BILATERAL DIFFERENCES IN LEG PERFORMANCE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

IMPLICATIONS FOR FATIGUE AND FUNCTION

by

REBECCA DANTI LARSON

(Under the Direction of Lesley J. White)

ABSTRACT

It is well recognized that Multiple Sclerosis (MS) can affect sides of the body asymmetrically, specifically the lower extremities; yet these disparities have not been systematically examined. **PUPROSE:** To determine whether ambulatory individuals with mild MS would display bilateral differences in physiological and functional measures during exercise and whether these differences contribute to premature muscle fatigue. **Methods.** Eight individuals with relapsing remitting MS (MS) and seven non-MS individuals (controls), similar in physical characteristics completed three series of unilateral cycling tests. Participant's legs were categorized into either stronger/less affected or weaker/more affected based on strength testing. To determine interlimb asymmetries, comparisons of submaximal fixed load ride times, VO_2peak, and peak workload were performed. Unilateral exercise was performed to determine any pre-post differences in strength, mobility, and foot tap speed. Data were analyzed using paired t-tests for between-leg comparisons and independent t-tests for group differences**.** **RESULTS:** Individuals with MS exhibited significant differences ($P < 0.05$) in: strength

(stronger leg: 95.31 ± 27.94 (lbs), weaker leg: 76.98 ± 19.60 (lbs)), submaximal fixed load ride time (stronger leg: 4.83 ± 0.33, weaker leg: 3.44 ± 1.51 min), peak oxygen uptake (stronger leg: 13.7 ± 3.2, weaker leg: 10.6 ± 3.0 ml/kg/min) and workload (watts) (stronger leg: 73.4 ± 22.3, weaker leg: 56.3 ± 26.2 watts) with no differences observed in the control group ($P > 0.05$). Significant differences ($P < 0.05$) were observed across groups for stride velocity and strength asymmetry ratios prior to unilateral exercise. Following exercise, the magnitude of asymmetry was reduced in the individuals with MS such that no differences were observed, whereas stride velocity remained slower. **CONCLUSION:** Ambulatory individuals with MS displayed leg asymmetry not observed in our control participants. Following unilateral exercise the MS group's strength asymmetry scores were no longer statistically different compared to controls and the MS individuals exhibited significant reductions in stride velocity and foot tap speed. These findings provide possible insight into the consequences of fatigue on lower extremity asymmetry and function and the need for new therapeutic interventions.

INDEX WORDS: Multiple Sclerosis, Bilateral, Asymmetry, Fatigue, Function, Strength, Mobility

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DEDICATION

I dedicate my dissertation to my parents, in-laws, and my loving husband.

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CHAPTER 1

INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive and degenerative autoimmune disease of the central nervous system (CNS) characterized by demyelination (1) and axonal deterioration (2). Common symptoms of MS include abnormal gait, deficient balance, muscle weakness, spasticity, and fatigue, all of which can reduce physical function and exercise capacity in a deleterious cycle profoundly impacting health and quality of life (1).

Fatigue impacts 85-95% of people with MS and is often “invisible”, yet it can be the most debilitating aspect of the disease. Fatigue has been defined as “a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with activities of daily living” (3). Fatigue can be caused by a variety of sources/mechanisms which can be separated into two broad categories; primary or secondary. Primary fatigue refers to factors associated directly with disease processes. For example, primary fatigue can be caused by inflammatory cytokines, demyelination, axonal loss and neuroendocrine abnormalities (4). Secondary fatigue has been associated with consequences from primary fatigue and may include lack of conditioning, depression, and medication side effects (4). Fatigue caused by primary and/or secondary factors has sometimes been referred to as symptomatic fatigue to distinguish it from muscular fatigue, but the relationship between symptomatic and muscular fatigue is complicated because of overlapping influences.

Skeletal muscle fatigue has been defined as a “failure to maintain the required or expected force” following repeated activity of that muscle (5). The mechanisms for the loss of maximum force production in individuals with MS have been described as being caused by central and/or peripheral impairments. The central component of muscular fatigue is represented by higher systems of control having either supraspinal or spinal contributions and refers to the decline in efferent motor outflow (neural drive) to the muscle, resulting in activation failure, reduced muscle recruitment (6), and/or delayed neural transmission (7,8). The peripheral component of muscular fatigue refers to fatigue of the force-generating mechanism within the muscle related to metabolic characteristics (9-12), alterations in skeletal muscle cross-bridge mechanics, (13) and/or autonomic dysfunction (14-22). While skeletal muscle fatigue is a common problem that limits function in people with MS, the exact pathophysiology remains unclear as well as how it interacts with the more global feelings of fatigue associated with MS.

