EXERCISE TO IMPROVE BLOOD FLOW AND VASCULAR HEALTH IN

THE LOWER LIMBS OF PARAPLEGICS

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EXERCISE TO IMPROVE BLOOD FLOW AND VASCULAR HEALTH IN THE LOWER LIMBS OF PARAPLEGICS (131 pp.)

INTRODUCTION: After incurring a spinal cord injury a paraplegic undergoes drastic and detrimental vascular remodeling which leads to numerous health consequences. Many rehabilitation modalities are aimed at increasing blood flow to the paralyzed lower limbs in this population to counteract these co-morbidities. Passive limb movement and upper body exercise may be two modalities that could aid this population. PURPOSE: The purpose of this study was to quantify the effectiveness of repeated bouts of passive limb movement and 10 minutes of upper body exercise to increase lower limb blood flow in paraplegics. METHODS: 9 paraplegics with a complete spinal cord injury between the 3rd to 11th thoracic vertebrae were recruited for the study. Subjects underwent 5 one minute bouts of unilateral lower body passive limb movement interspaced with 1 minute recovery. They also completed 10 minutes of upper body exercise with and without the addition of passive limb movement. RESULTS: During the repeated bouts of passive
limb movement a repeatable hyperemic response was observed. The bouts resulted in blood flow increases of 58, 52, 57, 50 and 63%. For the upper body exercise a blood flow increase of 42% was observed and also 28% increase with the addition of the passive limb movement.

**CONCLUSION:** Repeated bouts of passive limb movement, when interspaced with a one minute recovery period, has the ability to induce a sustained hyperemic response. While not statistically significant, the increases in blood flow observed during the upper body exercise may still have a clinical application.
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Romans 12:1
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CHAPTER 1

INTRODUCTION

Background

A spinal cord injury (SCI) can result in autonomic, neuromuscular and physiologic impairment of the legs, arms or trunk with the severity of the symptoms dependent upon the level and magnitude of the injury to the spinal column. A SCI to the cervical segments of the spinal column (C1-C8) down to the most proximal thoracic segment (T-1) often causes tetraplegia and results in impairment of the arms, trunk, legs, bladder, bowels and sexual organs. Any SCI occurring at the level of the 2nd thoracic vertebrae (T-2) or distally can result in paraplegia, with accompanying impairments of the trunk, legs and pelvic organs, with a decreasing severity of deficiencies the more distal incursion of the SCI. With the estimated prevalence of SCI at 1100 cases per million people, or approximately 273,000 persons in the United States and with an increased prevalence expected in the future, persons with an SCI represent a growing, chronically disabled population in need of new and novel rehabilitation modalities aimed to counteract many of the collateral health detriments associated with this condition.

Persons with a SCI have a reduced health status, decreased quality of life and increased rates of mortality compared to an able-bodied population. A few of the most common medical complications observed in the SCI population are muscular atrophy,
bone metabolism disorders, cardiovascular disease, and autonomic dysregulation. Many of these complications are the result of the removal of neural drive to the impaired muscles resulting in subsequent reduced metabolic demand accompanied by rapid and chronic deconditioning.

In the case of paraplegia, most rehabilitation modalities aim to improve overall health status by slowing the rate of deconditioning with the use functional electrical stimulation (FES) and passive limb movement (PLM) of the paralyzed limbs along with upper body exercises. These modalities aim to promote blood flow to both the non-paralyzed and paralyzed musculature in an attempt to slow the rate of atrophy and medical complications commonly observed in this population. While these modalities have the potential to be an effective rehabilitative technique to promote lower limb blood flow, present scientific literature is abound with physiologic limitations associated with FES along with discrepant conclusions of the effectiveness of PLM and upper body exercises to promote lower limb blood flow. The discrepant conclusions may be due current standards that classify SCI by motor and sensory deficits and do not consider autonomic integrity, specifically sympathetic innervation to the vasculature in the lower limbs.

Due to the limitations and conflicting results of these rehabilitation modalities, additional research is needed to quantify the effectiveness of PLM and upper body exercise to promote lower limb blood flow to promote vascular and whole body health in paraplegics.
Purpose of Study

The purpose of the proposed investigation was to examine the following:

1. To access effectiveness of 5 one minute bouts of PLM to increase blood flow to the lower limbs in the paraplegic population.

2. To access the effectiveness of a 10 minute bout of upper body exercise of two exercise intensities to collaterally increase blood flow to the stationary lower limbs.

3. To determine if the use of PLM and upper body exercise in combination results in greater increases in lower limb blood flow in paraplegics compared to the other modalities listed above.

Hypothesis

Based on previous studies that it is hypothesized following:

1. The repeated bouts of PLM will induce a hyperemic response but with each subsequent bout of PLM the magnitude of the response will be diminished.

2. The use of upper body exercise will allow for a significant increase in blood flow to the lower limbs as a collateral effect of the increase in cardiac output elicited by metabolic demand of the upper body exercise.
3. The combination of PLM to the upper body exercise will result in a more pronounced increased in lower limb blood flow compared to when upper body exercise is used in isolation.
CHAPTER II

REVIEW OF LITERATURE

Spinal Cord Injury

An injury to the spinal cord is a life altering experience. Without ascending neural feedback and descending motor control to the areas neutrally integrated below the level of the lesion there is a change in whole body function and physiology.

Prevalence

The prevalence of spinal cord injuries (SCI) in the United States in 1988 was estimated to be 721 cases per million people, or approximately 177,000 persons (Berkowitz, Harvey, Greene, & Wilson, 1992; Harvey, Wilson, Greene, Berkowitz, & Stripling, 1992). By 2005 the prevalence of SCI had increased 15% to approximately 200,000 persons with an incidence rate of 20,000 new SCI patients per year (Bernhard, Gries, Kremer, & Bottiger, 2005). As of 2013, the estimated prevalence of SCI is 273,000 persons with an estimated range of 230,000 to 332,000 persons (Burns & O'Connell, 2013). The prevalence of SCI is expected to rise to 1100 cases per million people, or approximately 280,000 persons by 2014 and the continued increase in prevalence over the foreseeable future expected to be approximately 27 to 81 cases per million persons per year (Wyndaele & Wyndaele, 2006).
The average life expectancy for an able-bodied person has increased approximately 5 years since 1980 from 73.9 to 78.7 years (Arias, 2011). Inappropriately, the average life expectancy of a person with an SCI has remained constant. The average individual who suffers a spinal cord injury resulting in paraplegia is 42.6 years old at the time of injury and if they survive the first 24 hours post injury incursion they have a life expectancy of 67.2 years. In the 1970’s and 80’s the leading cause of death for an individual with an SCI was renal failure but with significant advancements in urology management in this population the leading causes of death are now pneumonia and septicemia. It is estimated a person who sustains a SCI resulting in paraplegia will incur over $500,000 in medical expenses in the first year after injury and approximately $67,000 every subsequent year (Burns & O’Connell, 2013). The overall economic impact and estimated lifetime of medical expenses of a person who incurs a SCI at age 25 resulting in paraplegia is estimated to be greater than $2,300,000.

Classification of Spinal Cord Injury

After sustaining a SCI the classification of the extent of the injury is of the utmost importance and this have an impact on medical treatment and rehabilitation.

**Motor and neurological impairments.** The standard system used to classify persons with SCI is the *International Standards for Classification of Spinal Cord Injury* (ISNCSCI) (Appendix A) developed by Neurological Standards committee of the American Spinal Injury Association (ASIA). This standard has also been endorsed by the
International Spinal Cord Society and was last updated in 2011 (Kirshblum et al., 2011). The ASIA guidelines include a sensory and motor examination to determine the neurological level of injury which is defined as the most distal segment of the spinal cord with normal sensory and motor function. The sensory examination is performed via “pin prick” and “light touch” on each of the 28 dermatomes on both sides of the body with the use of safety pin and wisp of cotton, respectively. The SCI patient’s sensation of these pin pricks and light touches are scored on a three point scale using the same stimuli on the patient’s cheek as the baseline measure for comparison. The three point scale is defined as: 0=absent, 1=altered/impaired and 2=intact/normal. The motor examination is completed through the testing of specific muscle functions corresponding to 10 myotones. Each muscle function is then graded on a 5 point scale; 0=total paralysis, 1=palpable or visible contraction, 2=active movement, full range of motion (ROM) with gravity eliminated, 3=active movement, full ROM against gravity, 4=active movement, full ROM against gravity and moderate resistance in specific condition, and 5=normal active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors were not present. Information from these tests is then used to determine the most caudal region of complete sensory and motor responsiveness of the patient to determine the level and extent of the SCI.

SCIs occurring in the cervical segments of the spinal column (C-1/C-8) and in the high thoracic segment (T-1) are diagnosed as tetraplegia resulting in sensory and motor impairments in the legs, pelvic organs, trunk and arms. SCIs occurring in the thoracic
segments (T-2/T-12) are diagnosed as paraplegia with impairments of the pelvic organs and lower trunk. Additionally, SCIs occurring distal to the thoracic segments of the spinal column, in the lumbar or sacral segments, may result in impairments of the legs and pelvic organs. The level at which the SCI is incurred and the completeness, complete severance or partial severance, determine the degree of sensory and motor impairment that is observed (Figoni, 2009).

**Autonomic impairments.** Although there is abundant information on motor and sensory deficits in SCI, until recently, the preservation of supraspinal control of the autonomic nervous system (ANS) below the level of the lesion in the SCI population has garnered little attention. While recent studies have stated a complete loss of supraspinal control of the ANS below the level of the SCI in both tetra and paraplegics (Previnaire, Soler, Leclercq, & Denys, 2012), other studies have reported a partial or complete preservation of supraspinal ANS control (West, Romer, & Krassioukov, 2013; West, Wong, & Krassioukov, 2013). The lack of attention on ANS preservation is surprising as the absence of ANS innervation in the lower limbs can drastically increase the complications associated with this condition including poor blood flow and blood pressure regulation.

To better quantify autonomic control after an SCI the ASIA has recently issued the *International Standards to Document Remaining Autonomic Function after Spinal Cord Injury* (ISAFSCI)(Appendix B). These standards are meant to supplement the
ASIA ISNCSCI guidelines for neural and motor deficits and together provide a more robust evaluation of autonomic, neural and motor impairments after a SCI (Krassioukov et al., 2012). The ISAFSCI is a two part evaluation split between classification of general autonomic function and an assessment of urinary, bladder, bowel and sexual function. The general autonomic function assessment is structured to determine the present level of autonomic control of the heart, blood pressure, control of sweating, temperature regulation, and broncho-pulmonary system. Classification of autonomic function is categorized as normal, abnormal, unknown, or unable to assess. The lower urinary tract, bowel and sexual function assessment classifies impairments to these locations using a 4 point scale. Normal function is classified as a “2”, reduced or altered function is classified as a “1”, complete loss of control is classified as a “0” and unable to assess or concomitant problems is classified as a “NT”.

**Common Medical Complications**

A SCI can result in autonomic nervous system dysfunction and loss of afferent signaling and paralysis of the muscle groups below the level of the lesion (Teasell, Arnold, Krassioukov, & Delaney, 2000). The loss of neural innervation to tissue below the level of the lesion and subsequent decreased metabolic demand in the SCI population results in a rapid and chronic deconditioned state in the affected skeletal muscle. This introduces many challenges for persons with a SCI and plays a direct role in the decreased health status and increased rates of mortality observed in this population.
**Muscle atrophy and decreased bone mineral density.** After incursion of an SCI there is a severe and rapid change in whole body physiology, especially below the level of the lesion. Some common medical complications experienced in this population are muscular atrophy and bone metabolism disorders. It has been well established that chronic periods of muscle unloading can result in a severe reduction in muscle volume due to decreased muscle cross sectional areas (CSA). A study by Castro et al. (Castro, Apple, Staron, Campos, & Dudley, 1999) reported that within 6 weeks of incurring an SCI, patients exhibited a 45% reduction in CSA of muscle tissue in quadriceps femoris. Similar studies of bed rest and lower-limb suspensions of able-bodied populations have presented a much less severe atrophic response with decreases in quadriceps femoris CSA of only 14% (Berg, Larsson, & Tesch, 1997) and 12% (Hather, Adams, Tesch, & Dudley, 1992), respectively. It is hypothesized that the combination of muscular unloading in conjunction with removal of neural drive is responsible for the rapid and severe reductions in muscle CSA after sustaining an SCI. Additionally, rapid bone demineralization and decreased bone mineral density (BMD) is expected in the first year post SCI with one-third to one-half of pre-SCI BMD being lost in the supracondylar femur in both para and quadriplegics (Jacobs & Nash, 2004). This decrease in BMD leads to an increased rate of bone fracture, even after minimal exposure to trauma (Ragnarsson & Sell, 1981).

**Cardiovascular disease.** The reduction in cardiovascular health observed in persons with a SCI mimics what is observed in the normal aging process but at a much
faster rate (W. T. Phillips et al., 1998). A deadly combination of reduced metabolic rate (Mollinger et al., 1985), decreased muscle mass (Castro et al., 1999), increased fat mass and limited exercise options all increase the risk of developing cardiovascular disease. Furthermore, persons with an SCI commonly have increased rates of dyslipidemia and hyper-insulinemia compared to the able-bodied population. Interestingly, for the first year post SCI, LDL lipids levels are usually depressed (Apstein & George, 1998) before normalizing and continuing to rise. In addition, persons with an SCI commonly experience a marked reduction in the cardio-protective HDL lipoprotein (Bauman & Spungen, 2008). Greater than 40% of persons with an SCI have an HDL count of <35 mg/dl placing them at a greater risk for the development of cardiovascular disease. In regards to the heightened insulin resistance and resulting hyper-insulinaemia, the exact cause is unknown but likely results from the high rates of physical inactivity in the SCI population (de Groot, Hjeltnes, Heijboer, Stal, & Birkeland, 2003), increased truncal obesity (Buchholz & Bugaresti, 2005) and sympathetic dysfunction (Myers, Lee, & Kiratli, 2007).

**Deep vein thrombosis and pulmonary embolism.** The development of a deep vein thrombosis (DVT) is a major complication after an SCI in both the acute and chronic phases. Virchow’s triad describes three general factors thought to contribute to the development of a DVT including blood stasis, endothelial cell injury and hypercoagulability, all of which are common after an SCI. Specifically, SCIs result in an immobile state with a severe reduction in blood flow and tissue perfusion, due to reduced
metabolic activity of muscles and resulting atrophy of the blood vessels (Miranda & Hassouna, 2000). Together, the decreased blood flow, interruption of neurologic signaling, altered venous competence, decreased venous distensibility and increased venous flow resistance as a consequence of vascular remodeling lead to a DVT incidence rate that is three times higher in SCI compared to the able-bodied population (Miranda & Hassouna, 2000).

