, Startzell, Duncan, & Wallace, 2000) have suggested that  $60^{\circ} \cdot \text{sec}^{-1}$  is most appropriate for assessing knee extension/flexion strength in people post-stroke. The results of initial pilot data suggest an isokinetic extension/flexion protocol at  $150^{\circ} \cdot \text{sec}^{-1}$  for 40 repetitions per set. Individuals were given 30-second rest breaks in between each set. The participants were instructed to self-progress their exercise training with the goal of reaching 40 sets. Participants exercised at an intensity of 60% - 70% of maximal heart rate (determined by maximal effort exercise test) for the duration the exercise intervention period, which was 3 times per week for 4 weeks. During the 30-second rest, heart rate and perceived exertion were monitored. Each exercise session lasted 60-90 minutes depending on exercise duration. This allowed for pre and post-exercise stretching, patient set up and the exercise session. As a safety precaution, participants were educated for breathing techniques and to avoid valsalva maneuver during the exercise sessions.

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<sup>\*\*</sup> Biodex Medical Systems, Inc., 20 Ramsay Rd, Shirley, NY 11967-4704

### *Statistical Analysis*

The arithmetic mean and standard error were used for descriptive statistics. At baseline, paired t-tests determined significant differences between the hemiparetic and less affected limbs. We examined the effect of SLE on 1) blood flow, 2) arterial diameter and 3) peak blood flow velocity for both limbs, with three different two-way repeated measures ANOVA. Both factors: Side (hemiparetic, less affected) and Time (baseline, T1 and post) were within subject. A significant *Side \*Time* interaction suggested SLE effect and warranted further analysis. For post-hoc analysis, we calculated the percent change from baseline to post in diameter and blood flow velocity. Testing each side, a second set of repeated measures ANOVA determined if the percent change was significantly different from zero. In the hemiparetic side, paired t-tests were performed to determine significant differences in vascular conduction between baseline and post-intervention values.

To elucidate the relationship between the blood flow and lean muscle tissue in the hemiparetic limb, Pearson product moment correlations were calculated using baseline values. Following the intervention, correlations were also performed to assess the relationship between percent change scores for blood flow and lean tissue.

We calculated a traditional ABI, and because of the nature of SLE, also calculated a second ABI using only the hemiparetic side. Because of visual changes in variability of ABI across time, a linear mixed model (Breslow, 1993), tested for statistical significance across time. Data analyses were conducted with  $\alpha \leq 0.05$ .

## **5.4 Results**

### *Baseline Measures*

Baseline values between the hemiparetic and less affected limb were significantly different for resting femoral artery blood flow, diameter and peak blood flow velocity ( $p <$

0.0001). Femoral artery blood flow to the hemiparetic limb was 29.57% less compared to the other side. Baseline descriptive data are reported in Table 5.2. These findings support our previous work characterizing vascular remodeling that occurs after stroke (Chapter 4).

At baseline, DEXA scans were performed to assess lean tissue composition. Lean tissue between the hemiparetic and less affected limb was significantly different at baseline ( $p = 0.051$ ). Further, a weak, non-significant relationship between lean lower extremity tissue and femoral artery blood flow ( $r = 0.14$ ,  $p = 0.665$ ) was found.

#### *Femoral Artery Adaptation to SLE*

Overall, femoral artery hemodynamics improved in the hemiparetic limb after the 4-week SLE training period (Figure 5.4 and 5.5) while non-significant changes occurred in the control limb. Specifically, femoral artery blood flow significantly improved after SLE as indicated by an interaction of Side (hemiparetic, less affected) and Time ( $F_{(2,22)} = 12.12$ ;  $p < 0.0001$ , Figure 5.6). After the training period, a 41.84% increase in blood flow was observed. This resulted in a 4.37% deficit for leg blood flow in the hemiparetic leg when compared to the other side. Arterial diameter and blood flow velocity are intimately related to overall limb blood flow. Therefore, a two-way repeated measures ANOVA with an effect of *Side \* Time* indicated that both femoral artery diameter ( $F_{(2,22)} = 24.76$ ,  $p < 0.0001$ ) and blood flow velocity ( $F_{(2,22)} = 27.97$ ,  $p < 0.0001$ ) in the hemiparetic limb significantly improved after SLE (Figures 5.7 and 5.8). No significant differences were detected in the non-trained limb for femoral artery blood flow ( $F_{(2,22)} = .905$ ;  $p = 0.08$ ), diameter ( $F_{(2,22)} = 0.651$ ,  $p = 0.525$ ) and peak blood flow velocity ( $F_{(2,22)} = 1.28$ ,  $p = 0.297$ ) (Figures 5.4-5.6). Post-hoc analysis suggested a significant improvement in femoral artery diameter ( $p < 0.001$ ) and blood flow velocity ( $p < 0.001$ ) was found in the hemiparetic limb. The less affected limb did not



demonstrate significant improvements in arterial diameter ( $p = 0.777$ ) or blood flow velocity ( $p = 0.145$ ). Vascular conductance significantly improved ( $p < 0.0013$ ) was observed in the trained limb.

#### *Lean Tissue Composition and the Relationship to Blood Flow*

Since the SLE intervention was designed to be an aerobic protocol, lean muscle tissue did not significantly increase in the hemiparetic limb after the SLE intervention ( $p = 0.56$ ). While baseline values for lean tissue mass were significantly different ( $p = 0.051$ ), post-intervention values approached significance ( $p = 0.058$ ).

The relationship between the blood flow and lean tissue was also explored after the training intervention. The percent change in blood flow from baseline to post-intervention was not related to lean muscle tissue as evidenced by a weak correlation ( $r = -0.072$ ;  $p = 0.825$ ).

#### *Ankle-Brachial Index (ABI)*

ABI values were not significantly different after the training intervention ( $F_{2,22} = 0.211$ ,  $p = 0.811$ ). Further analysis of ABI only on the hemiparetic side also identified non-significant changes ( $F_{2,22} = 0.556$ ,  $p = 0.581$ ).

## **5.5 Discussion**

This study examined the effect of a 4-week single limb exercise (SLE) training protocol on cardiovascular changes and peripheral blood flow in the femoral arteries in people with chronic stroke. The primary finding was that the SLE training intervention that encouraged use of the hemiparetic leg resulted in structural vascular adaptations, with improved arterial diameter and blood flow to the trained limb.

### *Femoral Artery Characteristics and Blood Flow Prior to SLE*

After a stroke, arterial changes may occur if the more affected leg requires lower oxygen uptake than the other.(Ivey et al., 2004; Landin et al., 1977) (see Chapter 4) The premise behind these vascular alterations after injury has been attributed to the lack of active, physical exercise and reduced metabolic demand.(Gerrits et al., 2001) The baseline comparisons between the two femoral arteries in the present study display significantly lower values for resting femoral artery blood flow, diameter and peak blood flow velocity in the hemiparetic limb. In addition, our findings support and extend the literature that lean muscle tissue is significantly lower in the hemiparetic limb when compared to the less affected side.(De Deyne, Hafer-Macko, Ivey, Ryan, & Macko, 2004) However, the relationship between resting blood flow and lean muscle tissue demonstrated a weak, non-significant correlation. Therefore, the difference in blood flow may be due to lower oxygen demand or a higher resistance in the vascular system in the hemiparetic limb.(Gerrits et al., 2001) With the magnitude of these differences in the femoral artery vasculature, knowledge regarding an exercise intervention aimed at minimizing these adaptations would be valuable.

### *Effect of SLE Training*

The results from the present study suggest vascular changes that occur after stroke can be moderately reversed to that of the less affected leg using SLE. After the training period, a large increase in blood flow was observed. This resulted in only a -4.37% remaining deficit for femoral artery blood flow between the two limbs. This is not surprising since the effects of exercise are a potent stimulus for inducing vascular changes. Exercising muscles will require increased oxygen consumption in order to perform work. The response

of the body is to provide adequate blood flow in order to meet the working muscles' needs. This is supported in the literature that SLE increases limb blood flow (Asanoi et al., 1992; Bell et al., 2001; DeSouza et al., 2000; Klausen et al., 1982; Miyachi et al., 2001; Shoemaker et al., 1994) in the trained versus the untrained limb in healthy adults. Furthermore, as suggested in the animal model, changes (increase or decrease) in arterial blood flow may induce arterial remodeling such as vessel diameter.(Brownlee & Langille, 1991; Langille & O'Donnell, 1986; Tronc et al., 1996) In humans, vascular adaptations parallel the findings reported in the literature for animal studies.(Gerrits et al., 2001; Miyachi et al., 2001; Thijssen et al., 2006) Specifically, Miyachi and colleagues,(2001) reported in healthy adults 6 weeks of SLE training induced femoral artery remodeling. The authors reported a significant increase in the cross-sectional area (CSA) of the femoral artery after the training period. The participants then underwent a 6-week detraining period, which led to a significant decline in CSA. No significant changes were found in the non-trained limb. It was concluded that exercise-induced blood flow changes during training influence arterial diameter expansion and may be the mechanistic factor driving these vascular adaptations.

In the present study, we report similar vascular adaptations after the SLE training intervention. Femoral artery blood flow and diameter in the hemiparetic limb significantly improved after SLE while the untrained limb demonstrated non-significant changes. The percent change in blood flow from baseline to post-intervention was not related to increased lean muscle tissue. Therefore, vascular remodeling may be related more to exercise rather than tissue composition. Our findings support and extend the existing literature that blood flow may not be related to tissue composition (Ivey et al., 2004; Radegran & Saltin, 2000) but metabolic activity.(Radegran & Saltin, 2000) Gerrits and colleagues (2001) suggest that vascular adaptations could be the result of angiogenesis to improve blood delivery to the

working muscles. In the present study, vessel growth in the muscle tissue was not assessed. However, mean values for hemiparetic lower extremity muscle mass did not increase. One plausible explanation would be related to an adaptive process such as arteriogenesis.(Prior, Lloyd, Yang, & Terjung, 2003) Arteriogenesis would transpire from: 1) enlargement of the vessel to accommodate increased blood flow such as during an acute bout of exercise or in response to a chronic stimulus and 2) vascular adaptations modulated by the endothelial cells from a stimulus.(Prior et al., 2003) It is likely that the prompting stimulus for the vascular adaptations observed in the present study was indeed exercise and the increased demand for blood flow to the peripheral tissue.

The response of the body is to accommodate the working muscles by increasing both blood flow and diameter to allow for greater oxygen exchange capacity.(Miyachi et al., 2001; Parker et al., 2007; Prior et al., 2003) A peripheral “feedback mechanism”(Kamiya et al., 1988) known as the flow-diameter relationship (Ono et al., 1991) may also provide information regarding the vascular adaptations. With increased blood flow, greater sheer stress is placed on the arterial wall. The endothelial cells detect changes in wall tension and undergo structural modification to increase vessel diameter (Gerrits et al., 2001; Prior et al., 2003; Thijssen et al., 2006) We also report peak blood flow velocity also increased significantly in the hemiparetic limb, which suggest peripheral vascular adaptations occurred after training. While improvements in femoral artery blood flow have been reported after functional electrical stimulation (FES) in people with SCI, they were not statistically significant.(Thijssen et al., 2006) This may be due to the nature of the training where an outside electrical stimulus is providing muscle contraction for SCI rather than volitional active muscle contraction in the present study.

Our findings support the literature that exercise affects vascular properties in people with neurological injury.(Gerrits et al., 2001; Hopman et al., 2002; Thijssen et al., 2006) In the current study, we found significant vascular adaptations after 4 weeks of SLE. These data suggest that the continuous changes in the vasculature may be the result of active muscle contraction and the need to supply blood and oxygen during exercise. Therefore, SLE may be an ideal training intervention aimed at modifying the vascular adaptations that are present after stroke.

The intrinsic nature of the flow-diameter relationship would support the findings that vascular conductance improved after SLE. Vascular conductance is the product of mean arterial pressure and blood flow. The individuals in this study did not demonstrate a significant improvement in mean arterial pressure from baseline to post-training but blood flow significantly increased. Therefore, the improvement in vascular conductance likely resulted from peripheral rather than central adaptations.(Hopman et al., 2002; Miyachi et al., 2001) In order to improve central mechanisms such as blood pressure or cardiac output, the exercise training intensity and duration may not have been adequate. We exercised participants at the recommended 60-70% of maximal heart rate(J. Rimmer & Nicola, 2002) three times weekly for 4 weeks. However, exercise at a higher intensity such as 70-80% of maximal heart rate may have been required to elicit systemic changes.(Palmer-McLean, 2003)

ABI and ABI<sub>hemi</sub> measures did not demonstrate significant improvements after the 4-week SLE intervention. Despite the vascular adaptations that occurred for femoral artery blood flow and conductance, ABI values post-training did not support improved endothelial function as suggested by previous work.(Andreozzi et al., 2007) Our results may differ from those reported by Andreozzi and colleagues for several reasons. First, in the present study,

low ABI values ( $ABI < 0.90$ ) were reported for 4 individuals while  $ABI_{\text{hemi}}$  was found in 3 individuals. Since individuals in the present study were already considered in the normal range for ABI, (McDermott, Ferrucci et al., 2002; McDermott, Greenland et al., 2002; McDermott et al., 2006; Resnick et al., 2004) a ceiling effect is likely. Second, Andreozzi used 6 weeks of treadmill training at 60-70% of walking ability (defined by claudication pain during the exercise test). The present study used a SLE training protocol designed to improve peripheral circulation in the hemiparetic limb. One possible reason that SLE did not influence ABI or  $ABI_{\text{hemi}}$  is because systolic blood pressure in the arm may not be influenced by peripheral vascular changes. Finally, training duration may have been insufficient to elicit changes in ABI. As mentioned previously, Andreozzi assessed ABI after 18 days of treadmill training at 60-70% of their walking ability. Although the training intensity of the SLE protocol was similar, duration was shorter. 12 days of SLE compared to 18 days of treadmill walking.

## **5.6 Conclusion**

Our findings support our hypotheses that a 4-week SLE training program that encourages use of the hemiparetic limb improves femoral artery blood flow, diameter, peak velocity and vascular conductance. These peripheral vascular changes result from an exercise-induced stimulus that directly affects the flow-diameter relationship. Simply, if the arterial wall is chronically exposed to increased blood flow (i.e. exercise), then the diameter expands to accommodate a larger volume of flow. Finally, ABI was not significantly improved after a 4-week SLE training period.

Future research is needed to examine the role that exercise plays in the mechanisms behind vascular remodeling in the hemiparetic limb after stroke.