Potential mechanisms for muscle fatigue which have not been fully explored in this population include an imbalance in skeletal muscle oxygen delivery and extraction. Under normal submaximal conditions, muscle oxygen supply and demand adjust to meet the energy needs of an activity. However, at the onset of exercise there is a delay in oxygen supply such that people experience an accumulated oxygen deficit (23). Increased oxygen deficit (slower oxygen uptake kinetics) causes the muscle to rely on anaerobic processes causing phosphocreatine (PCr) concentration and muscle glycogen stores to be used to support energy demands. The use of anaerobic metabolic pathways causes accumulation of muscle metabolites that have been associated with muscle fatigue (H^+, ADP, and Pi) (24). A mismatch between muscle oxygen delivery and extraction

may further contribute to premature muscle fatigue thus reducing exercise capacity (25-28). A reduction in exercise capacity typically leads to fitness decrements and an increasing sedentary lifestyle (26). Additionally, the accumulation of muscle metabolites associated with the reliance on anaerobic metabolism may contribute to excessive and premature muscular fatigue in individuals with MS. This could have important clinical significance as it may augment local muscle fatigue as well as the generalized feelings of fatigue which are the most common complaints in MS (29-32) that interfere with everyday activities (29-31).

Deconditioning as a result of cardiovascular function may also contribute to altered muscle function as evidenced by changes in muscle metabolism (lowering mitochondria and oxidative capacity) related to reduced muscle blood flow (33). Maintaining skeletal muscle blood flow is important as it is essential for both ambulatory and postural control (34). Furthermore, during activities of increasing intensity, a mismatch between oxygen supply and demand could contribute to a reduced exercise tolerance related to not only muscle fatigue, but also a more generalized feeling of fatigue (34). One source of blood flow abnormality can arise from autonomic nervous system dysfunction which manifests itself as orthostatic hypotension (35). Individuals with MS often exhibit autonomic dysfunction however the incidence of autonomic dysfunction in MS remains unclear with some researchers suggesting 18% while others report as much as 80% (14-22). Autonomic dysfunction could result in limited redistribution of blood flow that further contributes to abnormal muscle fatigue in individuals with MS. Other than the disruption of muscle oxygen delivery and extraction related to inappropriate

muscle blood flow, there also remains the possibility that neural factors may impact skeletal muscle function (activation).

Muscle contraction requires a complex sequence of central and peripheral activation processes such that any failure along the sequence could result in muscle fatigue or loss of force production. Research has provided some evidence that muscle activation failure may precipitate muscular fatigue in individuals with MS (11). Additionally, reduced efferent motor outflow "neural drive" has also been observed in people with MS during both voluntary and electrically stimulated isometric contractions of the ankle dorsiflexor muscles (36). These findings suggest that muscular fatigue might be a consequence of central impairment. However, the observation of abnormal calcium pumping along with decreases in PCr and pH suggests peripheral fatigue might originate from impaired excitation – contraction coupling and abnormal energy metabolism (37). This information suggests that muscle fatigue is also related to peripheral mechanisms rather than central limitations exclusively.

Another possible explanation of premature muscle fatigue could be related to the etiology of MS and that the disease often affects the body asymmetrically. People with MS who experience significant bilateral differences between sides of the body might find activities that are bilateral in nature i.e. walking and cycling difficult to perform. As a result, one limb may perform a compensatory role, contributing to premature muscle fatigue. Currently, there is little published literature quantifying bilateral differences and whether it contributes to reduced function and premature muscle fatigue. A case study by White and Dressendorfer reported bilateral differences in leg strength and maximal oxygen uptake in an individual with MS who exhibited left leg exercise induced

monoparesis (38). Chung and colleagues observed that individuals with MS had lower knee extension power and that the asymmetry between legs was greater when compared to controls (39). Despite these findings and the knowledge that MS can asymmetrically affect the body, disparities between limbs of the body have not been systematically examined and quantified. Therefore, an enhanced understanding of bilateral discrepancies in leg function and performance coupled with inappropriate skeletal muscle oxygen delivery and extraction might contribute to a more advanced understanding of muscular and overall feelings of fatigue that people with MS experience. This information remains unavailable and might later contribute to the development of effective rehabilitation strategies to attenuate fatigue and prevent premature disability.

Purposes

Considering fatigue is the one of the most disabling symptoms reported to reduce quality of life and physical functioning in people with MS the goal of this study was to explore whether individuals with MS exhibit asymmetrical differences in physiological and functional measures during submaximal and incremental exercises. Therefore, two experiments were conducted. The purpose of the first study was to establish whether people with MS exhibit asymmetry in skeletal muscle energy demands, strength and performance. The purpose of second study was to quantify bilateral differences (asymmetry) in muscle performance and function following unilateral fatiguing exercise in individuals with MS.

Hypotheses

The hypotheses for Study 1 are:

H1) Ambulatory individual with MS exhibit asymmetry in strength, oxygen uptake kinetics, oxygen consumption, and work performed between legs.

H0) Ambulatory individual with MS do not exhibit asymmetry in strength, oxygen uptake kinetics, oxygen consumption, and work performed between legs.

H2) Individuals with MS exhibit asymmetry in muscle oxygen delivery relative to extraction during exercise between legs.

H0) Individuals with MS do not exhibit asymmetry in muscle oxygen delivery relative to extraction during exercise between legs.