**Pressure ulcers.** Any population in which mobility is limited has greater risks for the formation of pressure ulcers due to reduced rates of blood flow and pooling of blood in the extremities. Persons with a complete SCI are at elevated risk for the formation of pressure ulcers at all times post injury (Bogie, Wang, & Triolo, 2006). The formation of pressure ulcers are a direct result of constant external pressure over the surface of the skin, usually over bone protrusions, leading to a reduction in blood flow to the tissue. This causes a hypoxia state within the tissue resulting in ischemia and if unresolved, tissue necrosis (Hoff, Bjerke, Gravem, Hagen, & Rekand, 2012). In persons with an SCI the combination of immobility, muscle atrophy, reduced physical activity, autonomic dysregulation and most importantly no sensory feedback lead to the development of pressure ulcers in 40% of this population within 6 months of injury (Correa et al., 2006). Lifetime incidence of pressure ulcers in SCI is approximately 85% with 7-8% of SCI dying from pressure ulcer related complications (Medicine & America, 2000).
**Autonomic dysregulation.** After the occurrence of an SCI the autonomic nervous system goes into a state of near constant flux resulting in the disruption of cardiovascular homeostasis and altered responses to exercise. Arterial blood pressure is typically low in persons with an SCI due to a reduction in sympathetic nervous system activity below the level of the lesion (i.e. vasoconstriction that promotes blood return to the heart) (Myers et al., 2007). Without proper input from the autonomic reflexes of the carotid and aortic baroreceptors in conjunction with a decreased vascular tone, persons with an SCI are highly susceptible to orthostatic hypotension especially during physical activity and changes in body positioning (Claydon, Steeves, & Krassioukov, 2005). In addition, a far more serious hemodynamic response of SCI is autonomic dysreflexia which is characterized by a reflex overstimulation of the sympathetic nervous system below the level of the injury and results in a rapid, and potentially dangerous, increase in blood pressure (Myers et al., 2007). Autonomic dysreflexia occurs in both complete and incomplete spinal cord injuries but the highest prevalence is observed in persons in which the SCI is above the sixth thoracic vertebrae (Curt, Nitsche, Rodic, Schurch, & Dietz, 1997). In most cases the trigger for autonomic dysreflexia in a person with an SCI is a constant painful/noxious stimulus below the level of the lesion including distention of the bladder and urinary tract infections; symptoms are often exacerbated during movement or exercise (Elliott & Krassioukov, 2005).

**Arterial size and vascular function.** After a spinal cord injury there is rapid and extensive systemic vascular remodeling that occurs in response due to the reduced
metabolic demand, decreased need for oxygen, rapid cardiovascular deconditioning and absence of neural drive to the muscle. Previous investigators reported that within just six weeks post SCI the common femoral artery (CFA) and superficial femoral artery (SFA) can have radial reductions up to 25% and 16%, respectively (de Groot, Bleeker, van Kuppevelt, van der Woude, & Hopman, 2006). Within one year post SCI, the diameter of the CFA is expected to be up to 50% reduced compared to that of the pre-SCI diameter. (Boot, Groothuis, van Langen, & Hopman, 2002). However, it is unclear whether the reduction in CFA diameter causes the reduction in thigh volume or vice versa (Olive, Dudley, & McCully, 2003). In the unaffected limbs of paraplegics there seems to a preservation of brachial artery and carotid artery diameter. This suggests that the reductions in CFA and SFA and muscle volume are more directly related to the removal of neural drive then deconditioning as effects of whole body deconditioning would also be observed in the brachial and carotid arteries. However, it could be argued the preserved brachial and carotid artery could be the result of increased use of the upper body for propulsion and physical activity. The reductions of CFA diameter and leg volume mimic the physiologic adaptations seen in the classic deconditioning studies but occur at a much faster rate. In addition the reduction of arterial size and capillary density of the inactive muscle can lead to increased vascular resistance and decreased venous capacitance and compliance (A. A. Phillips, Cote, & Warburton, 2011) and ultimately hypertension.
When evaluating the ratio of the CFA to thigh volume, there is no difference between the SCI and able-bodied populations. (Olive et al., 2003). This has led researchers to look into whether or not vascular function is preserved in patients with a SCI even though they have marked reductions in CFA diameter and thigh volume. While some research has seen a preserved vascular function after an SCI (de Groot, Poelkens, Kooijman, & Hopman, 2004), most have observed a marked and decreased flow mediated dilation (FMD)(Stoner et al., 2006) indicating the presence of either endothelial or smooth vessel dysfunction. Because of the strong link between decreased peripheral vascular health and the development of central cardiovascular and metabolic diseases special attention should be given to preserving vascular health to the paralyzed limbs of persons with a SCI (Stoner et al., 2006).

**Common Exercise Modalities and Improvement in Vascular Function**

One of the most effective methods to increase vascular function and health in a specific region of the body is to locally increase blood flow to that region which can be achieved by increasing metabolic demand by the use of physical activity and exercise. The increase in blood flow and subsequent shear stress will result in vascular remodeling which will improves the compliance, density and overall functional capacity of those arteries (Davies, Spaan, & Krans, 2005). Repair of the injured spinal cord by regeneration therapy remains an elusive goal, therefore future voluntary physical activity is unlikely, additional research has focused on alternative methods of increasing blood flow aside from normal voluntary physical activity. Currently, the common
exercise/therapy modalities used in the SCI include but are not limited to: functional electrical stimulation (FES), passive limb movement (PLM) and upper body exercise (for example: arm ergometers, wheelchair ergometers, wheelchair treadmills, free-wheeling arm cycling, seated aerobics, swimming, and wheelchair sports) (Figoni, 2009).

**Functional Electrical Stimulation**

One of the most widely studied exercise modalities for persons with a SCI has been FES. FES exercise is achieved by placing muscle stimulators over specific motor points of de-innervated muscles or more invasively, directly placed onto the motor neuron and using electrical impulses to activate the muscle in synchronized manner to restore locomotion and/or perform exercise such as a cycle ergometer (A. A. Phillips et al., 2011). Previous investigators have reported FES has the potential to increase CFA blood flow and arterial function in the SCI population (Dela et al., 2003; W. Phillips, Burkett, Munro, Davis, & Pomeroy, 1995). Currently, the use of FES in the SCI has two clinical applications: functional and therapeutic. The functional application is to use FES to restore body functions that have been altered or lost due to the SCI, such use of hands and legs, control of bladder and bowel voiding, sexual function and respiration (Hamid & Hayek, 2008). Therapeutic applications include cardiovascular conditioning and prevention of muscular atrophy via exercise. However, the use of FES for therapeutic applications, while having great potential, does have several limitations. One of the greatest limitations of FES is the wide range of contractile response to electrical stimulation. Some patients with an SCI respond very well to FES while others seem to
be non-responders or need greater electrical stimulation in order to get the same muscular response. The level of the SCI has a great impact on the responsiveness to FES with the greatest response coming from SCI patients who have an injury in T4-T12. Additionally, completeness of the SCI injury (complete or incomplete), musculoskeletal integrity and present muscle spasticity also play a role in the effectiveness of FES (Graupe, 2002). There have also been reports of FES causing bouts of autonomic dysreflexia (Ashley et al., 1993). FES therapy is costly, effectiveness is dependent upon time since injury, can be invasive, time consuming and is only available to a small percentage of the SCI patients. Because of these limitations, additional research is needed in other rehabilitation modalities to promote exercise and increasing vascular health in persons with a SCI.

**Passive Limb Movement**

The passive limb movement (PLM) model for increasing blood flow shows great potential for increasing lower limb blood flow and improving lower limb vascular health in the SCI population. In an able-bodied person, limb specific increases in blood flow can be observed, without or with minimal concurrent increases in central factors such as increased heart rate and stroke volume, during a PLM protocol. Specifically when a technician or exercise ergometer moves the lower limbs through a large range of motion, in the absence of mental or muscular effort being exerted by the subject, there is an observed transient hyperemic response in the passively moved limb (McDaniel, Fjeldstad, et al., 2010). This transient hyperemic response results from several factors.
The rhythmic stretching-shortening of the skeletal muscle during a PLM protocol increases blood flow to the passively moved region via the skeletal muscle pump and mechanically induced vasodilation (Clifford, Kluess, Hamann, Buckwalter, & Jaspers, 2006). In addition, PLM activates type III sensory muscle mechanoreceptors which detect the mechanical distortion of the muscle fibers due to the PLM and send input to the cardiorespiratory control center of the brain and can cause acute increases in heart and stroke volume. The hyperemic response induced by PLM is transient - increases in blood flow last only approximately 45 seconds before returning to baseline values even if the PLM protocol continues. (For a more detailed physiologic response to PLM please see Appendix C.)

Paraplegics have a compromised ability to move their lower limbs and therefore a protocol in which a technician or exercise ergometer is used to passively move their lower limbs through a set range of motion could prove beneficial in this population if an adequate hyperemic response can be invoked. Ballaz and colleagues (Ballaz, Fusco, Crétual, Langella, & Brissot, 2007) investigated the effects of passive leg cycle exercise in persons with a SCI. Blood flow was measured as baseline and again at the conclusion of a 10 minute passive cycling bout. The results indicated a significant 23% increase in blood flow after the passive exercise bout in comparison to baseline values. However, the results of this study have been questioned (Groothuis & Hopman, 2007) as the increases in blood flow were likely in response to a change in posture that occurred when blood flow measurements were taken and not a result of the passive cycling. In a similar
investigation, ter Woerds and colleagues (Ter Woerds, De Groot, van Kuppevelt, & Hopman, 2006) measured the hyperemic response of PLM in the SCI population at baseline, during and after completion of a 20 minute passive cycling protocol. In contrast to Balaz, ter Woerds reported no increase in blood flow during and post passive cycle protocol. In the same investigation, ter Woerds also measured the hyperemic response to the passive movement of individual joints (such as the hip, knee and ankle) and reported no increase in blood flow.

Svensson et al (Svensson, Siösteen, Wetterqvist, & Sullivan, 1995) utilized PLM as a treatment to decrease DVT risk in the SCI population by increasing CFA blood flow. The study used acutely injured persons with an SCI, only 3-4 weeks post SCI incursion, and observed the effects of either five or 30 bouts of passive knee extension and flexion at a rate of 1 hertz. Similar to the study by ter Woerds, CFA blood flow measurements were taken at baseline and at the conclusion of the PLM protocol. This study concluded no increases CFA blood flow was observed during both the five and 30 bout PLM protocol.

As the hyperemic response to PLM appears to be transient and only incurs for a minute (Melissa A Hayman et al., 2010; McDaniel, Fjeldstad, et al., 2010; Trinity et al., 2011; Venturelli et al., 2014), it is likely ter Woerds missed the increase in blood flow by first taking blood flow measurements two minutes into the PLM protocol. Furthermore, Balaz may have reported greater increases in blood flow had measurements been taken
during the first minute of the passive cycling bout. In fact a series of the only set of studies to measure CFA blood flow in the SCI population in response to PLM continuously during the protocol instead of at the conclusion were conducted by Venturelli and colleagues (Venturelli et al., 2013; Venturelli et al., 2012). Both of these studies used a PLM protocol in which the knee was moved at a rate of 1 hertz for 2 minutes. The results of both of these studies showed significant increases in CFA blood flow for approximately the first 45 seconds after the start of the PLM with blood flow returning to baseline values within 60 seconds and staying stable for the last 60 seconds of the PLM protocol. The methodology of this study is advantageous in the fact that blood flow was continuously measured during the PLM protocol. This allowed the researchers observe the transient hyperemic as well as the returning of blood flow to baseline values even with continued PLM. Thus, these studies showed in great detail the potential for PLM to increase CFA blood flow in the SCI population but also the transient nature of the hyperemic response.

While previous studies have looked at the effects of PLM in the SCI populations many of these report conflicting results. Some studies have shown PLM has the ability to increase CFA blood flow in the SCI population while other studies have concluded the opposite. The results of these studies could be attributed to methodology, especially when and where CFA blood flow measurements were taken. Due to the transient nature of the hyperemic response during PLM blood flow measurements need to be taken within one minute of the initiation of PLM. Several of these studies did not start taking blood
flow measurements until several minutes into the protocol or after the PLM had ceased and this could explain why these investigators reported no increase in CFA blood flow in response to PLM. One may contend, that a transient 45 to 60 second increase in blood flow, despite continued PLM, is not physiologically significant and therefore not likely to result in improved vascular function. However, none of the previous investigators used more than one bout of PLM. Thus the repeatability of this transient hyperemic response is unknown. If the hyperemic response to PLM is repeatable, the summation of the transient responses over time may prove to be the proper stimulus for promoting vascular adaptation and maintaining skeletal muscle mass. A recent review article investigating the effects of differing modes of exercise as therapeutic interventions to improve arterial function in the SCI population concluded that additional, well performed research is needed in this area to clear up the incongruities of previous studies (A. A. Phillips et al., 2011).

**Upper Body Exercise**

The physiologic responses to upper body exercise in able-bodied individuals include increases in heart rate, increases in stroke volume and global vasoconstriction induced by the sympathetic nervous system. Metabolic by-products and other vasodilating agents in the active muscles will override sympathetic vasoconstriction resulting in a local vasodilation ensuring proper blood flow and oxygen delivery to the active muscles. The vessels in the non-active muscles, specifically in this case the lower limbs, will continue to be in a vasoconstricted state promoting proper blood redistribution.
to the working limbs and reduced blood pooling in the non-active limbs. (For a more detailed review of the physiologic responses to upper body exercise and redistribution of blood flow during exercise please see Appendix C.)

Unlike able bodied individuals, at the initiation of upper body exercise SCI individuals experience an increase in heart rate and stroke volume that is reduced in magnitude compared to an able-bodied population (Hopman, Pistorius, Kamerbeek, & Binkhorst, 1993). In addition, individuals with an SCI at the 12th thoracic vertebrae and above will often, but not always, have no sympathetic outflow to the lower limbs resulting in the absence of proper vasoconstriction and subsequently poor redistribution of blood flow from inactive to active tissue. The improper redistribution has been previously thought of as a major limitation to upper body exercise in the SCI population. However, this collateral increase in blood flow to the lower limbs may actually prove beneficial in maintaining vascular function in the paralyzed lower limbs of the SCI population. For example, Bidart and Maury (Bidart & Maury, 1973) reported that blood flow to the paralyzed lower limbs increased during four minutes of arm ergometry performed at 50 watts. A limitation to this study is the use of only one upper body exercise intensity was used and didn’t look at differing leg positions to determine the effect of gravity on blood flow measurements.