## Chapter 5 Tables and Figures

Table 5.1 Participant Demographics

Characteristics	n = 12	Mean $\pm$ SD
Sex: Men		5
Age (years)		60.6 $\pm$ 14.5
Race/ethnicity		
African American		2
Caucasian		8
Hispanic		1
Native American		1
Body Mass Index (DEXA scan)		29.7 $\pm$ 4.0
Medication		
Beta-blockers		4
Stroke Characteristics		
Time (months) post-stroke		69.1 $\pm$ 82.2
Right side weakness		5
Type of stroke:		
Ischemic		9
Hemorrhage		3
Stroke Severity		
LE Fugl-Meyer score		26.7 $\pm$ 3.8



Table 5.2 Baseline Hemodynamic and Body Composition Characteristics \* (n = 12)

	HP	NHP	p-value
Blood Flow(m*min <sup>-1</sup> )	519.18 ± 47.76	736.43 ± 59.17	p< 0.001†
Diameter(cm)	0.85 ± 0.03	0.93 ± 0.03	p < 0.001†
Peak Velocity(cm*sec <sup>-1</sup> )	70.14 ± 4.90	82.15 ± 4.50	p= 0.003†
V <sub>mean</sub> (cm*sec <sup>-1</sup> )	15.16 ± 1.56	17.49 ± 1.30	p= 0.017†
LE Lean Tissue(g)	7380.42 ± 544.85	7584.00 ± 567.76	p= 0.051

\*Values are expressed as Mean ± SE); † = denotes significance with  $\alpha \leq 0.017$ ; HP= hemiparetic; NHP= Less affected side; LE = lower extremity

Table 5.3 Effect of SLE on Hemodynamic and Body Composition \* (n = 12)

	PRE	T1	POST
Blood Flow(m*min <sup>-1</sup> )			
HP	519.18 ± 47.76 <sup>†</sup>	627.70 ± 45.95 <sup>†</sup>	735.72 ± 50.90
NHP	736.43 ± 59.17	719.07 ± 36.38	769.29 ± 54.63
Diameter(cm)			
HP	0.85 ± 0.03 <sup>†</sup>	0.91 ± 0.04 <sup>†</sup>	0.93 ± 0.04
NHP	0.93 ± 0.03	0.95 ± 0.03	0.95 ± 0.03
Peak Velocity(cm*sec <sup>-1</sup> )			
HP	70.14 ± 4.90 <sup>†</sup>	76.51 ± 4.81	81.74 ± 4.38
NHP	82.15 ± 4.50	83.82 ± 4.09	84.45 ± 4.79
V <sub>mean</sub> (cm*sec <sup>-1</sup> )			
HP	15.16 ± 1.71 <sup>†</sup>	16.66 ± 1.45	18.53 ± 1.52
NHP	17.49 ± 1.40	17.41 ± 1.14	18.23 ± 1.30
LE Lean Tissue(g)			
HP	7380.42 ± 544.85	N/A	7317.5 ± 498.21
NHP	7584.00 ± 567.76	N/A	7527.42 ± 519.98
MAP(mmHg)	69.59 ± 1.97	N/A	67.12 ± 2.09
ABI	0.96 ± 0.05	N/A	0.94 ± 0.02
ABI <sub>hemi</sub>	0.97 ± 0.04	N/A	1.00 ± 0.02

\*Values are expressed as Mean ± SE; † = denotes significance with  $\alpha \leq 0.05$ ; LE = lower extremity; N/A= not assessed

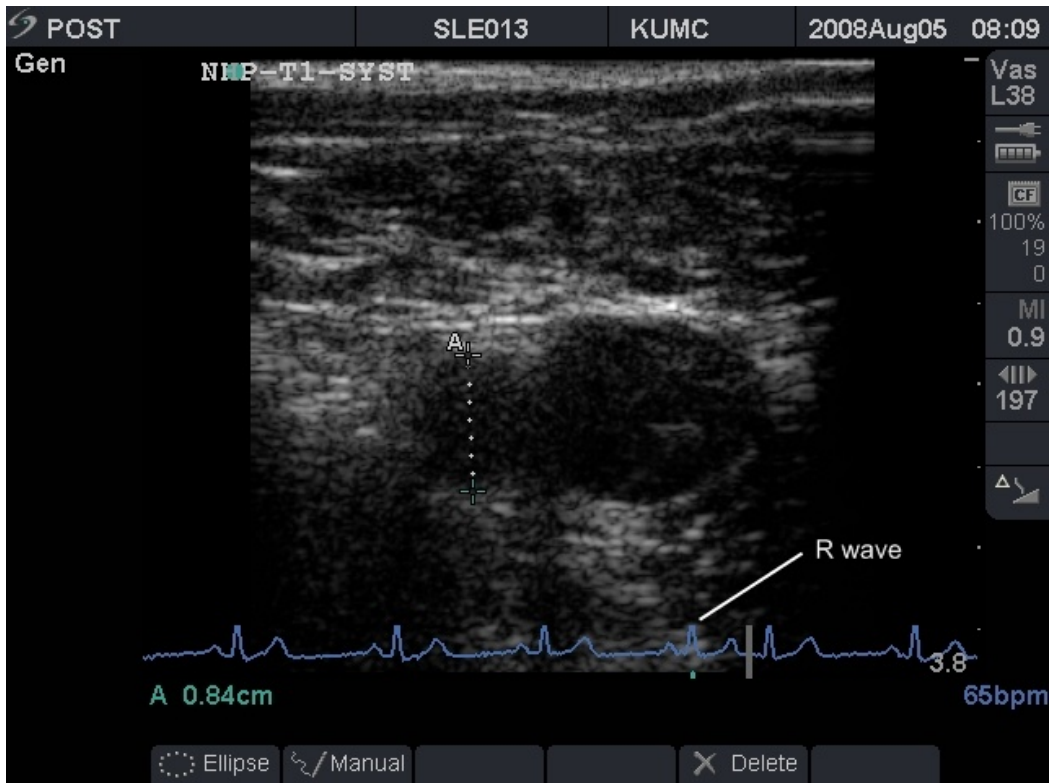


Figure 5.1 Femoral Artery Diameter at Peak Systole Located at the R Wave.

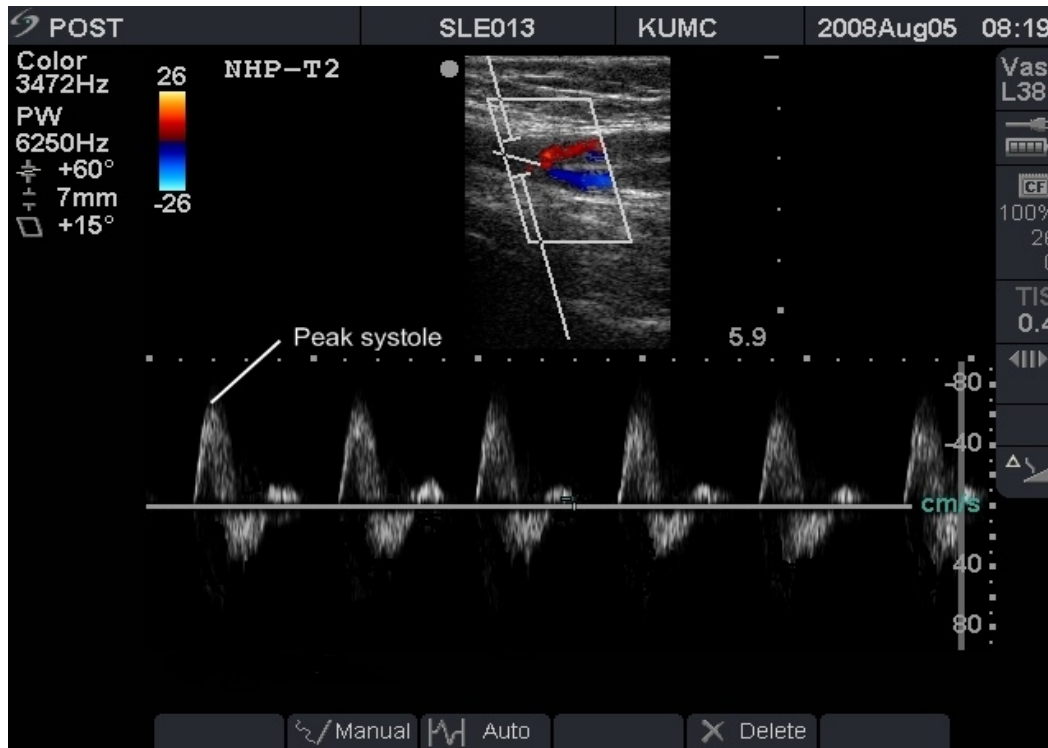


Figure 5.2 Femoral Artery Blood Flow Velocity at Peak Systole.

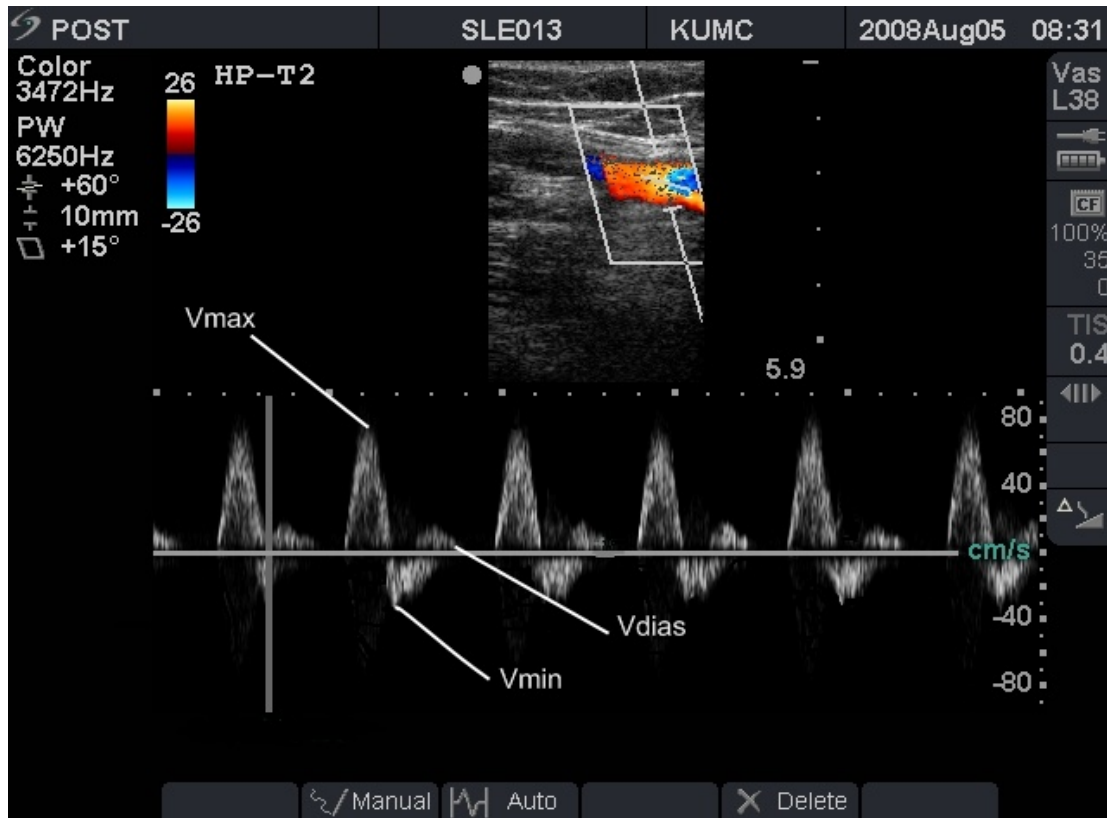


Figure 5.3 Doppler Ultrasound Waveform of One Cardiac Cycle

Doppler ultrasound waveform of the femoral artery consists of Vmax, the highest velocity; Vmin, the lowest velocity; and Vdias, the end of the diastolic phase during one cardiac cycle.