People with MS exhibit smaller muscle metabolic changes during exercise relative to non-MS individuals (36). During exercise, afferent nerve fibers are responsive to tension, temperature, and biochemical changes. These afferent fibers send impulses to the spinal cord which responds by modulating efferent signals to produced appropriate cardiovascular responses. Therefore, a blunted muscle afferent response might contribute to muscle fatigue due to the body's inability to respond appropriately. Additionally, deconditioning may also contribute to inappropriate metabolic responses to exercise as evidenced by changes in muscle metabolism and by reduced muscle blood flow (33). Therefore, during exercise the inability to properly modulate the cardiovascular response to exercise might translate into an abnormally slow increase in oxygen uptake both whole body and at the muscle level contributing to muscle fatigue.

The hypotheses for Study 2 are:

H1) Individuals with MS exhibit asymmetry in strength, stride velocity, and foot tap speed.

H0) Individuals with MS do not exhibit asymmetry strength, stride velocity, and foot tap speed.

H2) Unilateral exercise increases the magnitude of asymmetry between legs in strength, stride velocity, and foot tap speed.

H0) Unilateral exercise does not increase the magnitude of asymmetry between legs in strength, stride velocity, and foot tap speed.

Individuals with MS exhibit reduced neural drive (efferent neural outflow) to the muscle during exercise (12, 40). Bilateral differences in strength and function between limbs has been indentified in individuals with MS. The inability to equally activate lower body musculature will further contribute to muscle fatigue because of an unequal distribution in activation patterns causing a compensatory role in one limb contributing to early onset muscle fatigue.

Significance of the Study

Fatigue is a common complaint in those individuals with MS which leads to reduced physical activity and poor fitness in a deleterious cycle. Reduced daily activity predisposes people with MS to be at risk for other health conditions and also loss of independence. Presently the pathogenesis of muscular fatigue and exercise intolerance in MS remains unclear. Possible mechanisms involved in muscle fatigue that have not been adequately studied include bilateral differences in leg performance and oxygen consumption. This study will provide novel information regarding bilateral skeletal

muscle physiology and performance differences in individuals with MS. Study findings will help to establish new knowledge related to muscle fatigue in MS and contribute to optimizing patient care through prevention and rehabilitation programs allowing physicians and healthcare providers to prescribe exercise programs that have multi-dimensional health benefits.

CHAPTER 2

REVIEW OF THE RELATED LITERATURE

Multiple sclerosis (MS) is a progressive and degenerative autoimmune disease of the central nervous system (CNS) characterized by demyelination (1) and axonal deterioration (2). MS is a major cause of neurological disability in young adults (1) and is characterized by a variety of disabling symptoms including muscle weakness and fatigue, as well as deficient balance, spasticity, and autonomic dysfunction. Skeletal muscle weakness limits daily function and contributes to fatigue. The exact pathophysiology of fatigue remains unclear but has been described as the most disabling symptom for individuals with MS (1). This review of literature will describe the pathology/physiology of MS, disease patterns, and MS symptomology. A discussion of common mechanisms associated with skeletal muscle fatigue including abnormal cardiovascular reflexes as well as peripheral and central components will be presented. Lastly, additional factors that may play an important role in muscular fatigue in MS which include bilateral asymmetry of musculature, oxygen utilization, and oxygen extraction will be described.

Pathology of Multiple Sclerosis

Axons within the CNS are coated with an insulating fatty lipoprotein sheath called myelin, which functions to aid in the transmission of nerve impulses. This myelin coating is the most vulnerable target of attack during this disease. During periods of disease activity, white blood cells (leukocytes) are activated; a common immune system

mechanism referred to as an inflammatory response. In this disorder, neuronal damage follows the inflammatory response. Additionally, during an inflammatory episode, the myelin sheath can be damaged, resulting in slowed and/or blocked nerve impulse transmission. Inflammation can also damage the underlying axonal membrane; even killing glial cells, such as oligodendrocytes (41).

The destruction of axons typically follows a Wallerian degeneration pattern also known as orthograde degeneration. A possible theory for this pattern of degeneration is that the axons undergo apoptosis because of the reduced number of healthy oligodendrocytes which normally function to supply the axons with essential growth factors, such as Insulin-like Growth Factor-1 (IGF-1). Research findings using the animal model of MS, experimental autoimmune encephalitis (EAE), indicate that axons deprived of IGF-1 will eventually die (42).

Following inflammation and subsequent demyelination, several physiological adaptations may occur within the CNS. The neurons that are not damaged can resume proper function and some recovery/remyelination of the damaged areas (remission) may occur, usually in the early stages of the relapsing–remitting form of the disease (43). The demyelinated axons also may retain some ability to function despite myelin loss (43). Research suggests that the damaged axons can produce greater numbers of sodium channels as an adaptation to myelin loss (44). Sodium channels are integral in action potential propagation and increasing the number of sodium channels contributes to remission observed in MS (43). Additionally, oligodendrocytes can stimulate remyelination of damaged axons, although normal function often remains compromised (44). Scar tissue may also replace the myelin (44) and is the basis for the name Multiple

Sclerosis, as Sclerosis originally means scar forming, from the Greek skleros (hard). Scar tissue is also pathological, can block the formation of new myelin, and once axons have become scarred, neural function is generally compromised.