Another study by Burkett and colleagues (Burkett et al., 1988) measured lower limb blood flow during a maximal intensity arm cycle stress test via wheelchair ergometer. This study utilized toe plethysmography to record changes in blood flow
wave characteristics in the toe during the upper body exercise. Similar to the reports by Bidart and Maury, the study revealed increases in lower limb blood flow at all intensities of the arm cycle stress test. However of the 20 subjects recruited for the study, only 13 of them showed increases in lower limb blood flow with the other seven subjects showing a reduction in blood flow. While not directly addressed by the authors, one of the potential limitations for the current study was the wide variety of injury level within the SCI subjects recruited for the study. The population consisted of persons with an SCI occurring in the fourth cervical vertebrae (C-4) to the third lumbar vertebrae (L-3). Any SCI that occurs at the level of T-12 or below may still have sympathetic outflow to the lower limbs and these persons may have exhibited differing changes in blood flow compared to the subjects who had a SCI at T-6 or above. In addition, the study consisted of both incomplete and complete SCIs. A person with an incomplete SCI may still exhibit some level of sympathetic tone below the level of the lesion also resulting in altered responses to exercise in comparison to a person with a complete SCI.

Several studies by Hopman and colleagues (Hopman, Nommensen, Van Asten, Oeseburg, & Binkhorst, 1994; Hopman, Van Asten, & Oeseburg, 1996) have produced differing results on this topic compared to the studies reported by Bidart and Burkett. For example, Hopman recruited controls and subjects with a complete SCI occurring between T-4 and T-12 to perform 25 minutes of arm crank exercise at 50% of the individual’s specific maximum load. The data revealed no changes in CFA artery blood flow, diameter size or blood velocity in the SCI group during exercise. Interestingly, the
present study showed an increase in blood flow velocity in the lower limbs during the upper body exercise in the control group. These studies also have limitations in that the subject’s level of injury a large variation in the SCI population recruited.

A study by Kizner and Convertino (Kinzer & Convertino, 1989) recruited five paraplegics with an SCI ranging from T-6 through T-11 and aged-matched able-bodied controls to perform ten minutes of arm cycling at 35 watts. During exercise no significant increases in blood flow to the lower limbs, accessed via Doppler ultrasound, were observed in the control and SCI groups; however the study also showed the SCI group did exhibit greater increases in leg volume during the upper body exercise protocol compared to the controls suggesting a pooling of the blood in the lower limbs.

Overall these studies show conflicting results on the use of upper body exercise to increase blood flow to the lower limbs in persons with a SCI. These studies have several limitations which need to be considered including the level and completeness of the SCI and specific upper body exercise protocols. Many of these studies employed the use of a SCI population with wide ranges of the level of the injury which may have confounded their results. Thus, to better understand the influence of upper body exercise on lower limb blood flow a more tightly controlled study needs to be performed or the degree of autonomic function with the SCI subjects needs to be quantified. In addition, many of the previously stated studies used a single exercise intensity throughout their exercise protocol which limits the application of their results.
Sympathetic Integrity and Autonomic Function

After incursion of an SCI, persons with the same level of injury and same degree of completeness of injury may possess differing ranges of sympathetic integrity and remaining autonomic function. This is due to the differing locations of sensory and motor bundle tracts in the spinal column compared the autonomic tracts. Many of the ascending sensory tract bundles in the spinal column are located within the posterior column, spinothalamic tract and spinocerebellar tracts. Additionally, most of the descending motor tract bundles are located in the corticospinal tract, rubrospinal tract, vestibulospinal tract, reticulospinal tract and tectospinal tract which control both conscious and unconscious motor movements. While these tracts may be compromised after an SCI, the intermediolateral cell column which extends from the first thoracic segment to the second lumbar segment and contain autonomic motor neurons that may not be compromised and able to function properly. Please see Appendix D for a visual representation of tracts within the spinal column.

As previously mentioned, it was not until recently the preservation of autonomic control in persons with a SCI was not given its due credence. The absence of absence sympathetic nervous system activity and the subsequent inability constrict blood vessels of the lower limb could result in venous pooling, reduced stroke volume (Hopman et al., 1994) and improper maintained of blood pressure during exercise (Claydon et al., 2005) all of which can alter exercise tolerance. It is because of these complications that autonomic function should be accounted for in persons with a SCI as it such a profound
influence on bodily physiology and exercise response. Two tests that have been utilized to account for remaining autonomic functions in persons with SCI are the Skin sympathetic response (SSR) and cold pressor test (CPT). SSR is relatively easy technique that measures the sweat gland depolarization in the palms of the hands and dorsal surface of the foot in response to an electrical or noxious stimulus. The presence of SSR in the hands, but not the feet provides evidence for compromised, if not absent, sympathetic innervation to the lower limbs. The absence of lower limb SSR has been correlated with the degree of post exercise and orthostatic hypotension (Claydon et al., 2005). SSR therefore also likely correlates with the ability to control MAP and blood flow during exercise. Unlike the SSR, which measures somatomotor responses, CPT in combination with measurements of tissue oxygenation and blood flow can be utilized to quantify sympathetic integrity to the vessels in the lower limbs (Ogata, Hobara, Uematsu, & Ogata, 2012). However, the use of sympathetic innervation testing has yet to be used to help explain the variances in the hyperemic responses during exercise in SCI and ultimately determine which SCI patients have the most advantageous physiology to improve blood flow in the lower limbs with these various non-traditional exercise modalities.

**Project Aims**

Previous reports have indicated those with SCI have reduced arterial diameters (Boot et al., 2002), reduced capillary density (Martin, Stein, Hoeppner, & Reid, 1992), reduced blood flow (Hopman et al., 1996), increased lower limb vascular resistance
(Hopman, Groothuis, Flendrie, Gerrits, & Houtman, 2002), increased vessel stiffness
(Kooijman, Rongen, Smits, & Hopman, 2003) and, although currently debated
(Venturelli et al., 2014), decreased flow mediated dilation (FMD) indicating the presence
of endothelial dysfunction (Stoner et al., 2006). These physiologic deteriorations present
many challenges for individuals with SCI and likely play a direct role in the development
of cardiovascular disease and pressure ulcers. The increased arterial stiffness and
resistance along with autonomic dysregulation contributes to the cardiovascular disease
that affects many of these individuals. Poor tissue perfusion can also increase the risk of
pressure ulcers, the most common secondary complication following SCI. 40% of this
population will develop pressure ulcers within 6 months of injury (Correa et al., 2006)
with increasing incidence up to 85% during their lifetime and approximately 8% of SCI
dying from pressure ulcer related complications (Medicine & America, 2000). Both
cardiovascular disease and pressure ulcers affect the individual’s physical and
physiological well-being and also places a great financial burden on the health care
system. The recognition of a therapy aimed to increase blood flow and tissue perfusion,
maintain vascular health including decreased vessel stiffness would be greatly beneficial.

Aim 1

The proposed study will build upon the previous research studies by Venturelli in
which blood flow was measured during PLM to better quantify the hyperemic response to
PLM in the SCI population. In addition, this study will add to the body of literature by
using multiple short bouts of PLM to determine if the hyperemic response is repeatable.
The current study is novel in its attempt to use multiple short bouts of PLM with recovery in place of longer duration protocols of PLM in which no recovery time was provided. We hypothesize the use of multiple short bouts of PLM will result in repeated hyperemic responses with a diminished effect observed with each subsequent bout.

**Aim 2**

The proposed study will determine the effectiveness of low and moderate intensity exercise to increase lower limb blood flow in the paraplegic population. This will be done measuring femoral artery blood flow during 5 minutes of low intensity exercise followed directly by 5 minutes of moderate intensity exercise. In addition, we will try to quantify the magnitude of the blood flow response to the presence or absence of sympathetic nervous system activity below the level of the lesion. We hypothesize that both exercise modalities will elicit an increase in lower limb blood flow with a greater response being observed with the moderate intensity workload because of increased heart rate and subsequent cardiac output.

**Aim 3**

The proposed study will also determine the effects a hybrid exercise protocol employing upper body exercise in conjunction with passive movement of the lower limbs on increasing lower limb blood flow. We hypothesize that the combination of these two modalities will elicit greater increases in blood flow to the lower limbs compared to when either of these modalities are used alone. The summation of the increased cardiac output
induced by the upper body exercise and the activation of the skeletal muscle pump of the lower limbs induced by the PLM may promote increases in both arterial delivery and venous removal of blood to the lower limbs.
CHAPTER III

METHODOLOGY

Participant

A total of twelve persons with a complete spinal cord injury from the sixth thoracic (T-6) vertebrae to the 12th (T-12) vertebrae ages 18-55 who are otherwise healthy will be recruited for this study. Participants will be recruited from medical database at the Cleveland Louis Stokes Veterans Affair (VA) Hospital of inpatient and outpatient persons who meet the inclusion criteria. Subjects must be free from cardiovascular, pulmonary or metabolic disease that would increase the risk of performing moderate intensity upper body exercise in this population. Subjects must also be naturally free from spasticity or their spasticity needs to be pharmacologically controlled to a level in which they can perform passive leg cycling. Subjects will be recruited with a recruitment letter or email via the information obtained from the VA database. If interested, the potential subjects will ask to call the researchers. The researchers will explain the study in full detail and determine their interest in the study. If willing to participate, they will be scheduled to come into the physical therapy clinic located at the VA hospital. During the participant’s visit we will review the Consent and HIPPA release form and answer any questions they may have. They will be given as much time as needed to read through these forms and determine if they are willing to
participate in the study. If they decide to participate they will be asked to sign these two forms. Once consent is obtained the following protocols will be conducted. In addition, subjects will be asked to complete a brief medical history and current drug therapy questionnaire (Appendix E).

The participants will then be assessed with the use of the ASIA ISAFSCI and ISNCSCI evaluations forms to assess current autonomic, neural and motor impairments by a qualified physical therapist. The participant will then undergo the battery of exercise and autonomic tests listed below. The participants will also be required to empty their bladder before the start of any testing to reduce the chance of inducing an autonomic dysreflexia event during the protocol.

**Experimental Design**

In light of the current studies highlighting the importance of assessing remaining autonomic function after an SCI with the use of sympathetic skin response test.

**Sympathetic Skin Response**

For the sympathetic skin response (SSR) test electrodes will be placed bi-laterally on the palmar and plantar surfaces of the hands and feet. The electrodes will be able to assess depolarization of the cholinergic dependent sweat glands upon a noxious stimulus if sympathetic control is present in these areas. A noxious stimulus, small electrical current, will be administrated five times with various times (30-90 seconds) between the stimuli.
Exercise Tests

The series of 3 protocols (detailed below) will be performed using active upper body exercise and passive lower body limb movement, alone and in combination.

**Active upper body exercise.** For this protocol the use of a Monark Sports and Medical Rehab arm ergometer (Monark 881E, Monark, Vansbro, Sweden) will be used. Each subject will pedal the arm ergometer for a total of 2 five minute protocols, one low intensity and one moderate intensity. For the low intensity, the subject will be asked to use the Monark arm ergometer at a cadence and intensity they perceive to be an 8-9 on the Borg RPE scale, upon achieving the desired intensity the subject will crank at this intensity for 5 minutes and the work rate performed in watts will be recorded. Directly following the 5 minutes of low intensity exercise the subjects will be asked to increase their intensity to correspond with what they believe to be a 10-11 on the Borg RPE scale. Once again, upon achieving the desired intensity the subject will crank at this intensity for 5 minutes and the work rate performed in watts will be recorded. Overall, this protocol should take approximately 12 minutes: 1 minute self-selecting the low intensity exercise, 5 minutes of low intensity exercise, 1 minute self-selecting the moderate intensity exercise and 5 minutes of moderate intensity exercise. At baseline and during the upper body exercise femoral blood flow, skin perfusion, muscle oxygenation in the lower limbs, non-invasive beat by beat blood pressure and heart rate will be recorded during the each minute of exercise for a total of 10 one minute measurements. (note: We may determine the use of a finger cuff to measure beat by beat blood pressure during
upper body exercise is not possible due to movement and muscle contractions. In that case we will use a standard sphygmomanometer to measure blood pressure in the brachial artery and a heart rate monitor at the end of each 4 minute stage).

**Passive limb movement.** After a 15 minute recovery, protocol 2 will be conducted. The lower body passive limb movement will be achieved with the use of a programmed dynamometer (System 4 Pro, Biodex, Shirly, NY, USA). Participants will sit in an upright position on the dynamometer and the right leg will be moved in a range of 10° down to 90° of flexion and back at a rate of 1 Hertz. The dynamometer will be programmed to cycle at one minute intervals (one minute on/one minute off) for a total of 9 minutes. During the bouts of PLM femoral blood flow, skin perfusion, muscle oxygenation, non-invasive beat by beat blood pressure and heart rate will be recorded.

**Combination.** Following a 15 minute recovery period, the subjects will complete one more protocol that essentially combines the passive limb movement and upper body exercise. For the low intensity exercise the researchers will set the Monark to the corresponding work rate chosen by the subject in the low intensity exercise without the passive leg movement and after 5 minutes the researcher will increase the watts to the work rate chosen by the subject in the moderate intensity exercise without the passive leg movement for four additional minutes. During these ten minutes of combination exercise the subject will be ask to report their perceived exertion every minute and heart rate will also be recorded. During the protocol the right leg will be passively and continuously moved by the programmed dynamometer. Again during these 10 minutes femoral blood
flow, skin perfusion, muscle oxygenation, non-invasive beat by beat blood pressure and heart will be recorded.

**Experiment Equipment**

The following is a list of equipment used to collect the data for this experiment.

**Lower limb blood flow.** To access lower limb blood flow in the femoral artery for all three protocols we will utilize an ultrasound Doppler (Logiq 7, GE. Milwaukee, WI, USA) equipped with linear array mechanical sector transducers operating at an imaging frequency of 10-14 MHz. The probe will be placed in the inguinal crease and will be centered at least 2 inches proximal to the femoral artery bifurcation. Ultrasound gel will be used to assure good contact between the probe and skin and the area will be shaved if necessary. Vessel diameter will be determined at a perpendicular angle along the central axis of the scanned area, where the best spatial resolution can be achieved. The blood velocity profile will be obtained using the same transducers with Doppler frequency of 4-5.0 MHz. Blood velocity measurements will be obtained with the probe at an appropriate angle to maintain an insonation angle of 60 degrees or less and the sample volume centered. Using arterial diameter and mean velocity (Vmean), blood flow will be calculated as:  Blood Flow (mL/min) = Vmean • π • (Vessel Diameter/2)^2 • 60.

**Skin blood flow.** Changes in skin blood flow in the lower limbs during all three protocols will be determined via a Laser Doppler Perfusion and Temperature Monitor (moorVMS-LDF2, Moor Instruments, Axminster, UK). The head of the skin blood flow
probe will be secured to the skin superficial to the proximal portion of the vastus lateralis with the use of a temporary adhesion pad which can be easily removed upon completion of data collection.

**Tissue oxygenation.** Changes in tissue oxyhemoglobin, deoxyhemoglobin and total hemoglobin will be determined through the use of a Hamamatsu Niro-200 tissue oxygenation sensor (Hamamatsu Phototonics, Hamamatsu, Japan). This will require a small electrode to be secured to the skin over the belly of the vastus lateralis (thigh) and gastrocnemius (calf) muscle with the use of a temporary adhesion pad which can be easily removed upon completion of data collection.