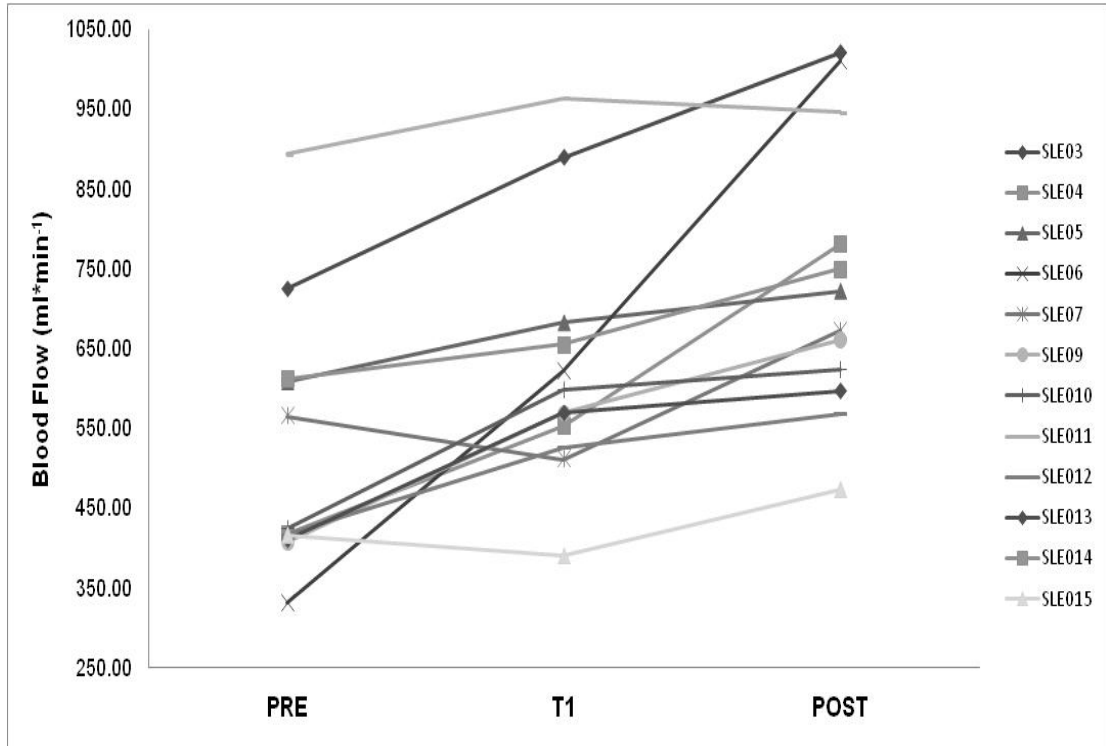


Figure 5.4 Individual Data for Femoral Artery Blood Flow Over the Intervention

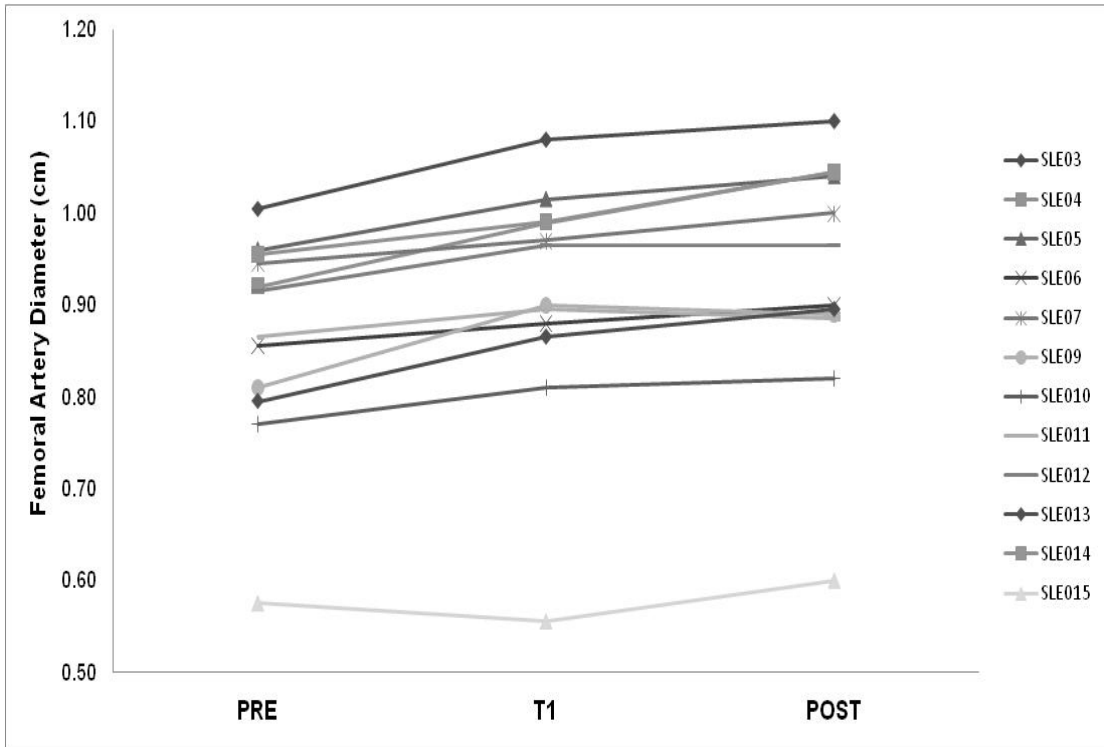


Figure 5.5 Individual Data for Femoral Artery Diameter Over the Intervention

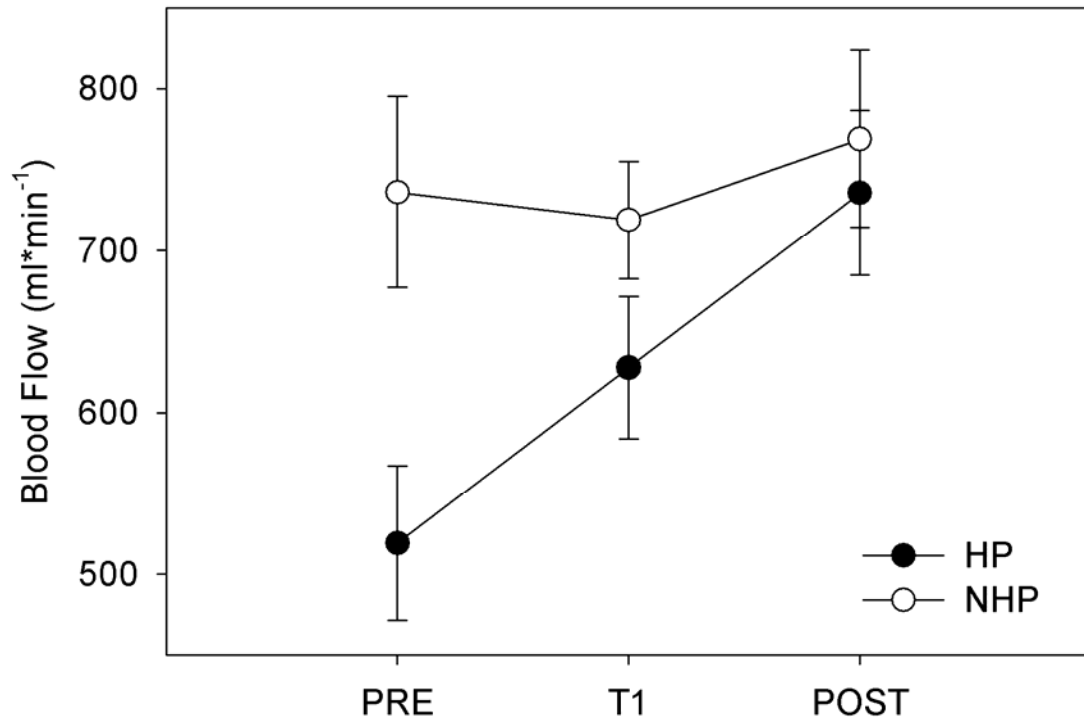


Figure 5.6 Femoral Artery Blood Flow Over the Intervention



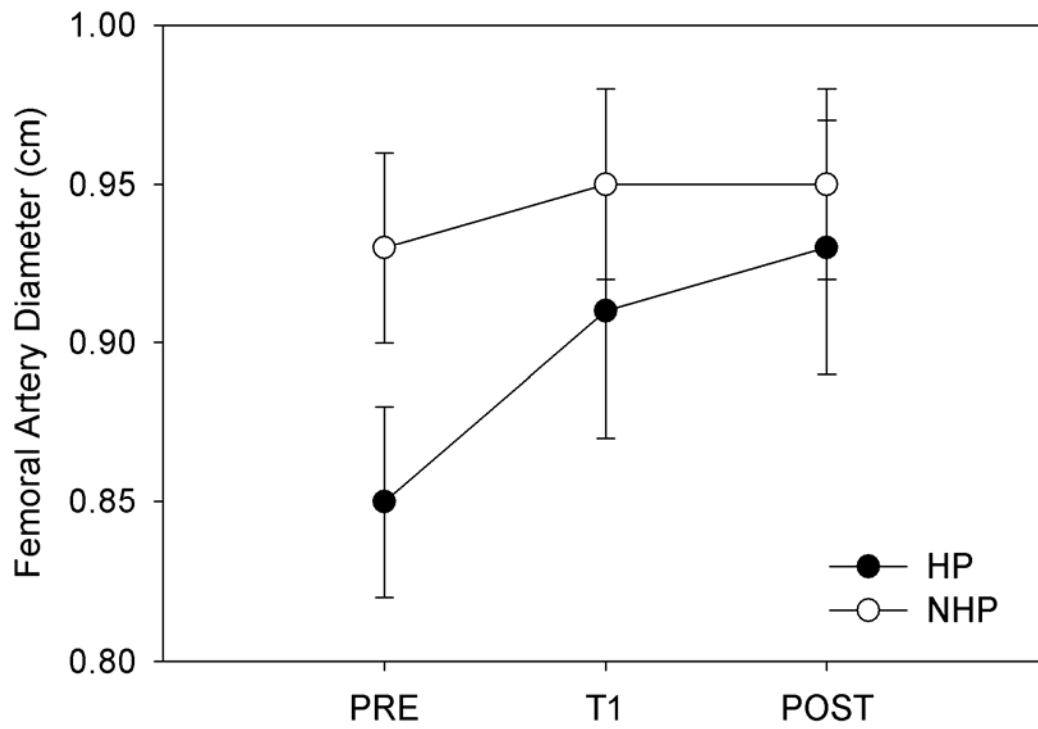


Figure 5.7 Femoral Artery Diameter Over the Intervention

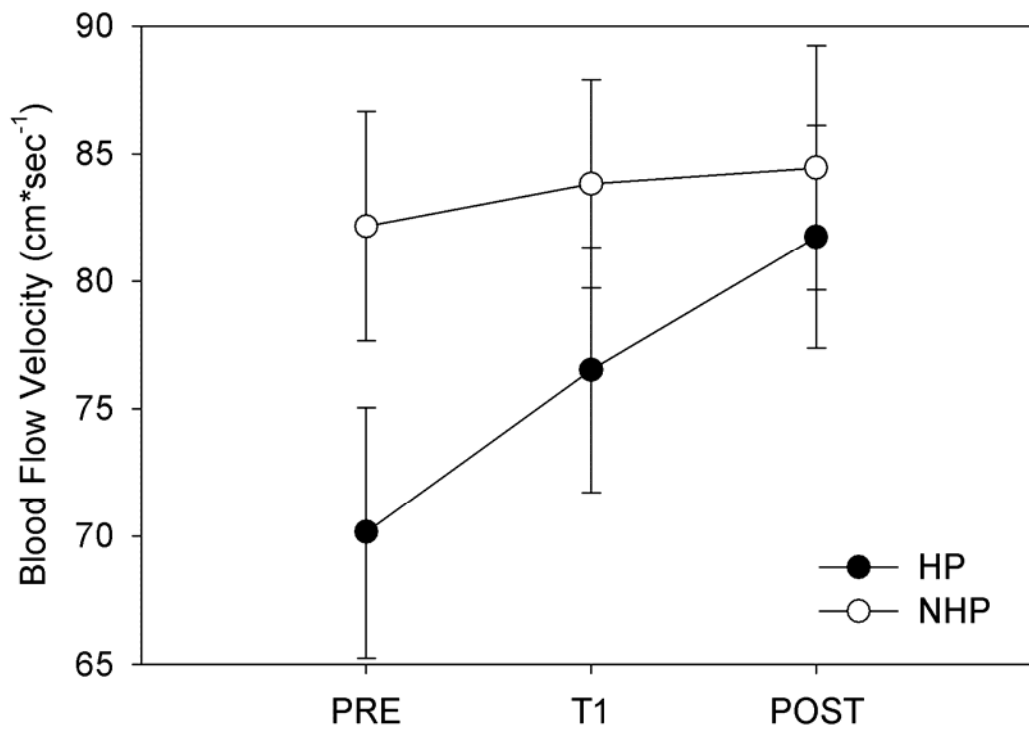


Figure 5.8 Femoral Artery Blood Flow Velocity Over the Intervention

## **Chapter 6 Preface**

Exercise testing (maximal or submaximal) is commonly used for assessing cardiorespiratory fitness, guiding exercise prescription and re-assessing whether a training effect has occurred after an intervention. Participants trained for 4 weeks using the identical experimental exercise model described in the previous chapter. The information presented in Chapter 6 sought to examine the effect of SLE on cardiorespiratory fitness. This was accomplished using two outcome measures for cardiorespiratory fitness: 1) peak oxygen uptake ( $\text{VO}_2$  peak) from a maximal effort graded exercise test and 2) oxygen uptake ( $\text{VO}_2$ ) during submaximal effort using the SLE protocol. In addition, it was questioned whether a SLE training protocol could potentially affect functional mobility such as walking. To address this concern, the 10-meter fast walk test was chosen.

## Chapter 6

Single Limb Exercise: The Physiological and Functional Responses to a Training Protocol  
that Facilitates Encouraged Use in the Hemiparetic Lower Extremity.

To be submitted to *Archives of Physical Medicine and Rehabilitation*, December, 2008

## 6.1 Abstract

Background: Stroke-related deficits can impede both functional performance and walking tolerance. Individuals with hemiparesis rely on the less affected limb during exercise and functional tasks. We chose to use a unique training intervention to encourage use of the hemiparetic limb as a method for increasing cardiorespiratory fitness. Objective: Determine the effect of a single limb exercise (SLE) training intervention on cardiorespiratory fitness parameters ( $\text{VO}_2$  peak and  $\text{VO}_2$ ). Design: Sample of convenience, within subject design. Participants: Twelve participants post-stroke (5 male) with a mean age of 60.6 (14.5) years and 69.1 (82.2) months post-stroke participated in the training intervention. Methods: Participants performed SLE three times a week for 4 weeks. Outcome measures for this study were: 1) Peak oxygen uptake ( $\text{VO}_2$  peak), and 2) oxygen uptake ( $\text{VO}_2$ ). Gait velocity was assessed in a subset of participants ( $n = 7$ ) using the 10-meter fast walk. Results: After the 4-week SLE training intervention, significant improvements were found for  $\text{VO}_2$  during submaximal work effort ( $p = 0.009$ ) and gait velocity ( $n = 7$ ), ( $p = 0.001$ ). Peak oxygen uptake did not increase ( $p = 0.41$ ) after the training intervention. Conclusion: These data suggest that SLE training was an effective method for improving oxygen exchange in the hemiparetic muscle tissue. Unilateral exercise focused on the hemiparetic leg may be an effective intervention strategy to consider for stroke rehabilitation.

## 6.2 Introduction

Stroke-related deficits can impede both functional performance (i.e. walking) and exercise tolerance.(Eng, Chu, Dawson, Kim, & Hepburn, 2002; Eng, Kim et al., 2002; Kelly et al., 2003; Macko et al., 2001) In those with chronic stroke, musculoskeletal, and cardiorespiratory impairments may develop. A sedentary lifestyle and various secondary effects such as an over-expression of fatigable type II muscle fibers,(De Deyne et al., 2004; Landin et al., 1977) lean tissue atrophy (Ivey et al., 2004; Ryan, Dobrovolny, Smith, Silver, & Macko, 2002) and higher energy expenditure during activities (Macko, DeSouza et al., 1997; Macko et al., 2001) increases the risk for decline in cardiorespiratory fitness. According to Shephard,(1986) a minimum fitness capacity of  $15 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  is needed to perform functional activities for independent living. His work illustrates an important relationship between cardiorespiratory fitness and the energy requirements needed for daily activities. For people post-stroke, compromised cardiorespiratory fitness (Mackay-Lyons & Makrides, 2002, 2004; Macko, DeSouza et al., 1997; Macko et al., 2001; Potempa et al., 1995; J. H. Rimmer, Braunschweig et al., 2000) may diminish recovery of functional activities (Jorgensen et al., 1995a, 1995b; Roth, 1993) and affect their quality of life.(Chatterton et al., 2008; Macko et al., 2008)

In response to the wide range of neuromotor dysfunction after stroke, rehabilitation research has attempted to identify exercise strategies to improve motor control,(Duncan et al., 1998; Duncan et al., 2003; Sullivan et al., 2007) functional performance (Duncan et al., 1998; Duncan et al., 2003; Macko et al., 2005; Sullivan et al., 2007) and cardiorespiratory fitness.(Duncan et al., 2003; Macko, DeSouza et al., 1997; Macko et al., 2005; Macko et al., 2001) Aerobic exercise training is one method that has been used in an attempt to maximize stroke recovery. In people post-stroke, many studies have reported benefits related to aerobic

exercise and cardiorespiratory health.(Duncan et al., 2003; Macko, DeSouza et al., 1997; Macko et al., 2005; Macko et al., 2001) However, several challenges exist for individuals post-stroke with the traditional modes of exercise (i.e. walking or biking).(S. A. Billinger, Tseng et al., 2008; Sibley et al., 2008) Of importance, studies have reported that exercise using bilateral lower extremity movement may hinder both functional(Chen et al., 2005; Landin et al., 1977; Sibley et al., 2008) and physiological performance (Landin et al., 1977) and physiological performance (Landin et al., 1977) of the hemiparetic limb after stroke. In a study by Landin and colleagues, individuals with chronic stroke cycled at a submaximal workload for 40 minutes.(1977) During the cycling exercise, the participants generated 65% more work with the less affected limb. This reduces the amount of work performed by the hemiparetic limb and increases fatigability in the less affected limb.(S. A. Billinger, Tseng et al., 2008; Mohrman & Heller, 2006) Thus, individuals post-stroke prefer to use the less affected limb during exercise and functional activities such as ambulation.(Brunt et al., 1995; Messier et al., 2005; Mizrahi et al., 1989; Yavuzer et al., 2006)

With such a strong tendency to use the less affected limb, the feasibility and effectiveness of training interventions that encourages use of the hemiparetic leg should be explored.(Sibley et al., 2008) Currently, research provides evidence that task specific unilateral activities improve motor function in the hemiparetic upper extremity.(Bowman et al., 2006; Butefisch et al., 1995; Page et al., 2004; Ro et al., 2006; Taub et al., 2006; Wolf et al., 2006) For example, constraint-induced movement therapy (CIMT) or modified CIMT (mCMIT) has been utilized to “force” individuals to use their affected limb to improve motor function. Forced-use therapeutic interventions such as CIMT for the lower extremity are cumbersome for functional activities.(Sibley et al., 2008) However, exercise training focused

on encouraged use of the hemiparetic lower extremity may be an advantageous therapeutic intervention for increasing cardiorespiratory fitness and functional outcomes.