While the cause of MS remains unclear, increasing evidence suggests that the immune system plays a pivotal role disease onset and progression. T- cells and other immune effectors infiltrate the CNS and attack the nerve cells, degenerating myelin and causing axonal destruction (45). Degeneration of the CNS results in a variety of clinical signs and symptoms which include sensory and motor disturbances, depression, and fatigue, all of which may result in decreased functional capacity and quality of life.

Diagnosis and Patterns of Multiple Sclerosis

Diagnosis of MS is often challenging because there is no specific test, and the criteria that have been established that are somewhat subjective. The disease course of MS is often described by four diagnosed patterns, although the distinction of each pattern is difficult (43). The basic patterns in order of severity are: relapsing/remitting, primary progressive, secondary progressive and progressive relapsing (43).

Relapsing Remitting. The relapsing-remitting pattern is present in 85 percent of people with MS and is considered the classic form of the disease (43). It is characterized by relapses that are clearly distinguished from periods of remission (43). A relapse, also known as an “attack”, “exacerbation” or “flares”, is a clinically significant event (meaning that is has outward signs and/or symptoms caused by an MS lesion on the brain or spinal cord). Typically, an attack is either the worsening or appearance of new symptoms (43). The periods between the relapses (remission) are characterized by a lack of outward disease progression (43). However, there is much information to suggest that

the disease progression may be silent, meaning that deterioration may be occurring without outward clinical symptoms (43).

Primary Progressive. The primary progressive form of MS is observed in approximately 10 percent of people with MS (43) and shows a nearly continuous worsening from onset, without distinct relapses or remissions. Occasional plateaus and temporary minor improvements may be observed in primary progressive patterns but often the individual shows a steady progression of disability with little or no acute relapse (43).

Secondary Progressive. The secondary progressive patterns of MS are characterized by continued relapses combined with a slow, steady loss of neurological function (43). Typically, individuals with secondary progressive MS were originally diagnosed with the relapsing-remitting form. Approximately 50 percent of individuals with relapsing-remitting MS will develop secondary progressive MS (43).

Progressive-Relapsing. The most aggressive form of MS is referred to as progressive-relapsing, which occurs in only about 5 percent of MS patients (43). This form of the disease is progressive from onset, with clear, acute relapses or exacerbations that may or may not resolve with recovery (43).

Multiple Sclerosis Symptoms

Individuals with MS often exhibit a variety of symptoms that vary widely in breadth and severity altering visual, motor, sensory, coordination and balance, bowel, bladder, sexual, cognitive function, and excess fatigue. Many of these symptoms can contribute to a reduction in functional and or exercise capacity. The following section will describe, motor function symptoms and autonomic dysfunction both of which could

contribute to increased levels of fatigue (MS-related and muscular) and also cause a reduction in functional and exercise capacity.

Motor Function Symptoms. The most prominent motor function symptoms in people with MS include, muscle weakness (50%), spasticity (40-60%), and fatigue (85-95%) which have been shown to compromise daily and leisure time activities with ensuing loss of physical function in a harmful cycle (1).

Muscle weakness is experienced in at least half of all MS patients and can lead to general lack of fitness, deconditioning, and or motor disturbances. People with MS have decreases in isometric, isokinetic, isotonic force, and slower muscle tension development in both the quadriceps and hamstrings (46-52). The potential mechanisms responsible for the observed reductions in muscular strength and function include; decreased motor unit firing, decreased motor unit recruitment, increased central motor conduction time, or blocked motor signals (11,40,53). Reduced muscle strength and function contribute to an overall general deconditioning and contributes to reduced exercise and functional capacity (10-12). Lack of leg strength contributes to impaired balance and mobility, all of which further compromise activities of daily living and quality of life (1). Research indicates that some strength deficits in people with MS are reversible based on evidence of strength gains following resistance training (54).

Spasticity, a prominent symptom in 40-60% of individuals with MS, consists of muscle hypertonia and exaggerated tendon reflexes (including clonus) (55,56). Analysis of muscle biopsy samples from spastic muscle show evidence of altered structure and function including distorted muscle fiber size and type, proliferation of extracellular matrix material, and biochemical changes (57). Researchers have observed increased

number of “rounded” fibers, “moth-eaten” fibers, increased lipid infiltration, and a possible increase in extracellular space (58-62). Contractile proteins, actin and myosin also appear to be altered in spastic muscle (63). Lieber and colleagues reported an increase in noncontractile extracellular material in the spastic muscle (64). Clinically, spasticity is characterized by weakness, slowness in building up of maximal power of muscle activity and relaxing again, and clumsiness of voluntary movements resulting muscle stiffness, spasms, pain, and contractures all of which can contribute to reduction in exercise and functional capacity (56).

Fatigue has been reported in as much as 85-95% of people with MS (30,31,65-67) with 40% identifying it as their most disabling symptom (29,31). People that do not have MS experience fatigue, which normally recovers with rest and does not typically interfere with activities of daily living. Fatigue in MS has been associated with central and peripheral nervous system disorder (4). While there are no universally accepted definitions of fatigue, different forms are often described. For example, primary fatigue has been described as being caused directly by the disease and/or secondary fatigue that is associated with poor fitness, deconditioning (11,12), depression, and side effects of immunomodulatory or symptom management medications (68,69).