**Mean arterial pressure and heart rate.** Mean arterial pressure and heart rate will be obtained via the use of a Nexfin system (ccNexfin, bmeycorp, Amsterdam, Netherlands). The Nexfin system employs a non-invasive, real time measurement of beat-by-beat blood pressure and heart rate. The device employs a simple style cuff to be placed on either the toe or finger of the subjects in the study.

**Rating of perceived exertion.** During all three protocols, the subjects will be asked to report the perceived exertion of the test via use of the Borg Rating of Perceived Exertion Scale. This scale ranges from 6-20, with 6 being sedentary with minimal discomfort and 20 being maximal effort. The protocols in this study will be performed in such a manner in which the higher number to be reported will not exceed a “15”. If any numbers 15 or above are reported by the subjects the test will be terminated and proper
intensities will be reassessed. The Borg RPE scale has been validated (Goosey-Tolfrey et al., 2010) and has been approved as a tool for selecting exercise intensity (Cowan, Malone, & Nash, 2009) in the SCI population.

**Statistical Analysis**

The independent variables are the three conditions of PLM, upper body exercise and combination. The dependent variables to be accessed are CFA blood flow, skin blood flow and tissue perfusion, tissue oxygenation, mean arterial pressure, heart rate and rating of perceived exertion. Interactions will be accessed via repeated measures two way ANOVA (condition x time) between conditions. Significant interactions between conditions and main effects will be teased apart with the use of paired samples t-tests. Results from the autonomic function testing will be used a covariate to control for any potential differences in autonomic function between the participants of the study. Statistical power and significance will be set apriori at $\beta>0.80$ and $\alpha<0.05$, respectively. With the use of published data from Venturelli and colleagues (Venturelli et al., 2014) and data collected in our laboratory in which CFA blood flow was measured during PLM, it is estimated the population needed to reach proper power and significance will be $n \geq 6$. This was determined by using standard significance and power values in accordance with difference in means of 430 ml/min and a standard deviation of difference of sample means of 243.3 ml/min for CFA blood flow values at baseline and peak hyperemic response observed during PLM. In addition, previous data has been used to calculate a high effect size of $r=0.71$ and a Cohen’s $d=2.06$. By accounting for
remaining autonomic function and only recruiting a specific injury level of SCI variance between participants should be reduced allowing for an adequate sample size to be achieved.
CHAPTER IV

THE EFFECTS OF REPEATED BOUTS OF PLM WITH ONE MINUTE RECOVERY PERIODS ON BLOOD FLOW IN PARAPLEGICS

Abstract

Previous reports suggest passive limb movement (PLM) could be used as a modality to increase blood flow and tissue perfusion in the paralyzed lower limbs of those with spinal cord injuries. However, the hyperemic response to PLM is transient, lasting only 30-45 seconds despite continued limb movement. The purpose of this investigation was to determine these hyperemic response can be repeated across multiple bouts of PLM.

Nine paraplegics with a clinically confirmed complete lesion between the 3rd and 11th thoracic vertebra participated in the study. The PLM protocol consisted of 5 bouts of passive knee extension/flexion at 1 Hz for 1 minute each bout. A 1 minute recovery period separated each bout. Femoral artery blood flow (FABF), skin blood flow (SBF) and tissue perfusion in the lower limb were recorded throughout each bout along with heart rate (HR) and mean arterial pressure (MAP).

One way repeated measures ANOVA showed a significant main effect of condition for both FABF and SBF (p<0.05). FABF increased 58, 52, 57, 50 and 63% with each bout of PLM, respectively. All but the 4th bout (50% increase) was statistically greater than the baseline value. SBF showed statistically significant increases of 405, 415,
447, 505 and 594% across the five bouts of PLM, respectively. HR and MAP were shown not to change during the bouts of PLM compared to baseline measures. Tissue perfusion was observed to have a slight decrease across the bouts of PLM.

These data indicate when repeated one minute bouts of PLM are interspaced with one minute recovery periods there is a consistent robust increase in FABF and SBF.
Introduction

Prolonged periods of immobility and physical in-activity can result in a severely deconditioned state. Effects such as muscle atrophy, increased risks of developing cardiovascular disease and attenuated blood flow which can lead to a reduced health status and quality of life are often observed. This is perhaps most evident in persons who have experienced a spinal cord injury (SCI). The immobile and physically in-active state after incurring an SCI makes this population a heightened risk of developing pressure ulcers (Bogie et al., 2006), accelerates the rate of developing cardiovascular disease (Myers et al., 2007; W. T. Phillips et al., 1998) and may result in decreased tissue health below the level of the SCI lesion. The increased incidence of these conditions may be due to decreased physical activity and alterations to the structure and function in the peripheral vasculature. Previous studies have observed a 30% reduction in femoral artery diameter (de Groot et al., 2003) and decreases in resting femoral artery blood flow (Hopman et al., 1996; Huonker, Schmid, Schmidt-Trucksäß, Grathwohl, & Keul, 2003) in this population.

To counteract these detrimental effects, previous investigators have sought to examine the efficacy of applying passive leg movement (PLM) to this population to invoke an increase in blood flow to the tissue. In an able bodied population, PLM elicits a significant, yet transient (i.e. 45 second) hyperemic response in the femoral artery (McDaniel, Fjeldstad, et al., 2010; McDaniel, Hayman, et al., 2010; Trinity et al., 2015). This response is due to alterations in the both central and peripheral blood flow regulators.
(Trinity et al., 2010; Trinity et al., 2011). Specifically, at the initiation of PLM there is a marked increase venous return due to the action of the skeletal muscle pump resulting in increased stroke volume. Concurrently, the movement causes activation of Type-III muscle afferents which signal the cardiorespiratory control centers of the brain resulting in a positive chronotropic response. The hyperemic response is thought to be the result of peripheral mechanisms including nitric oxide (NO) and mechanically induced vasodilation (Mortensen, Askew, Walker, Nyberg, & Hellsten, 2012; Trinity et al., 2012; Trinity et al., 2015) as well as mechanical distortion (M.A. Hayman et al., 2010) of the arteriole network in the shortening and lengthening muscles. Taken together, these physiologic effects result in a transient increase cardiac output and conductance which allows for more blood to be directed to the moving limb.

Due to the nature of a SCI there is no afferent feedback to the cardiorespiratory controls centers of the brain, thus the hyperemic response to a bout in PLM would be attributed solely to peripheral factors. While some studies have observed no increase in FABF during passive movements of the paralyzed limbs in the SCI population (Svensson et al., 1995; Ter Woerds et al., 2006) others have reported the opposite (Ballaz et al., 2007; Venturelli et al., 2014; Venturelli et al., 2012). These discrepancies could be the result of several of these investigations using wide range of SCI subjects, in both injury level and severity, and missing the transient hyperemic response due to the timing of their measurements. The recent investigations by Venturelli and colleagues controlled their SCI population and performed continuous blood flow monitoring and reported a 2-minute
bout of PLM (knee extension/flexion at 1 Hz) elicited nearly a twofold, yet again
transient, increase in femoral artery blood flow without the concomitant increase in heart rate. While the absolute magnitude of the hyperemic response invoked by PLM appears to be greater in the able bodied population compared to the SCI population, after normalizing hyperemic responses to thigh muscle mass PLM was shown to cause nearly identical hyperemic responses in these populations (Venturelli et al., 2014)

As the hyperemic response appears to be short lived, lasting approximately 45 seconds despite continued PLM, this may not provide a significant stimulus to maintain vascular and tissue health. However, if this hyperemic response can be replicated with repeated bouts of PLM there may be sufficient stimulus to maintain and promote vascular and tissue health in the SCI population. To this end, the primary aim of this study was to evaluate the efficacy of five 1 minute bouts of PLM interspaced with a 1 minute recovery between bouts to initiate a repeatable and robust hyperemic response. It was hypothesized that each one minute bout of PLM would elicit near identical responses because of the addition of the recovery period.
Methods

Nine paraplegics participated in the preset study. All subjects had clinically confirmed complete lesions (American Spinal Injury Association Grade A) between the 3rd and 11th (T3-11) thoracic vertebra (Kirshblum et al., 2011). Descriptive characteristics of the subjects are shown in Table 1. All procedures adhered to the standards outlined by the Declaration of Helsinki, and the Institutional review board at the Cleveland Louis Stokes Veterans Affair Medical Center approved the study and written informed consent was obtained from all subjects before their participation. Upon reporting to the laboratory, subjects were free from known pulmonary, cardiovascular and metabolic disease and displayed no spasticity in their paralyzed limbs. All protocols were performed in a thermoneutral environment (22°C). Subjects were asked to refrain from exercise for 24 hours before reporting to the laboratory and to report in a fasted state (4 hours) with no consumption of caffeine within the previous 8 hours. Subjects also were told to maintain their current medication regimen before coming in to participate in the study.

Experimental Protocols

Subjects were assisted into a comfortable seated-upright chair (Biodex Medical Systems. System 4 Pro, Shirley, NY, USA), rested for 15 minutes before the start of data collection and remained in this position for the duration of the study. The Biodex was calibrated to move the subject’s right leg through an 80° range of motion (10° to 90° of knee joint flexion) at an angular velocity of 180°/second (1 Hertz). The dynamometer
was programmed to cycle at one minute intervals (one minute on, one minute off) for a total of 5 PLM intervals. For the duration of the protocol, the subject’s contralateral leg remained stationary at a flexed position of 90°.

**Femoral artery blood flow.** Measurement of femoral artery vessel diameter and blood velocity were taken distal to the inguinal ligament and at least 3 cm proximal to the deep/superficial femoral bifurcation with the use of a Logic 7 ultrasound system (General Electric Medical Systems, Milwaukee, WI, USA). The ultrasound system was equipped with a M12L transducer operating at a frequency of 14 MHz (ultrasound) and 5 MHz (Doppler). Arterial diameter was measured at a 90° angle along the central axis of the scanned vessel. Velocity measurements were obtained with the transducer positioned to ensure an insonation angle of 60° or less. Mean blood flow velocity and arterial diameter were then combined to calculate femoral artery blood flow (FABF) in milliliters per minute with the following equation: mean blood velocity × π(vessel diameter/2)^2 × 60. All scanning and analyses were performed by experienced and skilled sonographers.

**Skin blood flow.** Skin blood flow (SBF) was determined via a Laser Doppler and Perfusion Monitor (moorVMS-LDF2, Moor Instruments, Axminster, UK) with the VP1/7 probe being placed on the anterior aspect of rectus femoris muscle over the middle of the muscle belly. Laser Doppler flowmetry is based on red blood cell (RBC) flux and is expressed as arbitrary “PU” units and calculated as product of RBC concentration and velocity and is indicative of superficial skin blood flow measurements (Bonner & Nossal, 1990; Nilsson, Tenland, & Oberg, 1980).
Central hemodynamics. Heart rate (HR) was determined with the use of a 3 lead electrocardiogram (ECG) streaming into a data acquisition box (Lab Chart 8 Pro, AD Instruments, Denver, CO, USA). Mean arterial pressure (MAP) was determined with the use of a Nexfin (Nexfin, bmeyecorp, Amsterdam, Netherlands). Before the start of data collection the Nexfin was allowed adequate time for self-calibration and the finger cuff remained inflated for the entire duration of the protocol.

Tissue oxygenation and skin blood flow. Changes in tissue oxy-hemoglobin (Oxy), total hemoglobin (Theme) and blood volume (nTHI) (Ferrari, Mottola, & Quaresima, 2004) were assessed with the use of a NIRS (near infrared spectroscopy) system (NIRO 200, Hamamatsu Phototonics, Hamamatsu, Japan) by placing electrodes on the anterior aspect of the right rectus femoris muscle. The laser on the NIRS system penetrates approximately 2cm into the muscle tissue thus changes in Oxy, THeme and nTHI are indicative of hemodynamic and tissue perfusion changes in the superficial aspects of the muscle.

Results

Throughout the protocol HR, MAP, tissue perfusion and SBF variables underwent analog-to-digital conversion and were simultaneously acquired (200 Hz) by commercially available data-acquisition software (Lab Chart 8 Pro, AD Instruments, Denver, CO, USA). The data were then averaged into a one minute baseline value and into 1 minute averages for each of the 1 minute LM bouts. For FABF and SBF the peak
3 second averages during each bout of PLM was also calculated. In addition, an overall average across the duration of all the PLM bouts was calculated to determine if the modality had the ability to invoke significant and prolonged changes from baseline values.

The dependent variables assessed were FABF, SBF, HR, MAP, Oxy, THeme and nTHI. Each dependent variable was initially assessed with the use of a one-way repeated measures analysis of variance (ANOVA) to assess whether a main effect of bout was observed between the baseline value and the 5 one minute averages obtained during the PLM bouts. In addition, for the peak FABF and SBF values the same statistical methodology was employed. If a main effect of PLM bout was detected post-hoc paired samples t-tests were used to determine which values from each of the 5 bouts of PLM were significantly different than the baseline values. Post-hoc comparisons were adjusted using the Benjamini-Hochberg false discovery rate correction equation (Benjamini & Hochberg, 1995). The significance \( p<0.05 \) and statistical power \( \beta>0.80 \) was set a priori. All data are presented as mean±SD. A power analysis was performed on previous data on PLM used in the SCI population and showed a subject population of \( n\geq6 \) would be needed to achieve statistically significant increases in FABF.

**Femoral Artery Blood Flow**

For all FABF measurements a population of \( n=8 \) was used as excessive thigh movement interfered with proper blood flow measurements in one subject.
For the 1 minute averaged values, the one way ANOVA showed a significant main effect of bout. At baseline, FABF was 120±91 ml/min and for each subsequent bout of PLM FABF was 189±150, 182±147, 188±148± 180±132 and 196±142 ml/min, respectively (Figure 1a). Post-hoc analysis showed all of these values to be significantly greater than the baseline average with the exception of the 180±132 ml/min average obtained during the 4th bout of PLM. The effect size of FABF during each bout of PLM was 0.27, 0.25, 0.27, 0.26 and 0.30, respectively. The average FABF value across the five bouts of PLM was 187±142 which was significantly greater than the baseline value with an effect size of 0.27.

For the peak 3 second values, the one way ANOVA once again showed a significant main effect of bout. The peak 3 second FABF value for each bout of PLM was 253±196, 248±204, 257±206, 245±178 and 227±168 ml/min, respectively, and all of these values represented a significant increase from the baseline average (Figure 1b). The effect size of FABF for each 3 second peak was 0.40, 0.38, 0.40, 0.40 and 0.37. The average 3 second peak value across all 5 bouts of PLM was 246±189 which was significantly greater than the baseline average with an effect size of 0.39.

**Skin Blood Flow**

For the 1 minute average values, the one-way ANOVA showed a significant main effect of bout. At baseline SBF was 18.3±10.0 PU and showed a significant increase during each bout with values of 83.4±26.0, 85.9±35.7, 94.9±52.2, 101.5±70.8 and
117±87.4 PU (Figure 2a), respectively. The effect sizes of these values are 0.85, 0.79, 0.72, 0.63 and 0.62, respectively. The average SBF across the 5 bouts of PLM was 96.7±50.6 PU which is a significant increase from baseline with an effect size of 0.73.