One modality that encourages use of the hemiparetic leg is single limb exercise (SLE). In healthy adults, this type of exercise training has been performed using a Biodex System (Shoemaker et al., 1994; Wernbom et al., 2006) or a cycle ergometer, common exercise modalities for training individuals post-stroke.(Asanoi et al., 1992; Bell et al., 2001; Davies & Sargeant, 1975; Hardman et al., 1987; Klausen et al., 1982; Miyachi et al., 2001; Paterson et al., 2005; Radegran & Saltin, 2000; Saltin & Landin, 1975) For healthy adults, the SLE training intervention improved cardiorespiratory fitness and peripheral physiological parameters such as oxygen uptake, muscle blood flow and citrate synthase activity in the trained leg.(Bell et al., 2001; Davies & Sargeant, 1975; Klausen et al., 1982; Miyachi et al., 2001; Saltin et al., 1976; Shoemaker et al., 1994) Based on the evidence in healthy adults and the potential for decreased work performed by the hemiparetic leg during bilateral training, we decided to explore SLE as an aerobic training intervention after stroke.

The purpose of this study was to determine the effect of SLE on central and peripheral cardiorespiratory fitness outcome measures. It was hypothesized that after 4 weeks of SLE training: 1) a significant increase in  $VO_2$  peak values would be observed and 2) oxygen uptake ( $VO_2$ ) would significantly decrease when compared to baseline values.

The initial five participants self-reported improved walking after the SLE intervention. Therefore, we added a secondary purpose to determine whether the SLE training could affect a functional task such as walking speed. In a subset of participants, the 10-meter fast walk (Macko et al., 2005; Sullivan et al., 2007) was chosen as the outcome measure. It was hypothesized that significant improvements in walking time would be observed after the training intervention.



## 6.3 Methods

### *Participants*

Twelve participants with chronic stroke (5 male;  $69.1 \pm 82.2$ ) months post-stroke completed this within subject design study (see Table 6.1 for baseline demographics). A subset of these participants ( $n = 7$ ) performed a 10-meter fast walk test.

Inclusion criteria included: 1) a diagnosis of hemiparesis from a stroke at least 6 months ago confirmed by clinical assessment (WHO, 2004) ; 2) the ability to transfer from a sitting to standing position with minimal assist; 3) the ability 10 meters independently with or without an orthotic or assistive device; 4) mild to moderate stroke deficits defined by a lower extremity Fugl-Meyer score (LEFM) score from 20 to 33/34 (Daly et al., 2006); 5) 35 degrees of active knee extension/flexion with movement against gravity and 6) medical clearance from the primary care physician for exercise testing. Exclusion criteria consisted of the following: 1) recent hospitalization with new diagnosis or severe cardiopulmonary conditions; 2) currently smoking, 3) type 1 or 2 diabetes; 4) current participation in single limb exercise or physical therapy; 5) peripheral vascular disease ( $ABI < 0.40$ ) or known stenosis of the lower extremity vessels 6) prescribed medications that improve vasodilation and 7) a difference  $\leq 2\%$  between the hemiparetic and less affected limbs for arterial diameter and blood flow velocity. Results for vascular outcome measures are reported elsewhere.

Institutionally approved informed consent was obtained in writing prior to participation in the study.

### *Single Limb Exercise (SLE) Intervention*

Single limb exercise (SLE) using the Biodex System 3<sup>§§</sup> involved only the hemiparetic limb. The knee attachment unit was used for the isokinetic extension/flexion protocol. During the initial training session, adjustments were made for leg length, chair height, and trunk support. These values were recorded and used for consistency with positioning during exercise sessions. Once this was completed, the trunk support straps, hip stabilization strap and leg strap were properly placed to limit any compensatory movements from the hip or trunk in an effort to assist the hemiparetic leg. (Flansbjer et al., 2005)

No studies are available to suggest a valid protocol as an exercise intervention using SLE in individuals post-stroke. Several studies (Eng, Kim et al., 2002; Flansbjer et al., 2005; Pohl et al., 2000) have suggested that  $60^{\circ} * \text{sec}^{-1}$  is most appropriate for assessing knee extension/flexion strength in people post-stroke. Since we were not interested in a strength-training protocol, we believed that participants in our study would not maintain the  $60^{\circ} * \text{sec}^{-1}$  pace intensity for an extended length of time. Initial testing in our lab revealed  $120^{\circ} * \text{sec}^{-1}$  was still too difficult to maintain for an extended period of time. However, pilot data suggested that the SLE protocol using  $150^{\circ} * \text{sec}^{-1}$  was well-tolerated by participants with stroke. In addition it was a feasible training intervention, which provided less resistance in order to facilitate aerobic training. Therefore, an isokinetic extension/flexion protocol at  $150^{\circ} * \text{sec}^{-1}$  for 40 repetitions per set with 30-second rest breaks in between each set was used. The participants were instructed to self-progress their exercise training with the goal of reaching 40 sets. Participants exercised at an intensity of 60% - 70% of maximal heart rate (determined by maximal effort exercise test) for the duration the exercise intervention period, which was 3 times per week for 4 weeks. During the 30-second rest, heart rate and perceived exertion

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<sup>§§</sup> Biodex Medical Systems, Inc., 20 Ramsay Rd, Shirley, NY 11967-4704

were monitored. Each exercise session lasted 60-90 minutes. This allowed for pre and post-exercise stretching, patient set up and the exercise session. As a safety precaution, participants were educated for breathing techniques and to avoid a valsava maneuver during the exercise sessions.

### *Primary Outcome Measures*

#### *Maximal Exercise Test*

Participants performed a maximal effort graded exercise test at baseline and after the exercise intervention to assess cardiorespiratory fitness (VO<sub>2</sub> peak) . Participants were instructed not to consume food, caffeine, or alcohol for 3 hours prior to exercise testing,(ACSM, 2006) but were allowed to hydrate with water ad libitum. Height, weight, and resting heart rate and blood pressure were obtained prior to exercise testing. Participants were familiarized to the testing protocol prior to the exercise test. The maximal effort exercise test used the TBRS<sup>\*\*\*</sup> and mTBRS-XT protocol as described previously in Chapter 3.(S. A. Billinger, Tseng et al., 2008) A metabolic cart<sup>‡</sup> was used to continuously collect and analyze expired gases through a two-way rebreather valve<sup>§</sup>. The metabolic cart was set to a 30-second averaging of the data collected for the sampling technique. Before exercise testing, all equipment was calibrated according to the manufacturer's recommendations.

During the exercise test, an exercise physiologist and physician continuously monitored heart rate and rhythm with a 12-lead electrocardiogram (ECG). Every 2 minutes

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<sup>\*\*\*</sup> NuStep, Inc, 51111 Venture Dr., Ann Arbor, MI 48108

<sup>‡</sup> Parvomedics, 8152 South 1715 East, Sandy, UT 84093

<sup>§</sup> Hans Rudolph, Inc, 7200 Wyandotte St, Kansas City, MO 64114

during the test, heart rate (HR), blood pressure (BP) and rating of perceived exertion (RPE) using Borg's 6-20 scale were recorded.

#### *Submaximal Exercise*

Oxygen uptake ( $VO_2$ ) was assessed during submaximal effort on Day 1 and Day 12 (final training session) of SLE training. The session was conducted using the SLE training protocol and the metabolic cart with open circuit spirometry to analyze gas exchange.  $VO_2$  and HR were the variables of interest for submaximal performance. Visual feedback from the Biodex was used to gauge force production during SLE. Since the protocol was isokinetic, muscle force generated by the hemiparetic leg was variable with each contraction. Mean values for force production (Ft\*lbs) from baseline submaximal performance were calculated. Individuals were then instructed to exert the same force during post-test exercise.

#### *10-Meter Fast Walk Test*

The 10-meter fast walk test was chosen to assess gait velocity.(Duncan et al., 1998; Sullivan et al., 2007) Participants were instructed to perform a fast walk with their usual walking device.(Sullivan et al., 2007) The participant's time was recorded for the middle 10 meters of the 12 meter walkway. A brief rest was given in between trials. Three trials were performed and the average was recorded for data analysis.

## *Secondary Outcome Measures*

### *Body Composition, Lower Extremity Force Production and Motor Performance*

Lean tissue mass and knee extensor strength was assessed pre and post-intervention to ensure: 1) the SLE protocol was an aerobic training intervention not resistive in nature to induce significant strength gains and 2) increased oxygen consumption was not the result of increased lean tissue in the leg. In addition, pre and post intervention, the LEFM was used to assess motor performance. This ensured that the training protocol did not elicit deleterious effects in the hemiparetic lower extremity.

Total body scans were performed using the DEXA<sup>||</sup> with participants in the supine position. Participants avoided food or water consumption 3 hours prior to the scan. An overnight fast was not performed since the DEXA and maximal effort exercise test were completed at the same session. Lean tissue and fat mass values of the lower extremities were obtained from both limbs. Tissue composition in grams was calculated from the region of the greater trochanter to the foot.

Bilateral knee extension muscle strength was measured prior to the start of the exercise intervention. Using the Biodex, an isokinetic knee extension protocol at  $60^{\circ} \cdot \text{sec}^{-1}$  was chosen based on the available literature for stroke.(Eng, Kim et al., 2002; Pohl et al., 2000) The system was calibrated and participant set up was completed according to the manufacturer's recommendations. Testing was performed within their available active range of motion. Participants were familiarized with the movement without resistance and to the strength test protocol prior to the test. The less affected leg was tested first and then the hemiparetic limb. Participants were asked to give a maximal effort for three consecutive knee extension movements to assess quadriceps strength. The mean peak torque (from the

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<sup>||</sup> GE Lunar, 726 Heartland Trail, Madison, WI 53717

three trials) was generated by the Biodex system analysis. Strength data was collected at baseline and post-training.

### *Data Analysis*

Based on the SLE intervention in healthy young (Davies & Sargeant, 1975; Hardman et al., 1987; Klausen et al., 1982; Saltin & Landin, 1975) and older adults,(Bell et al., 2001) a group of at least 8 individuals would need to participate in the study to detect changes in  $\dot{V}O_2$  peak and  $\dot{V}O_2$ . However, these studies failed to provide a power analysis or justification for their sample size. Since SLE is a novel exercise intervention for people after stroke, a precision argument was utilized a priori to justify the sample size for this study. The standard error of the mean (SEM) decreased drastically up to 20 participants and beyond this number there was a diminishing of return.

For our primary and secondary outcome measures, two tailed paired t-tests were used to detect whether significant differences existed after the intervention when compared to baseline values. Our secondary outcome measures of interest were muscle strength, body composition and LEFM scores. An effect size (ES) was calculated to assess a real and meaningful difference between pre and post measures for  $\dot{V}O_2$ , 10-meter fast walk and the LEFM.(J. R. Thomas, Lochbaum, Landers, & He, 1997) All statistical analyses were conducted using SPSS 16.0.<sup>#</sup> Alpha was set at 0.05 to detect significance.

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<sup>#</sup> SPSS Inc, 233 S Wacker Dr, Chicago, IL 60606.

## 6.4 Results

Twelve individuals completed the SLE training intervention without adverse events. Seven of the twelve participants completed all training sessions. Five individuals completed 92% (11 out of 12) of the SLE training sessions.

### *Cardiorespiratory Fitness*

SLE training did not elicit significant improvements in  $\text{VO}_2$  peak during a maximal effort graded exercise test (baseline:  $19.3 \pm 2.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  vs post-intervention:  $19.0 \pm 2.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $p = 0.41$ ). No significant changes were found for HR, respiratory exchange ratio (RER), and RPE. However, physiological responses during submaximal exercise improved after the SLE intervention.  $\text{VO}_2$  during SLE significantly decreased post-training when compared to baseline values ( $7.0 \pm 1.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  vs  $5.4 \pm 1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $p = 0.009$ ); representing a 20.3% decrease in energy expenditure during the exercise session. A large effect size (ES) of 0.899 suggests a real and meaningful difference between the amount of change from baseline to post-training. (J. R. Thomas et al., 1997) (Table 6.2)

### *10-Meter Fast Walk Test*

The results of the 10-meter fast walk indicated that after the 4-week SLE training, individuals ( $n = 7$ ) were able decrease their walk time from  $8.5 \pm 3.0$  seconds to  $7.4 \pm 3.0$  seconds ( $p = 0.001$ ), a 13.8% drop in ambulation time. A small to moderate ES of 0.386 was found, which indicates that there was a meaningful difference between pre and post-training gait velocity.

### *Body Composition, Lower Extremity Force Production and Motor Performance*

No significant changes were observed in either limb for knee extensor strength. Knee extensor peak torque generated for the hemiparetic was increased but was not significantly different baseline and post-training. No significant differences for the less affected limb were observed after the training intervention. Knee extensor strength for the hemiparetic limb was significantly lower ( $p = 0.003$ ) at baseline than the less affected limb. A significant difference ( $p = 0.018$ ) between the two limbs remained post-intervention (Table 6.2 for results).

At baseline, no significant differences were found between the less affected and hemiparetic leg for fat mass ( $p = 0.11$ ). A significant difference ( $p = 0.05$ ) in lean tissue mass was found between the two limbs. After the training period, no significant changes ( $p > 0.12$ ) in lean muscle tissue or fat mass were reported for either limb (see Table 6.2). However, post SLE training, no significant difference ( $p = 0.058$ ) in lean tissue between the limbs was found.

LEFM scores significantly improved after the training intervention (baseline:  $27.2 \pm 3.5$  to post-training:  $28.7 \pm 4.8$ ;  $p = 0.007$ ). A moderate effect size of 0.461 indicates a meaningful difference between the amount of change that was associated with SLE from pre to post-intervention LEFM scores.

## **6.5 Discussion**

The effects of a 4-week aerobic training intervention that focused on only the hemiparetic leg was conducted to determine whether improvements would be observed in 1)  $VO_2$  peak at maximal effort, 2)  $VO_2$  at submaximal effort, and 3) the 10-meter fast walk test. After 4 weeks of SLE training,  $VO_2$  peak during a maximal effort exercise test did not improve after the training intervention. Oxygen uptake ( $VO_2$ ) at submaximal effort was



significantly lower than baseline. These data suggest that enhanced  $VO_2$  in the hemiparetic limb may be attributed to peripheral mechanisms such as efficiency of oxygen extraction or vascular dilation (LeJemtel, Maskin, Lucido, & Chadwick, 1986) rather than central cardiovascular changes. (i.e. larger cardiac output) In addition, we found that participants decreased their time during the 10-meter fast walk test.