Mechanisms that have been associated with primary fatigue include modulation of pro-inflammatory cytokines, demyelination, and axonal loss (4). Research indicates that many of the proinflammatory cytokines (IL-1, IL-2, IL-6 and TNF alpha) are elevated in MS lesions, and can cause fatigue (70). Primary fatigue may also be related to increased amounts of demyelination and axonal loss (4). Individuals diagnosed with the progressive form of MS tend to report greater levels of fatigue than those with the

relapsing remitting form (71,72). Research has also shown that individuals with MS can increase central drive, as evidenced by increased EMG activity during a fatiguing exercise to a greater degree than non-MS controls, but the change in central drive was associated with a greater degree of perceived exertion (73). Marrie and colleagues used magnetic resonance spectroscopy (MRS) and found a link between the Fatigue Severity Scale (FSS) and brain atrophy in individuals with relapsing remitting MS (74). In contrast, studies assessing the relationship between self-reported fatigue and neurologic disability have found either no or modest associations (31,66,75).

Fatigue also may be related to secondary consequences of MS, such as depression, sleep disturbances, electrolyte imbalances, metabolic diseases, dehydration and even adverse effects from medications (4). Depressive symptoms are common in individuals with MS and include: lassitude, psychomotor retardation, decreased physical activity, and decreased motivation.

Overall fatigue can also be exaggerated by abnormal muscle fatigue. Skeletal muscle fatigue has been characterized by a decline in phosphocreatine and intracellular pH (12) which is considered different than more generalized forms of fatigue. Analysis of muscle biopsy samples from individuals with MS show a greater reliance on anaerobic energy supplies, possibly contributing to increased fatigue rates of the muscle (10,11). However, there is some evidence that fatigue and muscular fatigue are interrelated, but the mechanisms are unclear. Furthermore, the reasons for heightened muscular fatigue in MS remains unclear and controversial (76).

In summary, MS motor function symptomology appears to play a role in reducing physical activity and contributing to a reduction in physical function and exercise

capacity. However, the mechanisms for reduced exercise capacity and excess muscular fatigue remain unclear. The next section will focus on autonomic nervous system (ANS) dysfunction in individuals with MS, and discuss a possible link between ANS dysfunction and muscle fatigue.

Autonomic Nervous System

Autonomic Nervous System Anatomy and Physiology. Functioning largely below individual consciousness, the ANS is predominately an efferent organ system that sends nerve impulses from the CNS to peripheral organs (77). The ANS plays an important role in the control of heart rate and heart contractility, constriction and dilation of blood vessels, respiratory rate, contraction and relaxation of smooth muscle in various organs, and glandular secretions (77). There are also important autonomic afferent fibers that innervate baroreceptors and chemoreceptors in the carotid sinus and aortic arch which are also important in controlling heart rate, blood pressure, and respiratory activity (77). Disordered function of the ANS is manifested in problems such as orthostatic hypotension, heat intolerance, abnormal sweating, constipation, diarrhea, incontinence, sexual dysfunction, dry eyes, dry mouth, loss of visual accommodation, and papillary irregularities (35).

The ANS is divided into two opposing systems, the parasympathetic (PNS) and sympathetic systems (SNS) (78). The preganglionic outflow of the PNS arises from the brain stem (77). The vagus nerve (or 10th cranial nerve) carries fibers to the heart and lungs as well as other organs. The PNS functions mainly to conserve and restore energy balance by reducing heart rate and blood pressure and by facilitating digestion and

absorption of nutrients and discharge of wastes. The chemical transmitter at the synapse in the PNS is acetylcholine (77).

The SNS exits from the lateral horns of thoracolumbar spinal segments (thoracic (T1) through lumbar (L2)). The adrenal medulla is innervated by these fibers and responds to nervous impulses by secretion of hormones, for example, the catecholamines, epinephrine and norepinephrine (77). The SNS is also active during situations involving physical or psychological stress where much larger quantities of these hormones are released. In contrast to the PNS, the SNS enables the body to respond to challenges to survival (fight or flight), or situations of hemodynamic collapse or respiratory failure. Sympathetic nervous system responses include an increase in heart rate, blood pressure, and cardiac output; a redistribution of blood flow from the skin and splanchnic vessels to those supplying skeletal muscle; and bronchiolar dilation (77). Therefore, testing autonomic nervous system may provide important clinical/diagnostic information regarding the integrity of the SNS and PNS, both of which have profound impact on physiological function and possibly fatigue.

Autonomic Nervous System Dysfunction in Multiple Sclerosis. The incidence of autonomic dysfunction in MS remains debated with some suggesting a rate of 18% while others report a rate as high as 80%. Neubauer and colleagues observed reduced heart rate variability during deep breathing in people with MS compared to healthy non-MS controls and concluded that the reduced variability was due to vagal abnormalities (79). Flachenecker et al reported that 40% of patients with MS had abnormal responses during the reflex tests (80). However, later McDougall's work observed that only 18% of the study group displayed autonomic dysfunction (81). Based on these and other inconsistent

reports on the incidence of ANS dysfunction McDougall and colleagues concluded that autonomic abnormalities in people with MS are variable and heterogeneous (81).