For the peak 3 second values obtained during each bout of PLM the one way ANOVA showed a significant main effect of bout. The average peak 3 seconds of SBF for each bout was 91.3±27.7, 97.2±43.9, 104.0±60.1, 115.3±85.3 and 131.6±92.7 PU (Figure 2b) with each peak being significantly greater than baseline averages. The effect sizes for these bouts were 0.87, 0.78, 0.70, 0.62 and 0.65. The average peak SBF across the five bouts of PLM was 107.9±58.1 PU which was a significant increase from baseline with an effect size of 0.73.

Heart Rate

The one way ANOVA showed there was no main effect of bout for HR with no statistical increases in HR observed during each bout of PLM when compared to baseline values. At baseline, HR was 82±13 bpm. During the 5 bouts of PLM the average heart rates were 81±10, 81±10, 82±11, 80±11 and 83±7 bpm (Figure 3a). The average HR across the five bouts of PLM was 81±10 which was not statistically different than baseline HR.

Mean Arterial Pressure

The one way ANOVA showed there was no main effect of bout for MAP with no statistical increases in MAP observed during each bout of PLM when compared to baseline values. At baseline MAP was 99.6±19.2 mmHg, and for the average across the
bouts of PLM MAP was 101.0±17.1, 104.1±17.7, 103.4±16.4, 101.8±18.6 and 106.7±16.8 mmHG (Figure 3b). The average MAP across the 5 bouts of PLM was 103.4±17.3 mmHg which was not significantly greater than the baseline average.

**Oxy-Hemoglobin**

One way ANOVA showed no main effect of bout. At baseline Oxy was -0.80±3.30 and for the bouts of PLM the average Oxy was -2.47±2.53, -2.92±3.31, -3.03±3.60, -2.86±3.69 and -3.27±3.91, respectively. The average Oxy across the 5 bouts of PLM was -2.91±2.75 which was significantly lower than the baseline average with an effect size of 0.33.

**Total Hemoglobin**

The one way ANOVA revealed a main effect of bout, however, post-hoc analysis showed no statistical difference between the baseline value and the one minute averages values during each 5 bouts of PLM after the post-hoc correction was applied. At baseline THeme was 0.02±4.07 and during the 5 bouts of PLM THeme was -2.41±3.46, -3.61±5.3, -3.74±5.88, -3.64±6.17 and -3.90±6.54, respectively. The average THeme across the 5 bouts of PLM was -3.46±5.3 which was significantly lower than the baseline average with an effect size of 0.34.

**Normalized Total Hemoglobin Index**
Similar to Oxy, nTHI showed no main effect of bout across the baseline value and 5 bouts of PLM. At baseline nTHI was 1.01±0.07 and during each bout the PLM nTHI was 0.90±.021, 0.90±0.22, .90±.020, 0.90±.19 and 0.91±.21, respectively. The average nTHI across the 5 bouts of PLM was 0.90±0.20 which showed a trend towards significance ($p=0.09$) with an effect size of 0.34.

**Discussion**

The present study examined the effectiveness of repeated bouts of PLM interspaced with one minute recovery periods to elicit hemodynamic changes in the lower limbs of paraplegics. Specifically, we examined if this modality could result in consistent changes in FABF, SBF and tissue perfusion of the passively moved limb reoccurring with each subsequent bout of PLM. The present study demonstrates that repeated one minute bouts of PLM has the ability to generate similar increases in FABF. Also, the increase in SBF seems to have a compounding effect between bouts with a more robust response occurring with each subsequent bout of PLM. Our hypothesis was shown to be correct as the 5 bouts of PLM produced nearly identical changes in FABF with significant increases being observed in 4 out of the 5 bouts of PLM.

These data demonstrate that the hyperemic response is not facilitated by increased heart rate, or mean arterial pressure which were shown not to change in the current study. This is in agreement with previous studies that looked at heart rates responses during either passive cycling (Ballaz et al., 2007; Muraki, Ehara, & Yamasaki, 2000; Muraki, Yamasaki, Ehara, Kikuchi, & Seki, 1996) or PLM (Venturelli et al., 2014; Venturelli et
al., 2012) and saw no changes in HR during the experimental manipulations. It has been reported that in the able-bodied population 35% of the hyperemic response is from central factors and 65% is the result of peripheral mechanisms (Venturelli et al., 2012). However, in the SCI population, particularly in the ASIA A subgroup in which no sensory function remains, the generation of this hyperemic response is solely due to peripheral mechanisms as the afferent feedback to the cardiovascular control center is absent. This is demonstrated in the current investigation with the lack of an increase in HR and MAP with PLM. As such, it can be reasoned that the SCI population has a heightened vascular sensitivity below the level of the lesion as the hyperemic response between the able-bodied and SCI population are nearly identical after controlling for thigh volume and resting FABF (Venturelli et al., 2014).

As this hypersensitivity is likely in response to the chronically immobile state of the paralyzed leg being subjected to unaccustomed movements (Bentzer et al., 1997; Hershman, Taylor, & Fleming, 1993) it was unknown whether or not employing repeated bouts of PLM would diminish this hyper-sensitivity resulting in a decreased hyperemic response. However, the results of the present study are promising as each bout of PLM resulted in nearly identical hyperemic responses. This modality could prove beneficial to use in clinical settings such as in-patient hospital and long term rehabilitation centers to promote FABF and venous return which may lower the likelihood of deep vein thrombosis development (Merli, Crabbe, Paluzzi, & Fritz, 1993).

**Repeating the Hyperemic Response**
While previous investigators have used 1 and 3 second averages (McDaniel, Fjeldstad, et al., 2010; McDaniel, Hayman, et al., 2010) to look at blood flow kinetics during PLM. For the present study, 1 minute averages were elected to be used in an attempt to show PLM has the ability to invoke a sustained hyperemic response over the duration of each bout. This could have an impact for prescribing bouts of PLM with the one minute on, one minute off interval for sustaining an increase in blood flow.

Some investigations have reported no increase in FABF during passive movements in the SCI population (Svensson et al., 1995; Ter Woerds et al., 2006) while others show passive movements do increase FABF (Ballaz et al., 2007; Venturelli et al., 2014; Venturelli et al., 2012). The results of the current study are in agreement with the studies performed by Ballaz and Venturelli as the repeated bouts of PLM resulted in significant increases in FABF. Venturelli (2012 and 2014) reported peak blood flow responses to be nearly double baseline values during a sole bout of PLM. The results of the current study are nearly identical with an average peak blood flow of 105% above baseline values observed across the bouts of PLM. The current study is novel in the fact that these data indicate this hyperemic response can be repeated with a one minute period between each bout of PLM.

The investigations by Svensson (1995) and Ter Woerds (2006) examined the effectiveness of passive movements to increase FABF in the SCI population, however, both reported no changes. This was likely the result of the timing of the blood flow measurements as they did pre-post and not during the experimental manipulation. As the
increase in FABF has been observed to be transient, it likely these experiments caused a transient hyperemic response but were not observed by the researchers as they measured blood flow upon competition of the passive movements and not during.

Similarly, the study by Ballaz et al. did blood flow measurements pre/post a 10 minute bout of passive cycling and observed a modest increase of only 30%. The measuring FABF pre/post and by employing a single long bout of passive cycling was likely the reason for the smaller increase in FABF compared to when repeated short bouts and FABF measurement during the bout of PLM was employed showing almost a 60% average increase across all 5 bouts of PLM. Additionally, the methodology of the Ballaz article has been questioned (Groothuis & Hopman, 2007) as the participants changed positions between when blood flow measurements were taken and the passive cycling. Accordingly, the movement of the subjects and not the 10 minutes of the passive cycling may have attributed to the modest increase in blood flow. The results of the current study show that by interspacing 1 minute bouts of PLM with 1 minute rest periods a repeatable and prolonged hyperemic response can be observed.

**Skin Blood Flow**

Surprisingly, in contrast to the similar increases in FABF observed during the bouts of PLM, increases in SBF seemed to have a compounding effect with each subsequent bout of PLM resulting in larger increases in SBF. This could prove to be extremely beneficial at reducing pressure ulcers and improving skin wound healing in the SCI population. The nearly 500% increase in SBF observed during the last bout of PLM
is on par with other studies in the SCI population. An investigation by Sonenblum and colleagues looked at the effectiveness of pressure relief maneuvers to increase skin blood flow of the buttocks reported comparable increases in SBF to the current investigation (Sonenblum, Vonk, Janssen, & Sprigle, 2014). While these results are promising, the present study measured SBF on the thigh while pressure ulcers most commonly form in areas that are exposed to constant pressure and bony prominences such as the ischial and sacral regions (Garber, Rintala, Hart, & Fuhrer, 2000; Rabadi & Vincent, 2011). The present study provides motivation for future investigations to evaluate changes in SBF around the most commonly affected pressure ulcer areas in the SCI population.

**Muscle Tissue Perfusion**

While the present study showed increases in FABF and SBF in response to PLM the averages over the course of all the bouts of PLM showed a decrease in rectus femoris oxygenated hemoglobin (Oxy), total hemoglobin (THeme) and a trend towards a decrease for total blood volume (nTHI). In the SCI population, the loss of neural drive results in a failure of blood pressure regulatory mechanisms such as sympathetic vasoconstriction (Claydon et al., 2005). As a result, this population can have significant pooling of venous blood in the lower limbs when in a seated or standing position as the vasculature and the muscles are unable to effectively shunt blood back to the trunk, which ultimately leads to high rates of postural hypotension in this population (Mathias, 2006). The rhythmic movement of the hamstring and quadriceps muscle groups likely promoted venous return from the lower limbs via the skeletal muscle pump resulting in the reduced THeme and
Oxy exhibited during the bouts of PLM. This modality could prove beneficial in reducing deep vein thrombosis (DVT) which is three times higher in the SCI population compared to the able bodied population (Miranda & Hassouna, 2000) and is partially due to stasis of blood flow and endothelial injury (Lensing, Prandoni, Prins, & Büller, 1999). Thus PLM could aid in promoting increased blood flow to avoid stagnant and pooled blood while additionally promoting increased vascular health (Hellsten et al., 2008) both of which could lessen the impact of DVTs in this population.

**Conclusion**

Previous studies have observed that the hyperemic response in response to PLM is transient in nature lasting less than 45 seconds in the SCI population. This is the first study to report that a 1 minute rest bout between 1 minute bouts of PLM allows for a repeatable hyperemic response which could significantly impact this population. The repeated bouts of PLM also generated robust increases in SBF which could aid in lessening the impact of pressure ulcers in the SCI population. Additional studies should be performed to determine the optimum rest period bouts subsequent bouts of PLM as shorter recovery periods may result in similar increases in blood flow resulting in a more efficient use of time.
CHAPTER V

EFFECTIVENESS OF UPPER BODY EXERCISE AND PASSIVE LIMB MOVEMENT TO INCREASE LIMB BLOOD FLOW IN PARAPLEGICS

Abstract

Results from previous investigators on the ability of upper body exercise (UBE) to increase femoral artery blood flow (FABF) in the paraplegic population has produced a wide range of results. The use of a more tightly controlled population, controlling for both level and severity of injury, may add clarity to this question. In addition, previous reports suggest passive limb movement (PLM) could be used as a modality to increase femoral artery blood flow in this population. These two modalities used together may provide sufficient stimulus for a robust increase in femoral artery blood flow. As such, the purpose of this investigation was to determine the effectiveness UBE when used alone and in combination with PLM to increase FABF in the paraplegic population.

Nine paraplegics with a clinically confirmed complete lesion between the 3rd and 11th thoracic vertebra participated in the study. The subjects underwent 10 minutes of upper body exercise, 5 minutes at a low intensity and 5 minutes at a moderate intensity, during which blood flow was measured. After a 30 minute break, the protocol was replicated with the addition of repeated bouts of passive limb movement being conducted every other minute during the upper body exercise. During the experiment changes in
FABF, skin blood flow (SBF), heart rate (HR), mean arterial pressure (MAP) and tissue perfusion were measured.

Two way repeated measures ANOVA showed no statistically significant interactions between the two groups for changes in femoral artery blood flow. On average, femoral artery blood flow increased 41% for the upper body exercise and 26% with the addition of the passive limb movement compared to baseline measures. The two conditions were also observed to increase SBF, HR, MAP and tissue perfusion from baseline values.

These data indicate the upper body exercise when used in combination with passive limb movement has the ability to invoke a large increase in femoral artery blood flow. This could have a profound clinical application for this population.
Introduction

After incurring a spinal cord injury (SCI), a paralytic has reduced exercise tolerance for upper body arm exercise (UBE) compared to an able-bodied individual (Dela et al., 2003; Jacobs & Nash, 2004). This occurrence is due to the loss of neural control of the vasculature below the level of the SCI and therefore inability to produce an adequate sympathetic induced vasoconstriction in the paralyzed lower limbs. Thus the increased cardiac output during exercise is improperly distributed to the upper body as well as the inactive paralyzed lower limbs. Ultimately, cardiac output to the active muscle is reduced compared to able bodied individuals. However, while the inability to effectively constrict the vasculature of the lower legs may negatively impact upper body exercise capacity it may, indirectly, promote blood flow to the lower limbs thus increasing, or at least maintaining, vascular and tissue health in this region which is often compromised in this population (Simpson, Eng, & Hsieh, 2012). Previous investigators has sought to study the effectiveness of upper body exercise to increase blood flow to the lower limbs of paralytics with conflicting results as some studies have shown an increase (Bidart & Maury, 1973), no change (Hopman et al., 1994; Hopman et al., 1996; Kinzer & Convertino, 1989) and even decreases in blood flow (Burkett et al., 1988). This discrepancy may be due to the range of injury level and severity used in these investigations.

Recent literature has reported the ability of a passive limb movement (PLM) bout to induce a significant, yet transient, hyperemic response in the femoral artery in those
with a SCI injury. Studies by Venturelli and colleagues (Venturelli et al., 2014; Venturelli et al., 2012) have reported that during a bout of PLM in which a paralytic leg is moved through a 90° range of motion (0 to 90° of flexion) at a rate of 1 hertz, femoral artery blood flow nearly doubled baseline values. Because these studies have shown no changes in heart rate or cardiac output during the PLM protocol the hyperemic response is thought to be the result of peripheral mechanisms including nitric oxide (NO) and mechanically induced vasodilation (Mortensen et al., 2012; Trinity et al., 2012; Trinity et al., 2015) as well as mechanical distortion (M.A. Hayman et al., 2010) of the arteriole network in the shortening and lengthening muscles. While the response is transient, lasting less than 60 seconds even with continuation of a PLM protocol, it is robust and may provide sufficient stimulus for vascular remolding and improving tissue health in this population.