The American College of Sports Medicine (ACSM),(2006) states that improvements in aerobic fitness can occur as a result of exercise training when the heart rate response is lower at fixed workload over a period of time. Previous research conducted in healthy individuals demonstrate that “repeated bouts of exercise” (Scheuer & Tipton, 1977) such as SLE can produce a training effect such as decreased  $VO_2$  (Saltin et al., 1976) or heart rate at submaximal workloads.(Klausen et al., 1982; Saltin et al., 1976) It is known from previous work (Macko, DeSouza et al., 1997; Macko et al., 2001) that people with stroke can improve energy expenditure after a treadmill training intervention. Our findings support previous work,(Macko, DeSouza et al., 1997; Macko et al., 2001) and extend the literature to include encouraged use of the hemiparetic limb using SLE. Importantly, our study is unique because we evaluated  $VO_2$  specifically in the hemiparetic limb during an acute bout of exercise pre and post-intervention. We suggest that economy of movement (Schenkman, Hall, Kumar, & Kohrt, 2008) improved during a specific motor activity such as SLE. Presuming that these changes in  $VO_2$  occur in the peripheral vascular system,(LeJemtel et al., 1986) it may positively affect functional performance such as walking.

The 10-meter walk test is used to assess gait velocity because of its simplicity and recognition as a useful tool in research and rehabilitation.(Lord & Rochester, 2005) In the current study, the 10-meter fast walk test was used. After 4 weeks of SLE, we found a significant improvement in gait velocity. One possible explanation may be attributed to

decreased energy demand by the hemiparetic limb during walking. Assessment of  $\text{VO}_2$  during SLE showed decreased energy expenditure at submaximal workloads. Similarly, the improved peripheral mechanisms of oxygen exchange could result in greater intensity (walking more quickly) while participants perceived less exertion. Certainly, the encouraged use of the hemiparetic limb during an intense training intervention could result in improved walking speed. Although the training strategy used in the present study is not task specific such as a walking activity, increases in gait speed were reported after 12 training sessions. This training duration (12 exercise sessions) was similar to Sullivan and colleagues.(Sullivan et al., 2007) Anecdotally, participants in the current study reported that the affected limb didn't "feel as tired." The available literature suggests that lower extremity muscle strength can play an important role in walking speed.(Dean, Richards, & Malouin, 2000; Salbach et al., 2004; Sullivan et al., 2007) However, the results of the current study demonstrate improvements in gait speed can be obtained from an aerobic training intervention that encourages use of the hemiparetic limb without task-specificity and significant improvements in lower extremity strength.

Another potential explanation for increased gait velocity during the 10-m fast walk test could be related to motor performance. LEFM scores increased from baseline, which may be the result of repetitive exercise using knee extension/flexion. Recent studies suggest that task-repetitive training such as walking with or without body weight support elicits positive outcomes in cardiorespiratory fitness (Macko et al., 2005) and functional mobility.(Dean et al., 2000; Macko et al., 2005; Salbach et al., 2004; Sullivan et al., 2007) Our study included a repetitive task (knee extension/flexion) but the training protocol focused on encouraged use of the hemiparetic limb. As mentioned by Lang and colleagues, the difference between the animal and human model for stroke recovery may be related to the

amount of practice or repetition of an activity.(Lang, MacDonald, & Gnip, 2007) In our study, the lowest number of knee extension/flexion repetitions by an individual was 120 per session and the highest was 1,600. The mean number of repetitions performed during the 4-week training protocol was 899.4. It has been reported that high numbers of repetitions can induce neuroplastic changes. (Nudo, Milliken, Jenkins, & Merzenich, 1996; Nudo, Wise, SiFuentes, & Milliken, 1996) Although we did not use a task-specific activity, a moderate effect size 0.46 and statistically significant increase in LEFM scores were found post-SLE. However, it is unclear if a 2-point change in LEFM has clinical relevance. Therefore, the most plausible explanation would be improved cardiovascular performance. It seems likely that the increase in oxygen uptake during submaximal work may have had a positive effect on fast walking.

Previous literature suggests that improvements in  $VO_2$  peak using bilateral lower extremities can be observed after SLE in healthy adults.(Davies & Sargeant, 1975; Klausen et al., 1982; Saltin et al., 1976) The data from this study suggest contradictory results, which may be the difference in the training intensity, duration, or participant population used in our study. Davies and colleagues used SLE as a training intervention to assess central and peripheral cardiovascular responses to one and two leg exercise in healthy adults.(Davies & Sargeant, 1975) The authors state that a central component of the cardiovascular system (i.e. cardiac output) is sufficient to provide adequate oxygen uptake to the working muscles during SLE but the peripheral factors such as oxygen utilization limit continued exercise. Bilateral exercise places a greater demand on the cardiovascular system whereby cardiac output will not be able to meet the continued work demands and supply enough blood to exercising muscles. It is likely that our SLE training protocol lacked sufficient intensity to tax the central components of the cardiovascular system in these individuals post-stroke.

## 6.6 Conclusion

In physical therapy practice and stroke rehabilitation research, aerobic exercise and task specific training incorporate both lower extremities.(Macko et al., 2008; Macko, DeSouza et al., 1997; Macko et al., 2005; Macko et al., 2001; Potempa et al., 1995; J. H. Rimmer, Braunschweig et al., 2000; J. H. Rimmer, Riley et al., 2000; Sullivan et al., 2007; Vidoni, Tull, & Kluding, 2008; Yates et al., 2004)

This study examined the effect of a novel training strategy that encouraged use of the hemiparetic limb in people with stroke. The time course and intensity of the training intervention appear sufficient for improving  $VO_2$  during submaximal work efforts and gait velocity (10-meter fast walk). However,  $VO_2$  peak from a maximal effort exercise test did not improve after 4-weeks of training. These data suggest that SLE training was more effective at improving oxygen exchange in the periphery (hemiparetic muscle tissue) rather than central cardiovascular mechanisms. Single limb exercise that encourages use of the hemiparetic leg may be an effective intervention strategy to consider in stroke rehabilitation.

## Chapter 6 Tables and Figures

Table 6.1 Participant Demographics

Characteristics	n = 12	Mean $\pm$ SD	Range
Sex: Men		5	
Age (years)		60.6 $\pm$ 14.5	43-77
Race/ethnicity			
African American		2	
Caucasian		8	
Hispanic		1	
Native American		1	
Body Mass Index (DEXA scan)		29.7 $\pm$ 4.0	
Medication			
Beta-blockers		4	
Stroke Characteristics			
Time (months) post-stroke		69.1 $\pm$ 82.2	6-276
Right side weakness		5	
Type of stroke:			
Ischemic		9	
Hemorrhage		3	
Stroke Severity			
LE Fugl-Meyer score (34 maximum)		26.7 $\pm$ 3.8	20-32

Table 6.2 Outcome Measures at Baseline and Post-training (after 12 exercise sessions).

Values are reported as mean  $\pm$  SD.

	Baseline	Post-training	p value
<b>Cardiorespiratory Fitness</b>			
Maximal Effort			
VO <sub>2</sub> peak (ml*kg <sup>-1</sup> *min <sup>-1</sup> )	19.3 $\pm$ 6.9	19.0 $\pm$ 7.5	0.413
Peak HR (bpm)	136.5 $\pm$ 23.6	139.2 $\pm$ 21.8	0.740
RER	1.1 $\pm$ 0.10	1.1 $\pm$ 0.15	0.893
RPE	16 $\pm$ 2.61	17 $\pm$ 2.83	0.306
Submaximal Effort			
VO <sub>2</sub> (ml*kg <sup>-1</sup> *min <sup>-1</sup> )	7.0 $\pm$ 1.6	5.4 $\pm$ 1.5	0.009*
HR (bpm)	85.5 $\pm$ 16.6	80.6 $\pm$ 13.7	0.046*
Workload (Watts)	39.0 $\pm$ 20.5	41.4 $\pm$ 14.1	N/A
<b>Strength</b>			
Peak LE Extensor torque (ft*lbs)			
Hemiparetic Leg	53.3 $\pm$ 36.4 ‡	59.5 $\pm$ 34.1	0.060
Less Affected Leg	82.3 $\pm$ 35.0	78.6 $\pm$ 37.8	0.186
<b>LE Tissue Composition</b>			
Fat mass (g)			
Hemiparetic leg	5433.8 $\pm$ 2173.3	5582.2 $\pm$ 2246.0	0.118
Less affected leg	5582.2 $\pm$ 2246.0	5731.1 $\pm$ 2441.1	0.237
Lean tissue mass (g)			
Hemiparetic leg	7380.4 $\pm$ 1723.3	7317.5 $\pm$ 1587.8	0.563
Less affected leg	7584.0 $\pm$ 1910.6	7527.4 $\pm$ 1691.3	0.650
<b>LE Motor Function</b>			
10-meter fast walk (m*sec <sup>-1</sup> )	1.18 $\pm$ 0.6	1.35 $\pm$ 0.6	0.001*
(n = 7)			
LE Fugl-Meyer score	26.7 $\pm$ 3.8	28.7 $\pm$ 4.8	0.007*

\*= p  $\leq$  0.05 from baseline to post-training; ‡= p  $\leq$  0.05 between the hemiparetic and less affected limb

## **Chapter 7**

### Discussion and Conclusion

## **7.1 Summary of Findings**

The body of research presented in this dissertation represents a unique “fusion” of cardiopulmonary performance, vascular function and a therapeutic intervention using single limb exercise (SLE) in people with central nervous system damage. The genesis of SLE using only the hemiparetic leg is the result of: 1) vascular adaptations that have been reported in the hemiparetic leg after stroke, 2) the physical therapist in me who ponders, “What can be done to alter the post-stroke adaptations?” and 3) previous literature demonstrating vascular changes in response to SLE in healthy adults. The consequence is a series of novel experiments that examine the role of a 4-week SLE training protocol using only the hemiparetic leg. The findings reported in this dissertation suggest that the role of repetitive, encouraged use of the hemiparetic leg during exercise facilitates improved blood flow to the hemiparetic leg. However, the results of these studies suggest that contribution of the peripheral and central mechanisms of the cardiovascular system for improving leg blood flow are not cohesive.

In the following section, reasons for vascular remodeling in the femoral artery in people post-stroke and the differentiated findings regarding the cardiovascular system’s response are discussed. However, it is difficult to discern the multi-faceted mechanisms related to the vascular remodeling in a clinical population such as stroke. It is with great optimism that future work will build upon these findings and gain a better understanding of the causes and consequences of vascular remodeling in the hemiparetic limb. Perhaps this work will serve as a guide for both stroke rehabilitation and research to seek a greater understanding of the dynamic role that the cardiovascular/pulmonary system plays in stroke recovery.



*Chapter 2. Validity of a Total Body Recumbent Stepper Exercise Test (TBRS-XT) to Assess Cardiorespiratory Fitness*

Assessing maximal oxygen uptake in people post-stroke is difficult due to stroke sequelae. In addition, the stroke literature for modality and protocol selection are inconsistent for maximal effort exercise testing. In an attempt to resolve this issue, a set of experiments was conducted to design an exercise testing protocol using a total body recumbent stepper (TBRS). In order to determine the “best” exercise test protocol for individuals with stroke, the groundwork was laid in healthy adults.

The focus of Chapter 2 was to determine the validity and reliability of an exercise test (TBRS-XT) using the TBRS in healthy adults. The first experiment was designed to assess the validity of the TBRS-XT when compared to the “gold standard” Bruce protocol using the treadmill. The results suggested that a strong relationship for  $VO_2$  peak between the TBRS-XT and Bruce protocol. In experiment 2, individuals performed the TBRS-XT on 2 separate occasions at least one week apart. It was determined that the TBRS-XT was a reliable exercise test for obtaining  $VO_2$  peak. Therefore, the TBRS-XT should be included in the repertoire of exercise tests to assess  $VO_2$  peak.

*Chapter 3. Modified Total Body Recumbent Stepper Exercise Test (mTBRS-XT) to Obtain  $VO_2$  Peak in People With Chronic Stroke.*

To investigate different methods for assessing  $VO_2$  peak in people after stroke, individuals participated in 2 maximal effort exercise tests in random order. One exercise test used a cycle ergometer and the other used the TBRS. The TBRS-XT was modified (mTBRS-XT) to accommodate the decreased fitness levels found in people post-stroke. It was hypothesized that the mTBRS-XT would elicit higher values for  $VO_2$  peak. Therefore, this

exercise test may be a preferred method for assessing cardiorespiratory fitness. While the mTBRS-XT did produce significantly higher  $VO_2$  peak values than the cycle ergometer, two interesting findings surfaced. First, the TBRS accommodates a wide range of lower extremity deficits in motor performance. One individual who had a severe stroke was unable to pedal the cycle ergometer but was able to use the TBRS. Second, participants indicated that during the cycle ergometer exercise test, limb fatigue limited their performance while whole body fatigue was reported as the reason for termination of the mTBRS-XT. Therefore, these results suggest that modality and exercise test protocol are critical to accurately assessing cardiorespiratory fitness in people post-stroke.

*Chapter 4. Use of Doppler Ultrasound to Assess Femoral Artery Adaptations in the Hemiparetic Limb in People with Stroke.*

Arterial remodeling is a complex series of physiological changes that occur after neurological injury, decreased peripheral oxygen consumption, alterations in blood flow and pressure variations. The primary aim of this experiment was to use Doppler ultrasound and establish whether vascular remodeling occurs in the femoral artery of the hemiparetic leg in people post-stroke. If oxygen demand in the hemiparetic leg is decreased compared to the other, then femoral artery blood flow would be less. This could result in a smaller arterial diameter based on the flow-diameter relationship. As shown previously, individuals with diabetes and spinal cord injury present with femoral artery remodeling due to decreased blood flow to the legs. Based on the literature, it was hypothesized that femoral artery blood flow, diameter, and peak blood flow velocity would be lower in the hemiparetic leg when compared to the less affected limb. As expected, the results suggest that the components of blood flow (diameter and peak velocity) were significantly less in the hemiparetic leg when

compared to the other side. Interestingly, it was found that femoral artery wall thickness was greater in the hemiparetic limb, which suggests diminished vessel wall compliance. The results of this experiment highlight the vascular remodeling that occurs in the femoral artery post-stroke.

*Chapter 5. Vascular Remodeling of the Femoral Artery is Associated with Exercise-Induced Changes in the Hemiparetic Leg Post-Stroke.*

The aim of the present experiment was to determine the role of single limb exercise (SLE) training on modifying the vascular adaptations that occur in the hemiparetic leg post-stroke. In this experiment, the SLE training consisted of knee extension/flexion using a Biodex machine. In healthy adults, SLE was used as an exercise training method to induce vascular remodeling. Thus, based on the previous literature it was expected that the femoral artery in the hemiparetic leg would respond to an exercise stimulus and undergo vascular changes. The premise behind the hypothesized vascular changes was related again to the flow-diameter relationship. If increased blood flow was being delivered to the working muscles (increased oxygen demand/consumption) during an exercise-training regimen, then chronic adaptive changes such as arterial expansion would occur. The findings presented suggest individuals with a central motor neuron lesion such as stroke demonstrated the capacity to respond to an exercise-induced stimulus (i.e. SLE) and modify the vascular structure. The femoral artery in the hemiparetic leg increased resting blood flow, diameter and peak velocity. These vascular modifications post-training were in close proximity to those values for the less affected limb. Further, SLE and other training programs that increase metabolic demand in the peripheral muscles of the hemiparetic limb may be useful in preserving cardiovascular health.