Several groups have investigated the relationship between MS disease severity and ANS dysfunction. Kodounis and colleagues observed that people with MS are more likely to have impairment within the sympathetic versus parasympathetic nervous systems (82). Individuals with a higher incidence of PNS dysfunction typically have had the disease longer and have higher disability (82-84). However, SNS dysfunction maybe associated with clinical disease activity based on evidence of reduced catecholamine levels in a group of clinically active individuals compared to those who were stable (84).

Some researches have attempted to correlate autonomic dysfunction with CNS lesion load, specifically brainstem lesions (85,86). This relationship remains a matter of some debate due to inconsistent findings, although several reports indicate that ANS abnormalities are somewhat common in MS (87-90). It is also unclear whether autonomic dysfunction could be a potential mechanism for muscular fatigue.

Exercise and ANS Function in Multiple Sclerosis. In 1984, Senaratne and colleagues observed ANS dysfunction during exercise as evidenced by a blunted heart rate and systolic blood pressure response during progressive arm crank ergometry (20). In contrast, Ponichtera-Mulcare and colleagues reported normal cardiovascular responses during progressive leg ergometry (91). The lack of consistency in study findings may reflect the samples' varied levels of disability, duration of disease (yrs), and fitness level, as well as mode of exercise used in the evaluation. However, Ng and colleagues observed a blunted mean arterial blood pressure (MAP), but a normal heart rate, and a smaller than expected metabolic response as using measures of pH and inorganic

phosphate during voluntary isometric dorsiflexion in individuals with MS (47). These authors suggested that a possible mechanism was the inappropriate peripheral feedback (exercise pressor reflex) due to failure within the muscle rather than autonomic dysfunction (47).

Peripheral Mechanisms of Skeletal Muscle Fatigue

Chemoreceptors/Mechanoreceptors. Regulation of the exercise pressor reflex is both centrally (cardiovascular) and peripherally mediated (92). At the onset of exercise, the activation of the cardiovascular system comes from the higher brain centers (central command) which act in parallel with motor unit activation to increase heart rate (92-94). Additionally, cardiovascular activity can be modulated through peripheral components which include muscle mechanoreceptors, muscle chemoreceptors, and pressure-sensitive receptors (baroreceptors). Muscle chemoreceptors and mechanoreceptors respond to metabolic stimuli, (H+, lactate, and K+), and to the force/velocity of muscular movement respectively. Therefore, if the skeletal muscle is unable to respond appropriately to an exercise stimulus, the cardiovascular system might not correctly modulated heart rate, blood pressure, ventilation, blood flow and cardiac output all of which could contribute to failure within the muscle, muscle fatigue.

Metabolic Capacity and Fiber Type. In support of peripheral mechanisms contributing to muscle fatigue, Kent-Braun and colleagues observed a reduced oxidative capacity in the dorsiflexor muscles in individuals with MS as measured by abnormal recovery kinetics of phosphocreatine (PCr) using magnetic resonance spectroscopy (10,12). Additionally, the half-time (T1/2) of PCr recovery following exercise was

significantly slower (2.3 ± 0.3 min vs. 1.2 ± 0.1 min) in those with MS compared to controls providing evidence of impaired oxidative capacity in the skeletal muscle (10).

Biopsies taken from the anterior tibialis muscle of individuals with MS showed fewer and smaller type I fibers, lower succinate dehydrogenase (SDH) per unit cross sectional area (CSA) compared to matched non-MS controls (12). Lower SDH reflects the reduced ability of the muscle to supply energy aerobically, in particular to the type I muscle fibers. The observations of lower SDH/CSA suggested that there were possible alterations in oxidative capacity and mitochondrial function in skeletal muscle of people with MS. The observed reduction in SDH content per fiber volume in individuals with MS suggested that the absolute ability of muscle to supply energy aerobically was diminished, particularly in the type I fibers, which could contribute to elevated levels of muscle fatigue in individuals with MS (12). However, another group, Carroll et al in 2005 conducted a biopsy analysis of the vastus lateralis muscle in individuals with MS and they reported no differences in distribution of myosin heavy chain and fiber-type characteristics compared to controls (2), failing to corroborate previous findings by Kent-Braun. A noted dissimilarity between studies was the differences in muscles used for biopsy analysis which could explain the inconsistent findings.

Muscle Cross-Bridge/Mechanics. In addition to an altered metabolic response, impaired skeletal muscle contractile properties could further augment muscle fatigue which also supports the notion of peripheral mechanisms associated with muscle fatigue. During maximal isometric lower leg (anterior tibialus), exercise individuals with MS showed less potentiation of twitch tension than non-MS controls, providing evidence of either a reduced calcium release from the sarcoplasmic reticulum or decreased myosin

light chain phophorylation and light chain kinase activity at low pH (95,96). Additionally, the half-relaxation time of tetanic force in people with MS was longer than for control subjects suggesting abnormal calcium pumping (97,98). The observation of abnormal calcium pumping, coupled with decreases in PCr and pH, suggested that muscle fatigue might originate from impaired excitation–contraction coupling and abnormal energy metabolism (37). Garner et al in 2003 observed modest changes in cross-bridge mechanisms of contractions that could alter skeletal muscle function in individuals with MS, which could further contribute to muscle fatigue (13).