If a PLM protocol was to occur during upper body exercise in the paraplegic population, the combined physiologic stimulus of both modalities, increase in cardiac output during upper body exercise and vasodilation during passive limb movement, may prove to elicit a hyperemic response that is greater in magnitude compared to when these manipulations are used in isolation. Thusly, the primary purpose of the study was to use a tightly controlled population of paraplegics and examine the effectiveness of upper body exercise used alone and in combination with passive limb movement to increase blood flow the lower limbs in this population. It was hypothesized that both exercise protocols would elicit significant increases in blood flow but that the combination
protocol would elicit significantly greater increases compared to when upper body exercise is used in isolation.
Methods

Nine paraplegics were recruited for the present study and reported to the laboratory in a fasted state (4 hours). Subjects were asked to maintain their current medication regimen and to refrain from exercise for 24 hours and caffeine for 4 hours before reporting to the laboratory. A complete list of subject characteristics can be found in Table 1. All procedures adhered to the standards outlined by the Declaration of Helsinki, and the Institutional review board at the Cleveland Louis Stokes Veterans Affair Medical Center approved the study. Subjects were pre-screened to ensure meeting the inclusion criteria of the study including being free from cardiovascular, pulmonary and metabolic disease. Written informed consent was obtained from all subjects before their participation be a member of the research staff. All studies procedures were performed in a thermoneutral environment (22°C).

Autonomic Function Assessment

While subjects were ASIA grades A there is evidence the SCI populations may still have intact (either fully or partially) autonomic nervous system (ANS) integration below the level of the lesion (Krassioukov et al., 2012). To access this, a sympathetic skin response (SSR) test was performed on each subject. Electrodes were placed bilaterally on both hands and feet of the subject. A stimulating bar (AD Instruments, Denver, CO, USA) was then placed over the radial nerve and secured with an athletic bandage. An electrical pulse was then sent through the stimulating bar at random intervals (30-90 seconds) until a total of 10 pulses had been administered. Deflection of
the electrodes positioned on the limbs indicates depolarization of the cholinergic dependent sweat glands, and therefore intact ANS innervation.

**Upper Body Exercise**

Subjects were assisted into a comfortable seated-upright chair (Biodex Medical Systems. System 4 Pro, Shirley, NY, USA) at a 30-45° reclined angle for 15 minutes before the start of data collection and remained in this position for the duration of the study. The subjects were then familiarized with the Borg rating of perceived exertion chart, a valid instrument of prescribing workload in this population (Cowan et al., 2009; Goosey-Tolfrey et al., 2010). While the subjects rested they were outfitted with a finger blood pressure cuff, as well as heart rate, tissue perfusion and skin blood flow electrodes. Before the start of exercise a 1 minute baseline measurement for all variables was collected. For the UBE the subjects were instructed to pedal an upper body ergometer (Monark 881E, Monark Exercise AB, Vansbro, Sweden) at a cadence of 50 revolutions per minute. The subjects self-selected the resistance of the ergometer to an intensity they were told corresponded to a value of 9-10 (low intensity) on the Borg RPE chart. After the appropriate cadence and intensity were achieved, the subjects completed 5 minutes of upper body exercise. Upon completion of the low intensity exercise, the subjects continued to cycle the arm ergometer while the resistance increased such that it corresponded to values of 12-13 (moderate intensity) on the Borg RPE chart. Once again, after proper cadence and intensity were obtained, approximately within 30-60 seconds, the subject completed a second 5 minute bout of exercise. During the last 15
seconds of every minute of exercise subjects were instructed to operate the upper body ergometer with only their right hand and to rest their left hand on the table provided to allow for accurate blood pressure readings to be recorded. The exercise intensities achieved by the subjects in the low and moderate intensities (watts) were recorded by a member of the research team for subsequent use.

**Combo Protocol**

After a 30 minute recovery period, the Biodex was calibrated to move the subject’s right leg through an $80^\circ$ range of motion ($10^\circ$ to $90^\circ$ knee joint angle) at an angular velocity of $180^\circ$/second (1 Hertz). After another one minute baseline was taken, the subjects were then required to perform 2 five minute stages of arm ergometry at the same intensities as the first protocol. However, during this protocol the Biodex passively moved the subject’s right leg during minutes 1, 3 and 5 of each 5 minute stage. During the last 15 seconds of every minute of exercise subjects were instructed to operate the upper body ergometer with only their right hand and to rest their left hand on the table provided to allow for accurate blood pressure readings to be recorded. During this entire protocol the subject’s contralateral leg remained stationary at a flexed position of $90^\circ$.

**Dependent Variables**

Femoral artery blood velocity and vessel diameter distal to the inguinal ligament and at least 3 cm proximal to the deep/superficial femoral bifurcation was measured with a Loqic 7 ultrasound system (General Electric Medical Systems, Milwaukee, WI, USA).
The ultrasound system was equipped with a M12L transducer operating at a frequency of 14 MHz (ultrasound) and 5 MHz (Doppler). Arterial diameter was measured at a 90° angle along the central axis of the scanned area. All ultrasound scanning was performed with an insonation angle of less than 60° to ensure accurate blood flow velocities. Mean blood flow velocity and arterial diameter were then combined to calculate blood flow (ml/min) with the following equation: mean blood velocity \( \times \pi \frac{\text{vessel diameter}}{2}^2 \times 60.

All scanning and subsequent blood flow analysis were performed by experienced sonographers.

Heart rate (HR) was determined with the use of a 3 lead ECG streaming into a data acquisition box (Lab Chart 8 Pro, AD Instruments, Denver, CO, USA). Mean arterial pressure (MAP) was determined with the use of a Nexfin (Nexfin, bmeyecorp, Amsterdam, Netherlands). To ensure accurate readings, the Nexfin was allotted ample time to self-calibrate and the heart rate sensor was placed slightly superior to the xiphoid process. The finger pressure cuff remained inflated for the duration of the protocol.

Changes in tissue oxyhemoglobin (Oxy), total hemoglobin (THeme) and normalized index of tissue hemoglobin (nTHI), that represents changes in local blood volume (Ferrari et al., 2004) were assessed with the use of a NIRS system (NIRO 200, Hamamatsu Phototonics, Hamamatsu, Japan) by placing electrodes on the ventral aspect of the rectus femoris muscle. The NIRS signal penetrates approximately 2 cm, as such, changes in Oxy, Theme and nTHI reflect local hemodynamic and oxygenation changes in
the superficial aspects of the muscle. Oxy, TOxy and nTHI values represent relative changes from baseline values and will be presented without units.

Skin blood flow (SBF) was determined via a Laser Doppler and Perfusion Monitor (moorVMS-LDF2, Moor Instruments, Axminster, UK) with the VP1/7 probe placed on the ventral aspect of rectus femoris muscle. Laser Doppler flowmetry is based on red blood cell (RBC) flux and is expressed as arbitrary “PU” units and calculated as product of RBC concentration and velocity and is indicative of superficial skin blood flow measurements (Bonner & Nossal, 1990; Nilsson et al., 1980).

**Data Analysis**

MAP, HR, tissue perfusion values, and skin blood flow values underwent analog-to-digital conversion and were acquired at 200 Hz by commercially available data acquisition software (Lab Chart 8 Pro, AD Instruments, Denver, CO, USA). Data was then averaged into one value for each variable during the baseline measurement and single 5 minutes average for the low and moderate intensity exercise bouts for each condition. Five 1-minute averages were used to determine if these modalities provide sufficient stimulus to induce a prolonged hyperemic response. For FABF and SBF the peak 15 second averages during the low and moderate exercise intensities for both the UBE and combination (CMB) conditions were also calculated. This is due to the fact the hyperemic response observed during a bout of PLM is transient and often peaks within 20 seconds after starting the PLM (McDaniel, Fjeldstad, et al., 2010; Venturelli et al., 2012).
The dependent variables assessed were FABF, SBF, Oxy, TOxy, nTHI, HR, MAP. Initial 1-way repeated measures ANOVA of time (baseline, low and moderate intensity) were performed on both the UB and CMB protocol to determine the effectiveness of each protocol to elicit changes in the assessed dependent variables from baseline measurements. A two-way repeated measures ANOVA (2 condition x 3 time points) was then used to detect interactions between the conditions followed by post-hoc paired samples t-tests to detect specific differences. Post-hoc comparisons were adjusted using the Benjamini-Hochberg false discovery rate correction equation (Benjamini & Hochberg, 1995). The significance ($p<0.05$) and statistical power ($\beta>0.80$) were set a priori. All data are presented as mean±SD.

Results

No differences in baseline values were found between the upper body and combination conditions across all dependent variables. The average intensity achieved during the low intensity exercise was 54±6 watts, while the average intensity during the moderate intensity was 65±5 watts. Additionally, as only 2 of the 9 subjects had positive SSR responses we elected to group all participants for statistical analysis together instead of opposing groups. As this is only a pilot study, it is hoped the recruitment of additional subjects will allow for splitting the population into those with and without a SSR response.
Femoral Artery Blood Flow

For all FABF measurements a population of n=8 was used as one participant’s blood flow recordings could not be adequately analyzed. Both the UBE and CMB conditions were observed to not elicit significant increases in baseline FABF values and no interaction was observed between conditions. At baseline in the UBE condition, FABF was 113±78 ml/min and increased to 160±130 (p=0.06) and 162±131 (p=0.06) ml/min for the low and moderate intensities, respectively. FABF for the CMB protocol was 119±93 ml/min and increased to 150±125 (p=0.09) and 155±136 (p=0.13) ml/min during the low and moderate intensities, respectively (Figure 5a). While not statistically significant, the effect size for these results were rather robust with the UBE condition resulting in effect sizes of 0.21 and 0.22 for the low and moderate intensities, while the CMB condition resulted in effect sizes of 0.13 and 0.15, respectively.

Once again for peak blood flow no interaction was observed between the conditions. However, for both the UBE and CMB protocols the peak 15 second FABF values obtained were significantly greater than baseline values. For the UBE condition, FABF significantly increased to 192±137 and 194±146 ml/min for the low and moderate intensities, respectively. For the CMB condition, FABF significantly increased to 216±165 and 227±192 ml/min for the low and moderate intensities, respectively (Figure 5b). The effect size of these increases were 0.34 for both exercise intensities for the CMB condition and 0.33 for both exercise intensities for the UBE condition.
**Skin Blood Flow**

Both the UBE and CMB conditions induced significant increases in SBF from baseline values and a significant interaction was detected between conditions. At baseline for the UBE and CMB conditions SBF was 19.0±8.0 and 25.3±24.6 PU, respectively. For the low intensity exercise these values significantly increased to 31.3±13.0 and 78.0±67.8 and increased even further to 36.5±20.7 and 80.3±55.3 for the moderate intensity exercise, for the UBE and CMB conditions, respectively (Figure 6a). Post hoc analysis showed trends toward significance between conditions at each intensity with p values of 0.09 and 0.06 for the low and moderate intensities, respectively. The effect sizes across the low and moderate intensities were 0.48 and 0.47 in the UBE condition, respectively, and were 0.49 and 0.58 for low and moderate intensity in the CMB condition.

For peak SBF a significant interaction was once again observed. For the UBE condition peak SBF for the low and moderate intensity exercises were 38.8±17.3 and 44.4±24.6 PU. For the CMB condition SBF peak values of 122.7±124.7 and 121.3±93.0 PU were observed (Figure 6b). Post hoc analysis showed peak values for the CMB condition to be significantly greater than those observed in the UBE condition for the moderate intensity.
**Heart Rate**

Both the UBE and CMB conditions elicited significant increases in HR values from baseline values but no interaction was observed between conditions. Baseline values were 76±12 and 76±12 bpm for the UBE and CMB conditions. During the low intensity exercise, HR values significantly increased to 103±17 and 99±19 bpm for the UBE and CMB conditions. For the moderate intensities HR values were 115±15 and 110±18 bpm for the UBE and CMB conditions, respectively (Figure 7a).

**Mean Arterial Pressure**

Both conditions were shown to have significant increases in MAP from baseline values but no interaction was observed between conditions. For the UBE condition, MAP was 91.9±10.6 99.0±14.9 and 107.6±18.0 for baseline and the low and moderate intensity exercises. For the CMB condition, MAP was 93.2±11.8, 102.7±15.8 and 106.9±15.8 for baseline and the low and moderate intensity exercises. (Figure 7b).

**Oxy-Hemoglobin**

For oxygenated hemoglobin, there was no interaction between conditions and no significant changes from baseline values were observed during the exercise conditions. At baseline, Oxy values were 1.27±1.75 and 0.47±2.23 for the UBE and CMB conditions. During the low intensity exercise values decreased to -0.46±3.50 and -2.18±2.90 for the UBE and CMB conditions. During the moderate intensity exercise values were -1.98±4.03 and -2.07±3.25 for the UBE and CMB conditions. (Figure 8a)
**Total Hemoglobin**

For THeme there was no interaction observed between conditions and values obtained during the exercise bouts did not differ from baseline values in both conditions. For the UBE condition Theme was 1.05±2.27, -0.92±4.76 and -2.71±6.09 for baseline and the low and moderate intensities. For the CMB condition, THeme was 1.52±2.04, -1.92±3.12 and -1.61±4.30 for the baseline and low and moderate exercise intensities(Figure 8b).

**Normalized Total Hemoglobin Index**

For nTHI there was no interaction observed between conditions and values obtained during the exercise bouts did not differ from baseline values in both conditions. For the UBE condition nTHI was 1.07±0.11, 1.08±0.12 and 1.06±0.13 for baseline and the low and moderate intensities. For the CMB condition, nTHI was 1.04±0.08, 0.95±0.21 and 0.99±0.13 for the baseline and low and moderate exercise intensities. (Figure 8c).

**Discussion**

This pilot study examined the effectiveness of upper body exercise alone and in combination with passive limb movement to illicit hemodynamic changes in the lower limbs of paraplegics. Specifically, we examined whether these protocols could increase blood flow to the paralyzed limb in an attempt to promote vascular health and tissue perfusion. While neither condition resulted in statistically significant increases in FABF
and SBF across both the low and moderate intensity conditions there may be a clinically significant increase. The average percent increase in FABF was 42% in the upper body exercise condition and 28% in the combination condition. In this pilot study we have not observed an increase in averaged blood flow values with either modality, however, post-hoc power analysis showed inclusion of 4 more subjects will allow for statistical significance to be achieved. These data contradict with our hypothesis as both the upper body and combination conditions did not increase FABF to the lower limbs and the magnitude of the response was not greater in the combination condition compared to the upper body condition. In actuality, the addition of PLM to the upper body exercise resulted in lower increases in FABF. However, due to the clinical application of the results, these modalities could have profound to illicit hyperemic responses, promote skin blood.