*Chapter 6. Single Limb Exercise: The Physiological and Functional Responses to a Training Protocol that Facilitates Encouraged Use in the Hemiparetic Lower Extremity.*

The aim of the final experiment was to establish central and peripheral cardiovascular responses to a 4-week exercise training program. In addition, we sought to determine whether participating in SLE would improve a functional outcome measure such as gait speed in a subset of participants. The experimental protocol used here was identical to Chapter 5, which engaged only the hemiparetic leg in unilateral knee extension/flexion. It was expected that after the intense, 4-week training program, individuals would increase peak oxygen consumption ( $\text{VO}_2$  peak) during a maximal effort exercise test. Further, it was hypothesized that oxygen consumption ( $\text{VO}_2$ ) during submaximal effort using the SLE protocol would be significantly lower than baseline values. Post-test results from the maximal effort exercise test suggested that a central cardiovascular mechanism such as  $\text{VO}_2$  peak did not improve despite a thrice weekly exercise training program for 4 weeks. However, the results suggest that after the SLE, peripheral mechanisms in the hemiparetic leg such as improved oxygen exchange and blood flow may facilitate the lower  $\text{VO}_2$  and heart rate values during submaximal work. Further, despite varying levels of lower extremity motor performance in the participants, gait speed improved during the 10-meter fast walk test. These results provide some insight toward the benefits of an exercise training protocol aimed at encouraged use of the hemiparetic leg for physiological and functional outcome measures.

## **7.2 Possible Mechanisms for Vascular Changes Following Stroke**

Because little research is available that characterizes the femoral artery structural changes that occur after stroke, it can only be speculated as to why the arterial adaptations in

the hemiparetic leg occur. Therefore examining the changes that occur in older adults may give some insight into the possible mechanisms. The literature has suggested that arterial changes and vascular resistance occur with hypertension (Lind & Lithell, 1993) and aging (Dinenno et al., 1999; Dinenno, Tanaka, Stauffer, & Seals, 2001; Schmidt-Trucksass et al., 1999) due to increased sympathetic nerve activity.(Dinenno et al., 1999)

### *Vascular Sympathetic Tone*

The literature suggests that older adults have increased muscle sympathetic nerve activity (MSNA) and therefore, reductions in blood flow and vascular conductance are lower when compared to healthy young adults. Although increased MSNA has been observed in older adults even without cardiovascular disease,(Dinenno et al., 2001; Thijssen et al., 2007) information regarding the mechanisms is uncertain. In an attempt to address potential mechanisms, Dinenno and colleagues hypothesized that increased MSNA may be the result of long-term changes in alpha adrenergic activity.(Dinenno et al., 2001) This could be accomplished through greater release of adrenergic catecholamines, a higher affinity for binding to alpha adrenergic receptor sites and/or increase in the number of receptor sites for alpha adrenergics.(Dinenno et al., 2001) To test their hypothesis, they examine femoral artery blood flow and vascular conductance in a group of older and young males. At baseline, resting values for blood flow and vascular conductance was significantly decreased in the older male compared to younger males. Phentolamine, an alpha adrenergic receptor antagonist, was administered in the femoral artery of the experimental leg in both groups. The differences in femoral artery blood flow and conductance were no longer significant after phentolamine infusion. These results imply that increased sympathetic alpha adrenergic activity may influence sympathetic tone in older adults. However, other mechanisms that

influence vascular vasodilation such as nitric oxide (NO),(Hopman et al., 2002; Mohrman & Heller, 2006) eNOS availability (Hopman et al., 2002) or vasoconstriction mediated through endothelin-1 (Thijssen et al., 2007) need to be considered.

### *Endothelial-Dependent Factors*

Previous research using an animal model has indicated the endothelium is an integral component of arterial modulation in response to blood flow changes.(Brownlee & Langille, 1991; Langille & O'Donnell, 1986) Interestingly, results of one study demonstrated the intact endothelium increased arterial diameter in response to a greater volume of flow. However, the sections where the endothelial cells were removed, no changes in arterial diameter were reported. Therefore, endothelial-derived factors that affect vasoconstriction (Endothelin-1) or vasodilation (NO) are important factors to consider since it appears that the endothelial cells are most sensitive to alterations in homeostasis. People with spinal cord injury (SCI) demonstrate increased sympathetic tone in the lower extremities.(Hopman et al., 2002) Because of the nature of SCI, these changes are not due to substantial increases in MSNA but rather diminished NO production from physical inactivity.

Considering the results presented in Chapter 4 that found a significant reduction in femoral artery diameter and blood flow in the hemiparetic limb, we can only speculate why vascular adaptations occur. Since individuals post-stroke have reduced physical activity levels and tend to rely on the less affected limb during exercise, it would seem logical that decreased NO availability and/or eNOS production to synthesize NO would be one potential mechanism that could hamper vasodilation in the hemiparetic limb. While vascular tone was not directly assessed through NO production or MSNA, Ivey and colleagues reported endothelial dysfunction in the hemiparetic leg post-stroke through reactive hyperemia.(2004)

Their results identify that endothelial function is altered in the hemiparetic leg when compared to the less affected side. If, indeed, vascular adaptations post-stroke are endothelial-dependent, then interventions aimed at increasing these factors would be beneficial.

To counteract a reduction in NO availability, exercise has been shown to increase NO production, which decreases vascular tone (Hambrecht et al., 2000; Koller et al., 1995; Miller & Vanhoutte, 1988; Sessa et al., 1994; Watts et al., 2004) and would allow for a greater volume of blood flow. Since the results of the current project found improvements in arterial diameter and blood flow in the hemiparetic leg after the exercise training intervention, further studies are needed to analyze the mechanisms related to vascular tone.

### **7.3 Cardiorespiratory Fitness**

#### *Peak Oxygen Consumption ( $VO_2$ Peak)*

As mentioned in Chapter 3, obtaining  $VO_2$  peak in people post-stroke is challenging due to trunk weakness, poor postural control, hemiparesis and lower extremity incoordination weakness. Despite the challenges associated with stroke, all participants in this present body of work were able to participate in the maximal effort exercise test using the total body recumbent stepper (TBRS). The differences in age ranged from 43 to 77 years of age. However, the wide range of cardiorespiratory fitness values did not necessarily match the percentile standards for aerobic power.(ACSM, 2006) One female participant who was 46 years of age had a  $VO_2$  peak value of  $10.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , which was well-below the 10<sup>th</sup> percentile value of  $25.1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Conversely,  $VO_2$  peak for a 66 year old female participant was  $27.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . This is considerable higher than the 46 year old individual. ACSM reports that maximal oxygen uptake declines during the aging process due

to decreased maximal heart rate.(2006) However, in people with stroke, the observation is much different. The possibility exists that pre-morbid cardiorespiratory fitness values are decreased to begin with and combined with the sequelae post-stroke, a severely deconditioned state prevails.(MacKay-Lyons & Howlett, 2005) After stroke, it has been reported that increases in VO<sub>2</sub> peak are feasible with aerobic training albeit the gains are minimal.(Carr & Jones, 2003; Duncan et al., 2003; Kluding & Billinger, 2005; Macko et al., 2001; Potempa et al., 1995; J. H. Rimmer, Braunschweig et al., 2000) The current stroke literature supports aerobic exercise training to facilitate healthy lifestyles. However, much work is needed in this area to determine the mechanisms behind the reduction in cardiorespiratory fitness and best rehabilitation practice to improve fitness levels in people post-stroke.

#### **7.4 Limitations**

##### *Assessment of Cardiorespiratory Fitness*

All maximal effort exercise testing was performed using a total body recumbent stepper (TBRS). This modality engages all extremities during the exercise test while intensity increases every 2 minutes until participants reach maximal effort. This modality can be used for exercise testing in people after stroke,(S. A. Billinger, Tseng et al., 2008) but may not be sensitive to cardiorespiratory changes related to SLE. One possible solution would have been to have participants perform a maximal effort exercise test for each limb using a single limb exercise testing protocol. However, people after stroke are considered high risk for exercise testing (ACSM, 2006) and require physician supervision. Exercise testing at the University of Kansas Medical Center's General Clinical Research Center provides physician supervision but does not have a Biodex machine in which a single limb maximal effort test



could be conducted. Therefore, maximal effort exercise testing was performed using the TBRS to assess cardiorespiratory fitness.

#### *Unilateral vs Bilateral Exercise*

The present study was designed to determine the cardiorespiratory and vascular response to an exercise training intervention. In healthy individuals, several studies are available to suggest that single limb exercise (SLE) is an acceptable training method for inducing femoral artery changes in the trained limb.(Bell et al., 2001; Klausen et al., 1982; Miyachi et al., 2001; Shoemaker et al., 1994) However, to this author's knowledge, no information regarding this type of training is available in people after stroke. While the SLE training protocol is novel in people post-stroke, the availability of the Biodex and equipment for SLE is limited in the clinical setting. Nonetheless, our results suggest improved femoral artery characteristics after the training period. However, there may exist a greater benefit to perform bilateral exercise.

Older individuals that perform regular aerobic exercise such as running tend to have improved regulation of vascular tone when compared to sedentary older adults.(DeSouza et al., 2000) Further, when sedentary older adults participated in a 3-month walking intervention, the age-associated changes in vascular tone regulation were reduced when compared to baseline.

In clinical populations such as spinal cord injury (SCI), improvements in vascular tone have been reported after bilateral functional electrical stimulation (FES) cycling in individuals post spinal cord injury.(Gerrits et al., 2001; Thijssen et al., 2006) While bilateral exercise such as cycling and treadmill walking are common exercise interventions post-stroke,(Duncan et al., 1998; Macko et al., 2008; Macko, DeSouza et al., 1997; Macko et al.,

2001; J. H. Rimmer, Braunschweig et al., 2000; Yates et al., 2004) a few studies have reported the hemiparetic limb performs less work during bilateral activity.(Landin et al., 1977; Sibley et al., 2008) In light of the reported findings, the current study proposed SLE to solely engage the hemiparetic limb to maximize the potential effects of exercise. However, it is unclear whether exercise prescription intensity and duration could have been increased using bilateral exercise. If so, then the magnitude of improvements in femoral artery vasculature may have been greater.

Finally, in functional tasks and daily activities, both limbs work together to accomplish goals such as lifting, walking or turning. The SLE protocol focuses on training one limb. In the current study, the rationale for SLE was that people after stroke rely more on the less affected limb. We believed this training protocol would elicit the greatest changes in the outcome measures. After the SLE intervention, the participants in this study improved gait velocity, which requires a coordinative effort between both limbs. However, results should be interpreted with caution. Gait velocity was only assessed in 7 participants so our sample size was small. Additionally, we did not assess any other bilateral functional tasks so the carry-over from SLE may be limited to other activities.

#### *Cardiorespiratory Fitness at Maximal and Submaximal Effort*

The training intensity during SLE may have been insufficient to elicit significant changes in cardiac output, which ultimately affects peak oxygen uptake ( $VO_2$  peak). Since the SLE training was performed in only one limb, peripheral adaptations gained from the exercise protocol (Chapter 6) may not translate to central cardiorespiratory performance. In healthy adults, 5-6 weeks of SLE resulted in higher values for  $VO_2$  peak during bilateral lower extremities.(Davies & Sargeant, 1975; Klausen et al., 1982; Saltin et al., 1976) In

contrast, the results of the present study showed a miniscule decline in  $\text{VO}_2$  peak. The decline in  $\text{VO}_2$  peak may have been influenced by the fact that one person stopped the exercise test early secondary to being agitated by the mouth piece and head gear used in exercise testing. Consequently, this resulted in a  $2.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  lower value than baseline. However, even without this person's data, improvements in  $\text{VO}_2$  peak were not found.

Previous literature reporting increases in  $\text{VO}_2$  peak in healthy adults exercised at 80% or higher of the one-legged  $\text{VO}_2$  peak values. The individuals participating in the current study exercised in a range of 60-70% of  $\text{VO}_2$  peak during an all-extremity maximal effort exercise test. Although we followed the guidelines for exercise prescription for people post-stroke, (Palmer-McLean, 2003) the results suggest a higher training intensity may be needed to improve  $\text{VO}_2$  peak using SLE.

The equipment used for metabolic measurement during submaximal effort was identical to that during maximal effort testing. Submaximal effort was performed during baseline and post-intervention assessment of SLE. The design of the SLE protocol consisted of an isokinetic knee extension/flexion protocol that used  $150 \text{ degrees} \cdot \text{sec}^{-1}$  for the velocity. Therefore, individuals could generate variable force output during knee movements. During submaximal testing, participants were encouraged to use visual feedback on the Biodex in an attempt to maintain identical force production. Unlike bilateral exercise on a cycle ergometer, the workload could not be set and consistently maintained. Despite these challenges associated with maintaining a constant force production, the workload (watts) at baseline was  $39.0 \pm 20.5$  and  $41.4 \pm 14.1$  post-intervention. While there are some differences in workload, these were not statistically significant ( $p = 0.44$ ).

### *Medication*

Individuals taking  $\beta$ -blockers and were not excluded from participating in this study. There may be some effects of  $\beta$ -blockers on vascular tone in the periphery. However, research suggests the alpha adrenergic blockers have a greater effect on peripheral blood flow and vasodilatory effects related to vascular conductance than  $\beta$ -blockers. (Dinenno et al., 2001) No individuals in the present study were taking alpha adrenergic blockers and only 4 individuals were taking  $\beta$ -blockers. Additionally, five of the 12 individuals were taking anti-hypertensive medications other than  $\beta$ -blockers.

In the study by Ivey and colleagues 13 of the 19 participants were on anti-hypertensive medications. Yet, these individuals demonstrated endothelial dysfunction in the hemiparetic leg after stroke. In the present study, femoral artery blood flow and diameter were significantly different in the hemiparetic limb at baseline but those differences diminished post-intervention. Our results suggest that participants increased their peripheral vascular function despite using medications. This may imply that endothelial-mediated factors such as nitric oxide (NO) may have a greater role in peripheral vascular tone rather than independent endothelial factors such as medications that target the smooth muscle within the arterial wall.

### *Regression to the Mean*

This dissertation project used a sample of convenience for this within subject design. Individuals with mild to moderate stroke (LEFM score 20-33/34) participated in this study that used a SLE training protocol focused only on the hemiparetic leg. The less affected limb was the control leg. The results of the study suggest that 4 weeks of SLE training improved femoral artery blood flow and diameter in the hemiparetic leg. However, we cannot discount

the possibility of regression to the mean. The SLE intervention appears to be effective at improving femoral artery characteristics (ie: diameter and blood flow) but the possibility exists that these outcome measures increased to due chance or regression toward the mean.(Krause, 2007) For example, if those individuals with femoral artery blood flow and diameter measures below the population mean entered this study, then one could expect to see improvements toward the mean. While our results suggest that the SLE training was effective, it may be due to the fact that these individuals' outcome measures regressed toward the mean but may not significantly greater than the population mean. The best solution would have been to use a randomized control trial.(Krause, 2007)

#### *Lesion Location*

Lesion location was not identified for the present study. The hemiparetic limb was identified and confirmed using observation by a physical therapist, information from the participant and lower extremity Fugl-Meyer score.(Daly et al., 2006) The suprabulbar subcortical regions of the brain have been associated with peripheral sympathetic nervous system activity.(Esler et al., 2002) A lesion near this area of the brain may result in changes in sympathetic hormone discharge that could potentially alter peripheral vascular function. Despite the fact that lesion location was not identified, positive changes in femoral artery vascular structure were observed.