Central Mechanisms of Skeletal Muscle Fatigue

Skeletal Muscle Activation. Since MS is a neurodegenerative disease of the CNS, it is possible that muscle fatigue is related to the inability to recruit and activate the muscles. Muscle contraction requires central and peripheral activation processes such that a failure along the sequence could result in fatigue or loss of force production. In evaluating individuals with MS, Kent-Braun and colleagues observed smaller muscle metabolic changes relative to non-MS controls using the same relative exercise intensity. In this particular study the ankle dorsiflexors was studied using measurements of maximal voluntary force and changes of muscle metabolism (inorganic phosphate, phosphocreatine and pH) (11). During exercise a smaller metabolic change was observed for the individuals with MS at the same relative exercise intensity compared to the non-MS subjects. These results indicated some central activation failure but no neuromuscular junction impairment and that the measured metabolic factors did not play a significant role in the development of muscle fatigue in individuals with MS (11).

In support of muscle activation failure and reduced neural drive de Haan and colleagues found that individuals with MS were only able to voluntarily exert 75% of their maximal isometric quadriceps capacity compared to 94% observed in the control subjects (51). Reduced neural drive has been observed in people with MS during voluntary and electrically stimulated isometric contractions of the ankle dorsiflexor muscles (36). Maximal isometric voluntary contraction (MVIC) was 27% lower in people with MS compared to controls which suggests incomplete voluntary muscle activation reduces the overall performance capacity and metabolic demand of the muscle (36).

In general there appear to be alterations in the skeletal muscle characteristics of individuals with MS in both metabolism and activation. The alterations function and performance of skeletal muscle in individuals with MS might suggest that muscular fatigue and exercise capacity is limited by central and/or peripheral mechanisms. However, the mechanism for increased muscular fatigue still remains unclear due to its complexity. One possible explanation of premature muscle fatigue could be related to the etiology of MS and that the disease often affects the body asymmetrically.

Bilateral Muscle Function and Fatigue

People with MS often experience asymmetrical weakness, paralysis, and loss or impaired movement in the limbs which is known as paresis. Currently there is minimal data on the impact that paresis has on not only function, but on fatigue, both generalized and muscle. Paresis can occur at rest or be exercise-induced (38). In a case study by White and Dressendorfer (38) they observed exercise induced lower extremity monoparesis that was not present at rest. During unilateral leg VO_{2max} testing the subject was unable to obtain the criterion for reaching a V_{O2max} in the affected limb (left) but was

able to reach the appropriate criterion in the unaffected limb based on lactate values above 8 mmol. Although the study highlights an area for further investigation, no substantial conclusions can be drawn due to case study design. In a larger study, Kent Braun and colleagues in did observe that individuals with MS had lower knee extension power and that the asymmetry between legs was greater when compared to controls (39). Additionally, the research group was able to correlate knee extension power asymmetry with symptomatic fatigue and walk times (39). Studies have provided critical insight into the potential impact that asymmetry has on individuals with MS. The observation of bilateral differences may help explain why previous reports of altered skeletal muscle metabolism are inconsistent and why only moderate adaptations to aerobic exercise training programs have been observed in individuals with MS.

Aerobic Exercise and Multiple Sclerosis

Mostert and colleagues reported that individuals with MS had a 30% lower V_{O2max} and a significantly higher heart rate reserve (37 beats/min) than matched control subjects (99). This indicates an inability of some individuals with MS to stress the cardiovascular system maximally further suggesting that individuals with MS in fact have a blunted heart rate response to increased exercise stress. Individuals with MS also had significantly higher relative oxygen consumption and heart rates in comparison to healthy controls at identical workrates based on percent of VO_2, including zero workload (similar results in Tantucci 1996 and Olgiati 1986) (100-102). Some investigators suggest that spastic muscle or a paretic limb could contribute higher metabolic cost of exercise (12,102,103)). Additionally, muscular coordination problems resulting in uneconomical pedaling due to sensory-motor dysfunction could also contribute to increased oxygen consumption (101,102). Findings from these studies were from protocols using

conventional bipedal exercises such as cycling or combination of arm and leg ergometry which have the potential to mask the influence bilateral differences might have on premature muscle fatigue. In addition to leg asymmetry an imbalance in skeletal muscle oxygen delivery and extraction could further contribute to premature muscle fatigue that has not been fully examined in individuals with MS.