**Physiological Responses**

Previous studies that have examined the ability of upper body exercise to increase femoral artery blood flow in the paraplegic population have produced conflicting results with studies showing increases (Bidart & Maury, 1973), no change (Hopman et al., 1994; Hopman et al., 1996; Kinzer & Convertino, 1989) or decreases (Burkett et al., 1988). The results of this study shows that the average blood flow values were not significantly greater than baseline values but the peak blood flow values were which could have a profound clinical significance. Additionally, as this is only a pilot study, post-hoc power analysis revealed statistical significance could be achieved with the inclusion of more
subjects. In this study 6 of the participants showed large increases in FABF but the other 2 showed little increase or a decrease in FABF. For the 6 subjects who showed an increase they had an average increase of 55% for the UBE condition and 60% increase for the CMB condition. This is in contrast to the other two subjects who, on average, had almost no change in FABF. Not achieving statistical significance with such a robust increase in FABF was likely due to variability between subjects and these modalities should not be written off as effective means to increase FABF in this population. While the average FABF across the 5 minutes of exercise did not show statistically significant increases, when the peak 15 seconds were analyzed a significant increase was observed. For the UB condition the average peak FABF was a 71% increase and for the CMB protocol an average increase of 84% from baseline values were observed.

The increase HR and cardiac output initiated by the UBE results in increased blood flow to the lower limbs most likely the result of the inability to properly vasoconstrict the vasculature below the level of the lesion. While this collateral increase in FABF may limit exercise tolerance of the upper body due to reduced blood flow to that area, it may prove beneficial for maintaining vascular and tissue health in the paralyzed lower limbs. Previous investigations have shown that 6 weeks post SCI the common femoral artery (CFA) can have radial reductions up to 25% (de Groot et al., 2006) and one year post SCI this reduction can escalate up to 50% (Boot et al., 2002). In conjunction with the decreased radial diameter of the CFA, it has also been reported that a 45% reduction in cross sectional area of the quadriceps femoris can be observed within
just 6 weeks of incurring an SCI. It is unclear whether the reduction in CFA diameter causes the reduction in thigh volume or vice versa (Olive et al., 2003) however, a hypothesis is that a sustained increased in FABF could provide the needed stimulus to limit these reductions via increased sheer stress (Green, 2009), and ultimately improve endothelial function and increase capillary density (Robbins et al., 2011). This physiological stimulus could slow the rate of decline in CFA arterial diameter and muscular atrophy or at least lessen the overall magnitude of these detriments.

The results of the present study showed a significant impact in skin blood flow for both the UBE and CMB protocols, with greater increases being observed in the CMB protocol when looking at the peak 15 average. One of the most common medical complications in the SCI population is the development of pressure ulcers with a lifetime incidence rate of 85% with 7-8% dying from pressure ulcers related complications (Devivo, 2012). The formation of pressure ulcers are a direct result of constant external pressure over the surface of the skin, leading to a reduction in blood flow to the tissue resulting in ischemia and if unresolved, tissue necrosis (Hoff et al., 2012). Across both exercise conditions and exercise intensities increases in SBF in the rectus femoris ranged from 63% increase all the way up to 220% increase over the 5 minute averages. These substantial increases in skin perfusion could prove valuable in increasing oxygen delivery to the skin therefore reducing the ability for a hypoxic state to develop and thus maintain skin tissue health. While these results are promising, the present study measured SBF on the thigh while pressure ulcers most commonly form in areas that are exposed to constant
pressure and bony prominences such as the ischial and sacral regions (Garber et al., 2000; Rabadi & Vincent, 2011). However, the present study does provide proof of concept but future investigations are needed to evaluate changes in SBF of the most commonly affected areas for pressure ulcers in the SCI population.

While the results of the present study showed increases in peak FABF and SBF there was not a significant increase in superficial thigh muscle tissue perfusion in the rectus femoris. While in a seated position, usually in their wheelchair, persons with a SCI have increased venous pooling in the lower limbs (Claydon et al., 2005; Kinzer & Convertino, 1989). During the UBE and CMB protocols the rectus femoris leg muscle does not experience any changes in metabolism and therefore has no demand for increased blood flow. Since no changes in thigh muscle tissue perfusion were observed in this study but increases in FABF were observed it can be extrapolated that in addition to the increase in arterial blood flow there was also an increase in venous return from these muscle groups as they showed no changes in blood volume or hemoglobin content during the modalities. However, the results of this study cannot be compared to the Claydon and Kizner articles as they measured venous pooling by strain gauge plethysmography and therefore increased limb volume and not blood characteristics within the muscle tissue as the present studied employed. In addition, the subjects in the current study were in an upright seated position for 20-30 minutes prior to the start of data collection and remained in this position for the duration of the experimental
protocol. Thusly, venous pooling could be present but not properly measured since we didn’t measure changes in tissue perfusion in the supine and seated positions.

While no interaction occurred with HR between the UBE and CMB conditions, it appears that the addition of PLM resulted in a lower HR ($p=0.11$) when working at the same exercise workload. The addition of the PLM protocol may have facilitated venous return of blood flow to the heart via rhythmic action of the skeletal muscle pump resulting in an increased stroke volume and a lesser demand on heart rate to maintain the same cardiac output (Casey & Hart, 2008). It has been noted that paraplegics can have a reduced maximal exercise capacity for UBE exercise compared to the able-bodied population due to venous pooling in the lower limbs (Hoffman, 1986; Van Loan, McCluer, Loftin, & Boileau, 1987). The addition of PLM during UBE may facilitate a higher max cardiac output and increased exercise tolerance, especially if the modality was applied bi-laterally as the current study only performed PLM on a single limb.

**Combination Protocol**

Recent investigations has shown that in the able-bodied population (McDaniel, Fjeldstad, et al., 2010; McDaniel, Hayman, et al., 2010; Trinity et al., 2015; Trinity et al., 2011) and in the SCI population (Venturelli et al., 2014; Venturelli et al., 2012) the application of a PLM results in a robust, yet transient increase in FABF peaking within about 15 seconds after the initiation of PLM and lasting only approximately 45 seconds before returning to baseline. Based upon this evidence, it was believed the combination
of the UBE and PLM would result in greater FABF compared to when UBE was used in isolation. While the peak flow values showed an interaction between the UB and CMB conditions the FABF values averaged over the 5 minute exercise intensities did not differ between conditions. The studies by Venturelli hypothesized the increase in FABF observed when the PLM protocol was applied to the SCI population was due to mechanical distortion of the arteriole network, nitric oxide based vasodilation and skeletal muscle pump activity. Taken together these lower blood flow resistance and promote venous return for an increased stroke volume and cardiac output. In our model, PLM was used on top of UBE and as a result many of the physiological results observed when PLM is applied in a resting condition could have been overshadowed by the physiological mechanisms resulting in the increased FABF for the UB condition. The UB condition provided significant stimulus to increase heart rate, and presumably stroke volume and cardiac output, and when the PLM protocol was implemented in conjunction with UB there was not a summation of physiological responses but non-compounding phenomenon where there is no additive effect of using PLM on top of UBE to increase FABF. In addition, we employed five minute averages to determine a longer term effectiveness of the protocols to elicit increases in FABF, while increases in FABF could still have been present this method may have statistically washed out any of these increases. Also, by using 5 minute averages included periods without PLM, the positive hyperemic effect of PLM could have been washed out as well.
Level of Injury

While previous studies have sought to examine if UBE could increase FABF in this population there has been conflicting results. Previous studies have shown UBE to have no impact lower limb blood flow (Hopman et al., 1994; Hopman et al., 1996; Kinzer & Convertino, 1989) while other studies have reported that UBE can increase lower limb blood flow (Bidart & Maury, 1973) or split results showing some subjects to have an increase and others to have a decrease (Burkett et al., 1988). All of these studies used a wide range of SCI injury and did not account for the possibility of remaining ANS activity in the presence of muscles that are devoid of motor or sensory ability. By having a range of injury from the 3rd to the 11th thoracic vertebrae all of these subjects had complete neural innervation of the heart and had normal heart rate responses during exercise. By using only ASIA grade A paraplegics there is no impact from any remaining motor or sensory functions (Kirshblum et al., 2011) which lead to variation within the results.

Autonomic Function Assessment

Out of the 9 subjects recruited for this experiment only 2 had remaining autonomic function in their lower limbs as shown by the SSR test. As one of these two was also a subject in which blood flow values could not be properly analyzed there was insufficient data to separate out the subjects into those with and those without autonomic functions in their lower limbs. Future studies should try to employ groups of equal sizes
of paraplegics in both of these categories to try and quantify blood flow responses to upper body exercises.

**Conclusion**

The present study showed that UBE resulted in clinically significant increases in FABF and robust statistically significant increase SBF during low and moderate intensity exercise in a paraplegic population that was devoid of all motor and sensory function below the level of injury. The addition of PLM to the UBE protocol resulted in increased peak values of FABF and SBF but not in values averaged across the duration of the exercise intensities. As a result, UBE exercise when used alone and in combination with PLM resulted in increases FABF and SBF with higher peak averages being obtained when UBE and PLM were used in combination.
CHAPTER VI

SUMMARY

To our knowledge, no studies have investigated the effects of repeated bouts of PLM interspaced with recovery periods and upper body exercise used in combination with PLM to increase lower limb blood flow in paraplegics. The purpose of the present study was to determine if these modalities could elicit significant hyperemic responses which could aid in maintain vascular health in this population.

We reported that when PLM is interspaced with 1 minute recovery between bouts a significant increase in femoral artery blood flow and skin blood flow was observed in nearly every bout. These increases were obtained without increases in heart rate and mean arterial pressure meaning the responses were completely peripheral in nature with no influence from the central regulators of blood flow. While the increase in femoral blood flow seemed to be consistent between bouts, the increase in skin blood flow seemed to have a compounding effect with a large increase induced with each subsequent bout of PLM.

The present study also showed that upper body exercise when used in isolation and in combination with PLM did not result in statistically significant increases in femoral blood flow across the 5 minutes of each exercise intensity. While both conditions resulted in peak blood flow measurements that were higher than baseline values, the average increase was non-significant.
With these results in hand, it appears PLM when used in isolation has the ability to increase lower limb blood flow in the paraplegic population. Future research should be conducted to determine if this modality when utilized longitudinally as a rehabilitation tool results in an increase vascular and tissue health in this population. In addition, all the manipulations used in the current study resulted in significant increases in skin blood flow which could have a profound impact in the paraplegic population as pressure ulcers are a constant and severe medical complication.
Figure 1 The average (A) and peak (B) femoral blood flow values at baseline across the 5 bouts of PLM and the overall average value.

* Denotes a significant increase (p<.05) from the baseline value.
Figure 2 The average (A) and peak (B) skin blood flow values at baseline across the 5 bouts of PLM and the overall average value.

* Denotes a significant increase from the baseline value.
Figure 3 The heart rate (A) and mean atrial pressure (B) values at baseline across the 5 bouts of PLM and the overall average value.

No statistical increases from the baseline values were observed across all time points.
Figure 4 Changes in oxygenated hemoglobin (A), total hemoglobin (B) and relative blood volume (C) values at baseline across the 5 bouts of PLM and the overall average value.

* Denotes a significant decrease from the baseline value, # Denotes a trend towards a decrease from the baseline value.
Figures 5 The changes in FABF during the low and moderate intensity exercises for the UB and CMB conditions.

A significant interaction was detected for Peak Blood Flow. *Denotes significant increase from baseline for both conditions.
Figures 6 The changes in SBF during the low and moderate intensity exercises for the UB and CMB conditions.

A significant interaction was detected for both the Average Blood Flows and the Peak Blood Flows. *Denotes significant increase from baseline for both conditions. #Denotes CMB was significantly greater and then UB condition for that intensity.
Figure 7 Changes in HR during the low and moderate exercises for the UB and CMB conditions.

Figure 3b shows the changes in MAP during the low and moderate exercises for the UB and CMB conditions. *Denotes significant increase from baseline for both conditions.
Figure 8 Shows the changes in muscle oxygenated hemoglobin (Oxy), total hemoglobin (THeme) and blood volume (nTHI) across both exercise intensities for both conditions.
Table 1 *The physical and injury characteristics*

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<th>Subject</th>
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<th>BMI</th>
<th>Age</th>
<th>Post Injury</th>
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<td>A</td>
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<td>29</td>
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<td>27</td>
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<tr>
<td>Average</td>
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<td>-</td>
<td>-</td>
<td>27±5</td>
<td>48±6</td>
<td>17±12</td>
</tr>
</tbody>
</table>
APPENDICES
APPENDIX A

ASIA FORM
Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position.

5 = (normal) active movement, full ROM against gravity and full resistance in a muscle specific position expected from an otherwise unimpaired person.

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disease) were not present.

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50% of the range of motion).

ASIA Impairment (AIS) Scale

☐ A = Complete. No sensory or motor function is preserved in the sacral segments S4-S5.

☐ B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5, or deep anal pressure) and some motor function is preserved more than three levels below the motor level on either side of the body.

☐ C = Motor Incomplete. Motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury (NLI) are a muscle grade less than 3 (Grade 0-2). All below the NLI have a muscle grade of 3.

☐ D = Motor Incomplete. Motor function is preserved below the neurological level, and at least half (half or more) of key muscle functions below the NLI have a muscle grade of 3.

☐ E = Normal. If sensation and motor function is tested with the 5 sensory tests in all segments, and the patient has no deficit, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

**For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary and sphincter contraction or (2) intact sensory sparing with remaining function more than four levels below the motor level for that side of the body. The standards at this time allow ten-total muscle function more than five levels below the motor level to be usable in determining motor incomplete status (AIS B vs. C).

Steps in Classification

1. Determine sensory levels for right and left sides.

2. Determine motor levels for right and left sides.

3. Determine single neurological level.

4. Determine whether the injury is Complete or Incomplete.

5. Determine ASIA Impairment Scale (AIS) Grade.

Is injury motor Incomplete?

If YES, AIS=C and can record ZPP (bodily sensations or sensations on each side with some preservation)

Are at least half of the key muscles below the single neurological level graded 3 or better?