### **7.5 Clinical Implications**

According to the American Heart Association's *Heart Disease and Stroke Statistics, 2008 Update*, approximately 2,400 American people die each day from cardiovascular disease (CVD).(Rosamond et al., 2008) This translates to one death every 37 seconds.

Several risk factors for CVD include hypertension, dyslipidemia, body mass index  $> 30 \text{ kg}\cdot\text{m}^2$  and sedentary lifestyle.(ACSM, 2006) These same risk factors apply to stroke, which is “under the umbrella” of total cardiovascular-related diseases. Therefore it’s not surprising that in one year, 780,000 Americans experience a stroke (Rosamond et al., 2008) and most will require rehabilitation.(Taub et al., 2006) These cardiovascular consequences associated with stroke have serious implications related to physiological and functional performance. The findings of the current research project suggest that SLE may have positive effects on both aspects of performance.

### *Physiological Function*

Vascular function can be altered with respect to aging, disease processes such as hypertension and even neurological injury (SCI or stroke). It has been suggested that healthy older adults may exhibit decreased arterial diameter and blood flow due to muscle sympathetic nerve activity (MSNA). The physiological limitations of decreased blood flow and chronic hyperactivity of the sympathetic nervous system have been linked to hypertension, dyslipidemia and hyperinsulinemia, which are all components of metabolic syndrome (Lind & Lithell, 1993) and cardiovascular disease.(Rosamond et al., 2008) The ramifications of these disease processes can restrict functional performance (activities of daily living) and exercise tolerance. However, chronic, regular aerobic exercise may reduce the effects of MSNA during aging through improved endothelium-dependent vasodilatory properties (DeSouza et al., 2000) in addition to decreasing cardiovascular-related events.(Rosamond et al., 2008)

The experiments conducted in Chapter 4 illustrate the differences found in femoral artery blood flow and diameter between the two legs. Based on the research done in aging

adults and those with metabolic syndrome symptoms, it would be advantageous to develop clinical exercise protocols that would help restore peripheral vascular function. Furthermore, the findings in this body of work signify that SLE has a positive effect on femoral artery blood flow and diameter. Improvements in leg blood flow would provide greater oxygen supply and perfusion to the muscle tissue and enhance performance during submaximal efforts such as walking. These results reported in the current project suggest that aerobic exercise strategies such as SLE could be a component of stroke rehabilitation to counteract vascular adaptations that may occur after stroke.

#### *Cardiorespiratory Fitness and Function*

The goal of most exercise interventions is to improve cardiorespiratory health and preserve physical function as humans age. Work done by Macko (1997) and MacKay-Lyons (2002) reported  $VO_2$  peak values well below age-matched sedentary controls.

Cardiorespiratory fitness decline can negatively affect the endurance needed for community walking but also activities of daily living.(Cunningham et al., 1993) The exercise training intervention in the current study was designed to improve oxygen uptake at maximal and submaximal effort. The individuals participating in this study performed repetitive exercise that focused only on movement by the hemiparetic leg. We anticipated that the benefit to using SLE training would be the minimal compensatory techniques that could be used by the less affected limb during exercise. Thus, greater improvement in  $VO_2$  peak and  $VO_2$  measures post-intervention. The results from the current body of work found that when the hemiparetic limb is required to perform all of the work, a training effect can be elicited during submaximal effort. For instance, if a person after stroke demonstrates elevated energy expenditure during walking from the living room to the kitchen, then this may result in

hemiparetic leg fatigue or shortness of breath, which can be the result of a sedentary lifestyle. However, participating in regular exercise training such as SLE, improvements in oxygen consumption result from greater blood flow and/or increased oxygen exchange from the blood to the muscle and this directly affects functional performance of activities (walking) and life quality. (Seals & Dinunno, 2004)

Results from the 10-meter walk in the 7 participants hints at the possibility that SLE training may be influential in functional activities such as a fast walk. The 10-meter fast walk is a meaningful assessment of gait velocity in the clinic and research setting. (Lord & Rochester, 2005) The 10-meter walk may provide a “functional link” for justification of SLE as a therapeutic intervention in stroke rehabilitation. Not only were positive effects found in peripheral blood flow and oxygen uptake but these may have translated to an improved walking performance.

Finally, SLE may be considered a therapeutic intervention beneficial for physiological and functional outcomes in people post-stroke. However, information regarding dose/response for clinically meaningful outcomes was not available for the novel training protocol used in this study. Since individuals were allowed to self-progress their training sessions, further analysis of the SLE duration and intensity is warranted to provide greater insight exercise prescription.

## **7.6 Future Directions**

The primary purpose of the present work was to determine the effect of a 4-week SLE intervention on cardiorespiratory fitness and peripheral vascular adaptations in the hemiparetic limb in chronic stroke. The results of this work demonstrated that after the 4-week SLE intervention, femoral artery remodeling occurred in the hemiparetic leg. In



addition, we found SLE can positively affect  $VO_2$  during submaximal exercise but not  $VO_2$  peak during a maximal effort graded exercise test.

This project established the groundwork for femoral artery vascular remodeling in the hemiparetic leg after an exercise intervention. A long-term goal of this research is to better characterize vascular adaptations that occur in the affected limbs in people post-stroke. Therefore, the findings from this project coupled with the literature available present future research directions.

#### *Time-Course for Arterial Remodeling*

After stroke, the peripheral vascular system in the hemiparetic leg appears to undergo vascular remodeling (Chapter 4). However, the time during stroke recovery in which vascular remodeling begins is essentially unknown. People with spinal cord injury (SCI) demonstrate signs of vascular remodeling in bilateral lower extremities within three weeks of injury onset.(de Groot, Bleeker, van Kuppevelt et al., 2006) When compared to healthy age-matched controls, the individuals with SCI have decreased femoral artery blood flow and diameter. Interestingly, de Groot and colleagues reported that the brachial artery in people with SCI does not demonstrate significant differences in blood flow or arterial diameter when compared to healthy age-matched controls. This may be related to the sufficient arm strength and endurance needed to propel the wheelchair. Muscle mass, physical activity or lesion location in the spinal cord may have a role in the preservation of brachial artery structure and function.

Unique from SCI, individuals post-stroke may exhibit mild to severe deficits in the arm and leg on one side of the body. Therefore, it seems logical to examine the arterial vasculature in bilateral upper and lower extremities immediately following stroke to one-year

post to elucidate vascular differences that may occur between the affected and less affected sides over time. In addition, research investigating the relationship between acute stroke severity, recovery and functional performance to the cardiovascular adaptations may be useful in determining the most appropriate “timing and dose response” for minimizing vascular changes after stroke.(Morris et al., 2008) Lastly, assessing the time course related to exercise training and then a period of detraining in people with stroke would potentially provide insight to the exercise-induced vascular adaptations and the response to inactivity.

#### *Assessment of Mechanisms Related to Vascular Function Post-stroke*

Two studies have suggested that older adults present with increased muscle sympathetic nerve activity (MSNA) (Dinenno et al., 2001; Seals & Dinenno, 2004) in the lower extremities. Furthermore, MSNA has been suggested to exist in people after spinal cord injury despite the loss of sympathetic input below the level of lesion.(Hopman et al., 2002) This is an area of stroke research that requires further exploration. The possibility may exist that the stroke affected side of the body experiences hyperexcitability of muscle sympathetic nerve activity, which causes vasoconstriction of the vessel wall and decreased blood flow to the periphery. In addition, if indeed, increased excitation of MSNA does exist, then assessing potential regions of the brain that may be responsible for sympathetic control could be performed. One such study examined the subcortical suprabulbular area of the brain for norepinephrine discharge and spillover rate.(Esler et al., 2002) Those individuals with a higher amount of norepinephrine, demonstrated increased MSNA in the periphery.

Since vascular health depends on concomitant adjustments and function of endothelial-dependent and independent factors, examination of these factors requires further attention. As found in Chapter 5, SLE had a favorable effect on improving femoral artery

blood flow and diameter. We can only speculate that the changes were induced by the effects of physical activity such as increased nitric oxide (NO), which induces vasodilation and improves blood flow.(Dinenno et al., 2001) In addition, using Doppler ultrasound to assess changes in blood flow and diameter during an acute bout of exercise will provide an insight into the immediate vascular responses to acute exercise in the hemiparetic limb.

### *Exercise Interventions*

Exercise interventions have been designed to improve arterial function and sometimes, even reversed the arterial adaptations from aging (Dinenno et al., 2001) and neurological injury (Thijssen et al., 2006) and Chapter 5. While the research presented here demonstrated positive changes in femoral artery function (Chapter 5) and submaximal work (Chapter 6) after a 4-week exercise program, the focus of the intervention was targeted at the hemiparetic limb. However, consideration of bilateral exercise interventions (ie: treadmill or lower extremity ergometry) would provide insight to vascular responses related to both limbs.

Bilateral exercise training using the lower extremities such as cycling or treadmill walking is common in stroke rehabilitation and research.(Duncan et al., 1998; Duncan et al., ; Macko et al., 2008; Macko et al., 2001; J. H. Rimmer, Riley et al., 2000) However, to our knowledge, the effect of bilateral exercise training on the vascular outcome measures used in this dissertation work have not been previously examined. Therefore, future work should consider the effectiveness of bilateral exercise training on cardiovascular function and the vascular responses related to both limbs. One caveat to consider would be related to decreased use of the hemiparetic limb during bilateral activity such as cycling.(Landin et al., 1977) For example, if people post-stroke primarily use the *less* affected limb during activity, then the results may show greater femoral artery adaptations on the stronger limb and

minimal changes on the weaker side or no significant differences in outcome measures.(McCombe Waller, Liu, & Whittall, 2008; Morris et al., 2008) One solution may be a randomized control trial with one group performing bilateral exercise training while the other group participates in a combined bilateral and SLE regimine. This may elucidate a potential benefit of incorporating SLE into stroke rehabilitation. Finally, a combination of aerobic exercise and resistance training may produce the most favorable outcomes due to changes in muscle strength and endurance. A better understanding of the relationship between therapeutic exercise and physiological and functional outcome measures could contribute to the rehabilitation field by providing novel information and supporting evidence-based practice.

## **7.7 Conclusions**

The compilation of research presented in this dissertation is a “fusion” of cardiopulmonary and vascular function in a complex clinical population such as stroke. Cardiorespiratory fitness is critical to performance of daily tasks and walking. Clinically, this is important for participation in stroke rehabilitation and returning to the home environment. While regular aerobic exercise promotes increased levels of cardiorespiratory fitness, most individuals post-stroke do not engage in regular physical activity.(Gordon et al., 2004) Despite a training intensity at 65-70% of VO<sub>2</sub> peak, the present findings suggest that the unilateral exercise was not vigorous to increase peak aerobic capacity. In contrast, the repetitive, encouraged use of the hemiparetic limb to perform all of the work during SLE provided enough stimulation that a training effect was found at submaximal effort. Individuals in this study demonstrated decreased energy expenditure. That is, heart rate and oxygen uptake were lower during similar workloads post-training than at baseline. These

findings are important for functioning at home or in the community. If a person after stroke attempts a task such as vacuuming and now experiences higher energy expenditure and feels fatigued with the particular activity, then it is possible that person will no longer perform the task. However, if the person continues to perform the activity and regularly participates in physical activity or rehabilitation, then that individual should become less tired with a functional task over time. Rehabilitation professionals need to consider and emphasize the importance of regular physical activity to those individuals participating in therapy and when returning to the community.

The work presented on femoral artery adaptations in the hemiparetic leg supports the current literature and extends the findings related to vascular remodeling and exercise post-stroke. It appears that the hemiparetic limb responds to the needs for increased blood flow during exercise. Once exercise begins, increased blood flow is delivered to the working muscles. In addition, the artery must accommodate the greater volume of flow and diameter size increases. Over time, femoral artery diameter will adjust and maintain a greater diameter to support increased blood flow in order to meet metabolic demand. While the vascular response in the hemiparetic leg to acute exercise is not clear as outlined previously, we did observe femoral artery remodeling in response to SLE. The SLE training provided enough of a stimulus that these changes occurred and almost matched the less affected limb.

Maintaining adequate blood flow to the tissues is necessary for cardiovascular health. In consideration of the risk for cardiovascular events and even recurrent stroke after the initial stroke, it is imperative that rehabilitation professionals emphasize exercise training using the hemiparetic limb to preserve and maximize vascular health.

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## Appendix 1

*The Effect of Single Limb Exercise Training on Femoral Artery Blood Flow and  
Cardiorespiratory Fitness in Chronic Stroke: A Case Study*

Billinger, SA, Schippers, KA, Norstrom, JL, Kluding, PM. The Effect of Single Limb Exercise Training on Femoral Artery Blood Flow and Cardiorespiratory Fitness in Chronic Stroke: A Case Study.

### **A1.1 Abstract**

Purpose/Hypothesis: The purpose of this case study was to describe the effect of single limb exercise training on femoral artery diameter and blood flow velocity in the hemiparetic limb in one individual with chronic stroke. Methods: One male adult (81 years of age, 10.6 years post-stroke) with a right lower extremity Fugl-Meyer score of 33/34 participated in this case study. Doppler ultrasound was used to assess resting femoral artery diameter and blood flow velocity. Baseline femoral artery diameter was 1.03 cm for the hemiparetic limb and blood flow velocity was  $67.5 \text{ cm} \cdot \text{sec}^{-1}$ . Cardiorespiratory fitness ( $\text{VO}_2$  peak) was determined from a maximal effort graded exercise test. Baseline  $\text{VO}_2$  peak was  $19.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The participant performed single limb exercise training 3 times per week for 3 weeks using an isokinetic knee flexion/extension exercise protocol. Results: After a 3-week single limb exercise intervention using the hemiparetic limb, a 1% increase was observed for femoral artery diameter while a 10.7% increase (baseline:  $67.5$  vs post-training:  $74.7 \text{ cm} \cdot \text{sec}^{-1}$ ) for blood flow velocity was reported. Conclusion: This case study is an important step in understanding if vascular adaptations can be altered in the hemiparetic lower extremity following stroke.

## A1.2 Introduction

Despite rehabilitative efforts, approximately two-thirds (Taub et al., 2006) of individuals post-stroke experience a multitude of deficits. These include hemiparesis, decreased balance, muscle incoordination,(Taub et al., 2006)and lower cardiorespiratory fitness values,(Cunningham et al., 1993; Duncan et al., 2003; Macko et al., 2001; Teixeira da Cunha Filho et al., 2001) which can limit one's ability to return to prior level of function. In an attempt to improve cardiorespiratory fitness, aerobic exercise interventions have been recommended (Gordon et al., 2004) during rehabilitation and as part of a daily routine after discharge from therapy. The primary mode of aerobic exercise training after stroke has been bilateral activity such as the treadmill or cycle. However, it has been reported that individuals post-stroke prefer to use the less affected limb not only during stance, transfers and ambulation (Brunt et al., 1995; Messier et al., 2005; Mizrahi et al., 1989; Yavuzer et al., 2006) but also during exercise.(Landin et al., 1977) Landin and colleagues reported that during bilateral lower extremity cycling, individuals with stroke relied on their less affected limb during the cycling exercise. This could have affected the amount of work performed by the hemiparetic limb.(1977) The decreased demand for leg oxygen consumption(Dinenno et al., 1999) appears to have a deleterious effect on the arterial vasculature in the hemiparetic limb post-stroke. In individuals with chronic stroke, differences in arterial blood flow velocity between the lower extremities have been observed at rest (Landin et al., 1977);(Ivey et al., 2004) and during exercise.(Landin et al., 1977) We have observed that in addition to differences in blood flow velocity, femoral artery diameter is reduced in the hemiparetic leg (Chapter 4).

These adaptations in the femoral artery vasculature have been reported in the literature during periods of bed rest,(Bleeker, De Groot, Poelkens et al., 2005) and after

unilateral limb suspension,(Bleeker, De Groot, Rongen et al., 2005) which may mimic the changes that occur in the hemiparetic limb. However, it is important to emphasize that these between-limb differences have not been observed in healthy adults for femoral artery diameter (Bleeker, De Groot, Poelkens et al., 2005; Miyachi et al., 2001; Radegran & Saltin, 2000) and blood flow velocity.(Bleeker, De Groot, Rongen et al., 2005; Davies & Sargeant, 1975) Since between-limb differences are found post-stroke, an exercise intervention that focuses only on the hemiparetic limb may be beneficial to improve femoral artery diameter and blood flow velocity in people with chronic stroke. One potential avenue for training would be single limb exercise using either a cycle ergometer (Asanoi et al., 1992; Bell et al., 2001; Davies & Sargeant, 1975; Hardman et al., 1987; Klausen et al., 1982; Miyachi et al., 2001; Paterson et al., 2005; Radegran & Saltin, 2000; Saltin & Landin, 1975) or Biodex System 3(Shoemaker et al., 1994; Wernbom et al., 2006) (Biodex Medical Systems, New York, New York). The Biodex has been used to examine blood flow during a bout of exercise and as a modality for single limb exercise to assess cardiorespiratory fitness and the peripheral vascular system changes after the training period in healthy adults.(Bell et al., 2001; Davies & Sargeant, 1975; Klausen et al., 1982; Miyachi et al., 2001; Saltin et al., 1976; Shoemaker et al., 1994) These studies report single limb exercise training demonstrated improved femoral artery diameter (Miyachi et al., 2001) and blood flow (Klausen et al., 1982; Shoemaker et al., 1994) in the trained limb when compared to the untrained limb.

The purpose of this case study was to characterize the effect of single limb exercise training on: 1) femoral artery diameter and blood flow velocity in the hemiparetic limb and 2) cardiorespiratory fitness in an elderly individual with chronic stroke. To our knowledge, no literature is available for the effects of single limb exercise on femoral artery diameter and



blood flow velocity post-stroke. Therefore, we hypothesized that single limb exercise would be an efficient training strategy to improve vascular health in an individual post-stroke.

### **A1.3 Case Description**

#### *Patient Description*

The participant in this study was an 81-year old male who was 10.6 years post-stroke. His self-reported medical history was a single ischemic stroke that affected the left side of his brain, hypertension, hypercholesterolemia, and atrial fibrillation. He was not participating in physical therapy but did engage in water Tai Chi activities for 1 hour 3 times per week. His Body Mass Index ( $BMI = \text{kg} \cdot (\text{m}^2)^{-1}$ ) was 26.8, which is considered overweight. (ACSM, 2006) This individual was a community ambulator and did not use an orthotic or assistive device.

#### *Examination and Evaluation*

The participant met the inclusion criteria for this study, which included: 1) single stroke at least 6 months ago 2) stand and walk 30 feet with/without assistive device, 3) mild to moderate stroke defined by a lower extremity Fugl Meyer (LEFM) score from 20 to 34/34, (Daly et al., 2006) 4) a minimum of 35 degrees of active knee extension/flexion against gravity, 5) a score of  $> 24$  on the Mini Mental Status Exam (MMSE) to establish the ability to give informed consent for this study, 6) receive medical clearance from the primary physician for exercise testing and training, (7) no diagnosis Type 1 or 2 diabetes; and (8) no single limb exercise using the hemiparetic limb or current physical therapy treatment. This individual's lower extremity Fugl-Meyer score was 33/34, MMSE score was 30/30 and his knee flexion/extension active range of motion was 104 degrees. After the screening process was

completed, institutionally approved informed consent was obtained in writing prior to participation in the study.

#### **A1.4 Methods**

##### *Baseline Testing*

Prior to the 3-week training intervention (see Table 1), the participant several completed baseline test and measures:

##### *Femoral Artery Diameter and Blood Flow Velocity*

Doppler ultrasound has been used to quantify both arterial diameter and blood flow velocity in humans. (Kooijman et al., 2008; Newcomer et al., 2004; Newcomer et al., 2005; Osada, 2004) After lying supine on a therapy mat for 30 minutes, Doppler ultrasound (Sonosite, Inc, Seattle, WA) was used to scan bilateral common femoral arteries. Femoral artery diameter was measured in cross section. With the ultrasound image frozen on the screen, arterial diameter measurements were taken just above the bifurcation of the artery at peak systole. Blood flow velocity was obtained from a longitudinal view of the femoral artery 1 cm proximal to the bifurcation (Newcomer et al., 2005; Osada, 2004) at a 60° inclination angle, and with the velocity gate open wide to obtain the average blood flow in the entire arterial wall.

Similar to our previous work (Chapter 4), lower values were found for femoral artery diameter and blood flow velocity for the hemiparetic when compared to the less affected limb. Baseline values for femoral artery diameter were: 1.03 cm for the hemiparetic limb and 1.05 cm for the less affected limb while blood flow velocity for the hemiparetic limb was 67.5 cm\*sec<sup>-1</sup> and the less affected limb was 74.5 cm\*sec<sup>-1</sup>.

### *Cardiorespiratory Fitness*

A maximal effort graded exercise test using a recumbent stepper (S. A. Billinger, Tseng, B.Y., Kluding, P.M., 2008) (NuStep, Inc, Ann Arbor, MI) was used to assess cardiorespiratory fitness and obtain values for peak oxygen uptake ( $\text{VO}_2$  peak). At maximal effort, he exceeded his age-predicted heart rate maximum (APHRM) of 139 beats per minute (bpm) and reached 166 bpm. His peak respiratory exchange ratio (RER) was 1.2 whereas the criterion for maximal effort is  $\geq 1.1$  (S. A. Billinger, Loudon et al., 2008; Loudon et al., 1998; Macko, Katznel et al., 1997; Meredith et al., 1989) and he reported a rating of perceived exertion at 19 on the Borg 6-20 scale. (1970) His baseline  $\text{VO}_2$  peak was  $19.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , which is similar to older adults his age. (Arnett, Laity, Agrawal, & Cress, 2008)

During the exercise test, oxygen uptake was measured and analyzed through collection of expired gases using the ParvoMedics (Parvomedics, Inc, Sandy, Utah) metabolic measurement system. Heart rate and rhythm were continuously monitored using an electrocardiogram (ECG). Standard guidelines prior to exercise testing were used: The participant was 1) asked to refrain from food, caffeine, and alcohol for at least 3 hours prior to testing; (ACSM, 2006) 2) familiarized with the recumbent stepper prior to the exercise test and 3) instructed and familiarized with the Borg Rating of Perceived Exertion (RPE), 15-point scale (6-20).

### *Intervention*

#### *Single Limb Exercise Training*

The exercise training intervention was 3 times per week for 3 weeks using only the hemiparetic limb. For our study, the Biodex System 3 was used with an isokinetic knee

extension/flexion exercise protocol. The pace was  $150^\circ * \text{sec}^{-1}$  at 40 repetitions per set. The protocol allowed for progression to 20 sets on the Biodex machine. Heart rate was monitored throughout the sessions by palpation of the radial pulse at rest and during the training sessions to ensure he maintained the target heart rate range (HRR) of 66 bpm to 116 bpm, which was determined from the maximal effort exercise test. This individual was able to keep his heart rate between 100 and 116 bpm for each training session during the training protocol. The intensity level was maintained by increasing the number of sets during the intervention to maintain the target HRR. Each exercise session lasted 45 – 60 minutes. This allowed for machine set up and exercise parameters to be adjusted. Actual exercise time was 20-30 minutes with 30-second rest breaks in between each set.

### **A1.5 Outcomes**

The participant completed all 9 training sessions and maintained his target HRR at 60% - 70% of maximal heart rate. This individual began with 5 sets and progressed to complete the maximum of 20 sets during the 3-week training intervention using a flexion/extension isokinetic protocol. Results for the outcome measures are summarized in Table A1.2.

#### *Femoral Artery Diameter and Blood Flow Velocity*

After the training intervention using only the hemiparetic limb, the participant had a 1% increase in arterial diameter from baseline (1.03 cm) to post-intervention (1.04 cm). Femoral artery blood flow velocity for the hemiparetic limb increased 11% from baseline measures ( $67.5 \text{ cm} * \text{sec}^{-1}$ ) to post exercise training ( $74.5 \text{ cm} * \text{sec}^{-1}$ ). The less affected limb had no change (0%) in arterial diameter (baseline: 1.05 cm and post-training: 1.05 cm) and a

small decrease in blood flow velocity (-1.7%) from baseline (74.5 to post exercise  $\text{cm}\cdot\text{sec}^{-1}$ ) to post-test (73.5  $\text{cm}\cdot\text{sec}^{-1}$ ).

#### *Cardiorespiratory fitness.*

Contrary to our expectations, peak oxygen uptake ( $\text{VO}_2$  peak) did not increase after the exercise training intervention (baseline:  $19.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  versus post training:  $18.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). His maximal heart rate was 168 bpm, which was 2 beats higher than baseline and his RER was 1.2. Also, his perceived exertion (RPE =18) at maximal effort was lower than baseline (RPE = 19). This may suggest that his perceived maximal effort was not as difficult after the exercise intervention. Of importance, this individual experienced a traumatic family event 2 days previous to the final exercise test. He was given the opportunity to reschedule the exercise test but declined.

### **A1.6 Discussion**

This individual who was elderly with chronic stroke demonstrated differences in femoral artery diameter and blood flow velocity in the hemiparetic leg when compared to the less affected leg. Although he was a community ambulator and participated in 3 hours of physical activity each week, femoral artery diameter and blood flow velocity in his hemiparetic leg improved after a 3-week single limb exercise intervention. Single leg exercise has been shown to increase leg blood flow more effectively than bilateral exercise.(Davies & Sargeant, 1975; Klausen et al., 1982; Landin et al., 1977) Young healthy adults participating in single limb exercise have shown improvements in femoral artery diameter(Miyachi et al., 2001) and blood flow velocity.(Klausen et al., 1982; Shoemaker et al., 1994) Since

individuals post-stroke rely on the less affected limb during bilateral activities such as walking (Brunt et al., 1995; Messier et al., 2005; Mizrahi et al., 1989; Yavuzer et al., 2006) and cycling,(Chen et al., 2005; Landin et al., 1977) a single limb intervention focused on the hemiparetic limb appears to be a feasible training strategy. The results from this case study suggest that an individual with chronic lower leg hemiparesis can demonstrate arterial adaptations after an exercise training intervention similar to those observed in young healthy adults (Klausen et al., 1982; Miyachi et al., 2001; Shoemaker et al., 1994) and spinal cord injury.(De Groot et al., 2003; Hopman et al., 2002; Taylor et al., 1993; Thijssen et al., 2006)

This individual attended all 9 exercise sessions on the scheduled days. He tolerated the single limb training sessions without adverse events related to the exercise protocol and maintained a training intensity between 60-70% heart rate max. Exercise progression consisted of increasing exercise duration by incorporating additional sets to the training protocol. This individual reported that during the training period, his affected leg didn't seem as tired during the exercise and during his daily activities. This may be a training effect from the single limb exercise protocol whereby the result is improved blood flow and oxygen delivery and utilization.(Davies & Sargeant, 1975) Exercise training has been instrumental for improving arterial wall vasculature and regulating adequate blood flow necessary for cardiovascular health.(Green, Maiorana, O'Driscoll, & Taylor, 2004; Heidarianpour et al., 2007; McAllister, Newcomer, & Laughlin, 2008; Suzuki et al., 2001)

In healthy adults, a training intervention consisting of single limb exercise has demonstrated improved values for VO<sub>2</sub> peak.(Bell et al., 2001; Davies & Sargeant, 1975; Klausen et al., 1982; Miyachi et al., 2001; Saltin et al., 1976; Shoemaker et al., 1994) After the 3-week training period, this individual's results from the maximal effort exercise test showed a slight decrease in VO<sub>2</sub> peak while his maximal heart rate increased. In addition his

perceived exertion during the exercise test was lower at maximal effort (18 post-training vs 19 at baseline), which may be an effect of training. However, for this individual psychological stress may have potentially influenced his performance on the post-intervention maximal effort exercise test. Furthermore, a 3-week training intervention may be insufficient in length to produce improvements in  $\text{VO}_2$  peak.

In this case study, we did not address oxygen uptake ( $\text{VO}_2$ ) during the single limb training task. It may be beneficial to assess whether a training effect was observed in peripheral cardiovascular mechanisms such as oxygen utilization or improved energy expenditure using  $\text{VO}_2$  by the exercising hemiparetic leg muscle. In a study by Macko and colleagues, (Macko et al., 2001) treadmill training decreased energy expenditure during submaximal effort. The authors stated that decreased energy expenditure during submaximal exercise or functional tasks is advantageous for people post-stroke since this population uses more energy for movement secondary to increased tone or incoordination of the hemiparetic muscles. Additionally, incorporating a functional outcome measure such as the 10-meter walk test would have been beneficial. This may address whether a focused training intervention such as single limb exercise would have translated to a functional task such as ambulation. However, this case study does highlight physiological changes that can occur in the femoral artery with respect to diameter and blood flow velocity in the hemiparetic leg after single limb exercise.

### **A1.7 Conclusion**

Single limb exercise using only the hemiparetic leg was a feasible exercise protocol to improve femoral artery diameter and blood flow velocity in a chronic stroke survivor. Single leg exercise may be used to improve femoral artery blood flow in the hemiparetic

limb. Future studies are needed to examine the potential effects of a single limb training protocol for decreasing energy expenditure during leg exercise. This case study is an important initial step in understanding the effects of single limb exercise on altering femoral artery adaptations that have occurred in the hemiparetic leg following stroke.



## A1. Tables and Figures

Table A1.1 Protocol Timeline

<b>Week 0</b>	<b>Week 1</b>	<b>Week 2</b>	<b>Week 3</b>	<b>Week 4</b>
Baseline measures for: 1) Femoral artery diameter and blood flow velocity 2) Maximal GXT for cardiorespiratory fitness.	Exercise training period begins (3x/week for 3 weeks)	Exercise training period	Exercise training period	Post-intervention: 1) Femoral artery diameter and blood flow velocity 2) Maximal GXT for cardiorespiratory fitness.

Table A1.2 Results of Single Limb Exercise

	<b>Arterial Diameter (cm)</b>	<b>Blood Flow Velocity (cm*sec<sup>-1</sup>)</b>	<b>VO<sub>2</sub>Peak (ml * kg<sup>-1</sup> * min<sup>-1</sup>)</b>
<b>Hemiparetic Leg</b>			
Baseline	1.03	67.5	
Post-intervention	1.04	74.7	
<b>Less Affected Leg</b>			
Baseline	1.05	74.7	
Post-intervention	1.05	73.7	
<b>Cardiorespiratory Fitness</b>			
Baseline			19.5
Post-intervention			18.7