If NO, AIS=D

If YES, AIS=B and can record symptom level. (motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

NT is not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50% of the range of motion).
APPENDIX B

ASIA AUTONOMIC FUNCTION FORM
### Appendix B

**ASIA Autonomic Assessment Form**

#### General Autonomic Function

<table>
<thead>
<tr>
<th>System/Organ</th>
<th>Findings</th>
<th>Abnormal conditions</th>
<th>Check mark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic control of the heart</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Bradycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Other dysrhythmias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unable to assess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic control of blood pressure</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Resting systolic blood pressure below 80 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Autonomic dysreflexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unable to assess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic control of sweating</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Hyperhidrosis above lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Hyperhidrosis below lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Unable to assess</td>
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<tr>
<td>Temperature regulations</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Hyperthermia</td>
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</tr>
<tr>
<td></td>
<td>Unknown</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Unable to assess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic and Somatic Control of Broncho-pulmonary System</td>
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</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Unable to voluntarily breathe requiring full ventilatory support</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Impaired voluntary breathing requiring partial ventilatory support</td>
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<tr>
<td></td>
<td>Abnormal</td>
<td>Voluntary respiration impaired does not require ventilatory support</td>
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<tr>
<td></td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unable to assess</td>
<td></td>
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</tr>
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#### Lower Urinary Tract, Bowel and Sexual Function

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<tr>
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<th>Score</th>
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<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>Awareness of the need to empty the bladder</td>
<td></td>
</tr>
<tr>
<td>Ability to prevent leakage (continence)</td>
<td></td>
</tr>
<tr>
<td>Bladder emptying method (specify)</td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td></td>
</tr>
<tr>
<td>Sensation of need for a bowel movement</td>
<td></td>
</tr>
<tr>
<td>Ability to Prevent Stool Leakage (continence)</td>
<td></td>
</tr>
<tr>
<td>Voluntary sphincter contraction</td>
<td></td>
</tr>
<tr>
<td>Sexual Function</td>
<td></td>
</tr>
<tr>
<td>Genital arousal (erection or lubrication)</td>
<td>Psychogenic Reflex</td>
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<tr>
<td>Orgasm</td>
<td></td>
</tr>
<tr>
<td>Ejaculation (male only)</td>
<td></td>
</tr>
<tr>
<td>Sensation of Menses (female only)</td>
<td></td>
</tr>
</tbody>
</table>

2—Normal function, 1—Reduced or Altered Neurological Function
0—Complete loss of control, NT—Unable to assess due to preexisting or concomitant problems

Date of Injury: __________________ Date of Assessment: __________________

This form may be freely copied and reproduced but not modified.
This assessment should use the terminology found in the International SCI Data Set (ASIA and ISCoS - http://www.iscos.org.uk)

Examiner: __________________
APPENDIX C

SUPPLEMENTAL REVIEW OF LITERATURE
Appendix C

Supplemental Review of Literature

A. Upper Body Exercise

The use of arm cycle exercise in the SCI population is very prevalent and has numerous potential health benefits. However, there are differences in the physiologic responses to upper body exercise compared to lower body exercise at maximal and submaximal workloads.

Submaximal Exercise

At the same absolute workload above 25 watts VO2, heart rate, cardiac output and perceived exertion has been shown to be higher using an arm ergometer compared to a leg ergometer resulting in a less efficient exercise modality(Kang, Chaloupka, Mastrangelo, & Angelucci, 1999). In addition, at the same work rates arm ergometry has been shown have higher blood pressure, ventilation and blood lactate response. The increased physiologic stress of upper body exercise may be due in to a slower kinetics of oxidative metabolism leading to increased rates of glycolysis and subsequent higher values lactic acid and ventilation (Pendergast, Bushnell, Wilson, & Cerretelli, 1989) and increased sympathetic nervous system activation(Freeman, 2006)
**Maximal Exercise**

During a VO$_2$Peak protocol using an arm ergometer there peak values of cardiac output and heart rate will be less compared to when using leg ergometry (Toner, Sawka, Levine, & Pandolf, 1983). A VO$_2$Peak protocol with an arm ergometer will result in values of approximately only 70% of the values obtained during a VO$_2$Peak protocol using leg ergometry (Pendergast et al., 1989; Sawka, Foley, Pimental, Toner, & Pandolf, 1983). During VO$_2$Max testing using upper body exercises the limiting factors to performance are different compared to the limiting factors during lower body exercises. For lower body exercise the limits to VO$_2$Max are controlled to extrinsic factors to the muscle. The large amount of muscle mass needed to complete the exercise results in a physiologic state in which VO$_2$Max is limited by the ability of the cardiorespiratory system to deliver oxygen to the working muscles and it not limited by the ability of the working muscle to utilize oxygen (Bassett & Howley, 2000; Saltin & Calbet, 2006). However, during exercises in which only small muscle mass is require, such as single leg cycling and arm ergometry the limits to performance are intense in nature. During VO2Max tests employing an arm ergometer is expected to have lower max cardiac output, heart rate, stroke volume and absolute work rate achieved compared to lower body exercise (Miles, Cox, & Bomze, 1989). This reduced central stress can also be used to explain the faster heart rate recovery seen in upper body exercises compared to lower body exercises in after both maximal and submaximal testing (Ranadive et al., 2011).
B. Blood Flow Regulation During Exercise

To ensure adequate blood flow during exercise there is integration of numerous physiologic systems resulting in an adequate rise in blood flow to the active muscle to ensure proper nutrient delivery and removal metabolic byproducts. These physiologic systems responsible for blood flow regulation during exercise are both central and peripheral in nature and include cardio-acceleration as a result of muscle chemoreceptor and mechanoreceptor feedback (Adreani, Hill, & Kaufman, 1997; Adreani & Kaufman, 1998; Herr, Imadojemu, Kunselman, & Sinoway, 1999) flow-mediated dilation (Kooijman et al., 2008; Pohl, Holtz, Busse, & Bassenge, 1986) mechanical distortion of the arterioles (Segal, 2000), mechanically induced vasodilation (Clifford et al., 2006; Kirby, Carlson, Markwald, Voyles, & Dineno, 2007; Tschakovsky & Sheriff, 2004), the skeletal muscle pump (Laughlin, 1987; Sheriff, Rowell, & Scher, 1993), reduced parasympathetic nervous system tone and increased sympathetic nervous system activation (Joyner, Nauss, Warner, & Warner, 1992).

In an able-bodied individual the initiation of exercise causes a reduction in parasympathetic nervous system (PNS) a activation of the sympathetic nervous system (SNS) causing the release of catecholamines which attach to alpha and beta receptors on the smooth muscle of blood vessel and the heart, respectively, causing systemic vasoconstriction as well as increases in heart rate, cardiac output and blood
pressure (Freeman, 2006). However, active skeletal muscle needs a constant and adequate supply of blood to ensure for proper delivery of nutrients and removal of waste and vasoconstriction of the arteries feeding these active muscles would be counter-production. The body ensures the proper blood flow to working muscles by creating a paradox where the systemic vasoconstriction is overridden in the active skeletal muscle resulting in vasodilation and adequate blood flood.

It was once believed that the active skeletal muscle stopped receiving sympathetic nervous system signals and that is what resulted in the local vasodilation, however, a study by Joyner et al. (Joyner et al., 1992) showed that the active skeletal muscle still received neural input from the SNS but that vasoconstriction of the SNS was overridden by local factors, primarily metabolic byproducts of muscle contraction. The resulting functional sympatholysis (Buckwalter & Clifford, 2001) of the active skeletal muscle ensures proper blood flow to the active skeletal muscle. The metabolic byproducts that commonly are attributed to this vasodilating response are increased lactic acid, increased ADP, increase PCO2, decreased PO2, increased bradykinin, increased nitric oxide production and attenuation of alpha receptors and p2x purinoreceptors (Buckwalter & Clifford, 2001).

During upper arm ergometry it is expected that the systemic vasoconstriction will result in the reduction of blood flow to the lower limbs via the femoral artery and redistribute that blood to the upper body to be used in ensure proper delivery or nutrients.
and removal of waste to the active muscles. However, persons with a SCI above twelfth thoracic vertebrae (t-12) do not have SNS innervation of the lower limbs. During upper body exercises this removal of SNS innervation could result inability for the blood vessels in the lower limbs to vasoconstrict and ensure proper blood redistribution to the working muscles of the upper limbs. This could be a possible physiologic mechanism resulting in the decreased exercise capacity seen in this population (Schneider, Sedlock, Gass, & Gass, 1999). Mentioned previously, several studies have looked blood flow responses to the lower limbs in SCI patients during upper body exercise and have produced confliction results. Additional research is needed to clear up this topic of blood flow redistribution during exercise in the SCI population.

C. Passive Limb Movement

Recently, the use of passive limb movement (PLM) to induce a transient hyperemic response in the limb being moved elicited numerous scientific studies. Numerous studies have shown the ability of passive limb movement of the knee to increase femoral artery blood flow for a transient period of time in able-bodied persons (McDaniel, Fjeldstad, et al., 2010; Wray, Donato, Uberoi, Merlone, & Richardson, 2005) diseased (M.A. Hayman et al., 2010; Venturelli et al., 2013) and aging populations(McDaniel, Hayman, et al., 2010). However, a single continuous bout of passive limb movement only sees increases in blood flow for less than one minute before returning to baseline values.
Central and Peripheral Factors to PLM

The central factors that are responsible for the increase in blood flow to the moving limb in response to PLM are CO, HR, SV and MAP. Without any neural drive or production of metabolic byproducts in response to PLM there is no influence from the higher cardio control centers of the body. As for the peripheral factors they include mechanoreceptors, skeletal muscle pump, vascular distortion, limb blood flow and limb vascular conductance.

Several studies have attempted to differentiate the central and peripheral responses resulting in limb hyperemia induced by PLM. By using populations in which the central or peripheral factors responsible for the hyperemic response may compromised the influences of both the central and peripheral factors can be established. A study by Hayman et al (M.A. Hayman et al., 2010) used a heart transplant population which results in heart denervation where both afferent and efferent cardiac control mechanisms are interrupted to look at the influences of only the peripheral factors in response to PLM. The results of the studied showed persons who underwent a heart transplant had a reduced sensitivity to PLM. There was an increase in limb blood flow but not to the extent of the able-bodied population. This was primarily due to no increase in heart rate, the first response to PLM in the able-bodied population, for the duration of the protocol. Any increase in CO was solely in response to SV as a result of increased venous return.
via the skeletal muscle pump. While the hyperemic response in the heart transplant population was not to the extent of the able-bodied population it did show PLM can still invoke a hyperemic response in the absence of central factors aiding to the increased blood flow.

Additionally, studies using a spinal cord population have sought to establish the influence of the peripheral factors during PLM. A study by Venturelli et al. (Venturelli et al., 2013) showed that in response to PLM persons with an SCI did show increases in limb blood flow but no changes in CO, HR and SV. Without afferent signaling induced by the activation of type-III mechanoreceptors there was no signal to increase HR. However, the activation of the skeletal muscle pump still elicited increased blood flow independent of activation of type-III mechanoreceptors.

Sequence of Events Resulting in Hyperemia During PLM

At the onset of PLM the mechanical distortion of the moving muscle results in the activation of type-III muscle sensory neurons which feedback to the cardiovascular control center (Trinity et al., 2011) to increase HR and consequently increase CO (de Wilde, Geerts, Cui, Van Den Berg, & Jansen, 2009). This then causes the increase in limb hyperemia with five seconds of starting PLM and is a result of a combination of the increased CO and increased vascular conductance (McDaniel, Fjeldstad, et al., 2010). Approximately 10-12 seconds after starting PLM there is secondary increase in CO due to an increase in stroke volume with little to no increase in mean arterial pressure. This
lag in increases in SV may be a result of the absence of the global vasoconstriction seen during active movement. Without the global vasoconstriction there is no rise in blood pressure to facilitate venous return and right atrium filling. In the case of PLM, increased venous filling and subsequent increased stroke volume may be delayed because the increased blood flow to the limb undergoing PLM must travel through the arterial and venous system in response of the rhythmic movement and the resulting effects of the skeletal muscle pump before increasing venous return to the right atrium. With PLM there is an overall increase blood flow because of increases in both antegrade and retrograde blood flow, with the increases in antegrade blood flow much greater than the increase in retrograde (McDaniel, Fjeldstad, et al., 2010). Within 60 seconds of starting PLM the net blood flow values (Antegrade-Retrograde) return to baseline values. However, the absolute value of both antegrade and retrograde are still higher than baseline values. While net blood flow to the limb undergoing PLM maybe the same 60 seconds into PLM compared to baseline values the absolute increases antegrade and retrograde blood flow may still be physiologically beneficial. The increased antegrade and retrograde blood flow results in an increased shear rate against the lining of the artery and may elicit vascular remodeling and greater vascular health (Green, 2009; Tinken et al., 2010).
Transient Nature of Response

Within 60 seconds of the start of PLM many of the physiologic changes that resulted increases in blood flow for approximately 30-40 seconds have become attenuated and blood flow values return to baseline values (McDaniel, Fjeldstad, et al., 2010). With PLM there is neither increased skeletal muscle metabolism nor descending motor command signals (González-Alonso et al., 2008; Hellsten et al., 2008) needed to elicit metaboreceptor afferent signals typical in active exercise to ensure proper blood flow. It is probable that without these two mechanisms in combination the attenuation of type-III mechanoreceptors (Baum, Selle, Leyk, & Essfeld, 1995) facilities in the drop in HR, CO and SV to baseline levels shortly followed by the concomitant drop in blood flow to baseline values (McDaniel, Hayman, et al., 2010). While a single bout of continuous PLM have been shown to have a transient response due to the attenuation of type-III mechanoreceptors there are no current studies looking at the effects of repeated bouts of PLM with rest to allow for the “resetting” of type-III mechanoreceptors and bypassing the attenuation response resulting in prolonged durations of increase in blood flow of greater than one minute.
APPENDIX D

AUTONOMIC TRACT BUNDLES
Appendix D

Autonomic Tract Bundles

Source: Adams Medical Images
APPENDIX E

MEDICAL HISTORY FORM
Appendix E

Medical History Form

Subject #__________________  Date___/___/____

Name__________________________________________________________

Address____________________________________________________________________________

Phone Number____________________________________________________

Age_______ (must be 18)  DOB_____/_____/_____  Sex  m  f

Height _______ in  Wt _______ lbs

Height _______ cm (inches *2.54)   Wt _______ kg (lbs/2.2)   BMI

____ kg/m^2

Which ethnic group do you most identify with (circle response):

American Indian or Alaskan Native  Asian or Pacific Islander  Black, not of Hispanic Origin

Hispanic  White, not of Hispanic Origin

Other__________________________

Y/N

____ Has a doctor ever said that your blood pressure was too high or too low?

____ Have you ever had pain in their heart or chest?

____ Have you ever notice extra heart beats, skipped beats or a racing heart?

____ Has a doctor ever said that you have heart trouble, an abnormal electrocardiogram (ECG or EKG), heart attack, or coronary?

____ Do you often have trouble breathing?

____ Have you ever been diagnosed with asthma?

____ Have you ever been diagnosed with diabetes?
Do you have any orthopedic limitations to physical activity?

Do you have any other medical conditions other than SCI that affect your ability to safely participate in physical activity? If yes, explain.

________________________________________________________

________________________________________________________

Time post SCI injury?____________________

Are you currently taking any medication(s)? Y N
If yes, please list the medication(s)_______________________________________

________________________________________________________

________________________________________________________

Do you exercise regularly? Y N
If yes, what types of exercise and how many times per week?

________________________________________________________

Do you have any questions?

Does the subject seem eligible? Y N

Date of first appointment: _________________________________
REFERENCES
REFERENCES


*Spinal Cord, 36*(1).


alpha 2 subunit isoform of Na+/K (+)-ATPase. Molecular Pharmacology, 43(6), 833-837.