Maximal Oxygen Uptake and Kinetics

The two principal components of VO_2max are maximal stroke volume and maximal cardiac output which implies that the supply of oxygen could limit exercise performance (104-108). Therefore, if delivery of oxygen to a working muscle is compromised, using conventionally measured whole body assessment of oxygen consumption may not accurately indicate the maximal aerobic capacity of a specific group of working muscles, for examples the quadriceps (109). Therefore the full aerobic potential of an individual muscle group (VO_2peak) might not truly be measured during conventional whole body maximal oxygen uptake procedures (110-113). Applying this concept to individuals with MS who might exhibit significant bilateral differences in leg function using conventional bipedal whole body oxygen uptake procedures to measure aerobic capacity and exercise tolerance might be misleading.

Additionally, at the onset of exercise, the rate at which oxygen uptake (VO_2 kinetics) adjusts to the energy demand strongly influences the amount of "O_2 deficit" accumulated and the extent to which the muscles and the systemic homeostasis is agitated (23). Faster VO_2 kinetics can minimize anaerobic muscle metabolism and thereby attenuate the fall in PCr and utilization of muscle glycolytic metabolism and thereby limit the accumulation of metabolites that have been associated with muscle fatigue (H+,

ADP, and Pi) (24). To date, results of studies assessing oxygen uptake kinetics in individuals with MS have not been published. Therefore the following section will briefly describe the response of oxygen consumption during exercise observed in a variety of clinical populations including type II diabetes and individuals with chronic fatigue syndrome to help explain possible outcomes in individuals with MS.

Type II Diabetes. Individuals with type II diabetes exhibit an abnormally slow increase in oxygen uptake (VO_2 kinetics) during the onset of exercise (27,114) which contributes to a greater perturbation of intramuscular homeostasis in response to any exercise challenge, potentially contributing to premature muscular fatigue (115) and consequently reducing exercise capacity (26-28). Slowed VO_2 kinetics can result in a prolonged periods of adaptation to any acute submaximal exercise demand, such as those regularly encountered activity during daily living resulting in greater oxygen deficit and hence greater dependence upon substrate level phosphorylation (phosphocreatine degradation and glycolysis). In addition to a slowed oxygen uptake kinetics research has suggested that an impaired skeletal muscle capillary hemodynamics (116) and an abnormal capillary PO_2 response during exercise (116) may limit oxygen transfer and utilization in individuals with type II diabetes (116,117).

Slower blood flow kinetics in individuals with type II diabetes could be related to central limitations of cardiac output. However, Bauer and colleges observed similar cardiac outputs between subject groups concluding the blood flow abnormalities were probably due to specific control of blood flow of the exercising muscle. Impaired microvascular oxygen delivery and exchange in human skeletal muscle could contribute to a reduction in exercise capacity and physical function in individuals with type II

diabetes. As discussed earlier in this review the blunted metabolic response seen in individuals with MS by NG and colleagues was associated with an inappropriate exercise pressor reflex response which also appears to occur in individuals with Type II diabetes which may be a mechanism for muscle fatigue.

Chronic Fatigue Syndrome (CFS). Individuals with CFS often complain of muscle weakness and pain which is possibly caused by excessive intracellular acidosis which alters muscle bioenergetics (118-120). Many individuals with CFS also exhibit autonomic dysregulation (121-124) which could affect blood flow to active muscles (125) which may possibly explain altered skeletal muscle metabolism compared to controls. McCully et al in 1996 observed significant differences in oxidative capacity, as measured by rate of recovery of phosphocreatine, following submaximal exercise in individuals with CFS compared to sedentary controls (126). McCully and colleagues also found that people with CFS has reduced oxygen delivery compared to sedentary people (120). Reduced oxygen delivery could result in reduced oxidative metabolism and consequently diminished exercise capacity because oxygen delivery is a major determinant of muscle exercise capacity (127). In 2003 McCully and colleagues tested the hypothesis that people with CFS would have decreased muscle blood flow and metabolism compared to sedentary controls (128). However, they were unable to corroborate their own previous results finding. The lack of consistent findings by McCully's group may be explained by the fitness level of the research participants. Inactivity has been shown to have a negative impact on both muscle metabolism and muscle blood flow (129,130). This is significant because inactivity can be reversed and

training studies have provided this evidence that blood flow and metabolism can be enhance following a training program.

Summary

Fatigue in MS (symptomatic and or muscular) is often expressed as the most disabling symptom. Additionally, muscular fatigue has been associated with reduced exercise capacity and function in daily activities. The etiology of muscular fatigue in MS remains relatively unexplored despite its prevalence. Possible mechanisms which have not been adequately studied include skeletal muscle oxygen uptake kinetics and muscle activation with physical activity of increasing intensity. Additionally, individuals with magnified unilateral symptoms may experience heightened fatigue because of poor efficiency or other compensatory mechanisms related to asymmetry. This information will not only help to establish new knowledge related to muscle fatigue but also contribute to optimizing patient care, allowing physicians and healthcare providers to prescribe exercise programs that have multi-dimensional health benefits.

References

(1) Romberg A, Virtanen A, Aunola S, Karppi SL, Karanko H, Ruutiainen J. Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. Mult Scler 2004 Apr;10(2):212-218.

(2) Carroll CC, Gallagher PM, Seidle ME, Trappe SW. Skeletal muscle characteristics of people with multiple sclerosis. Arch Phys Med Rehabil 2005 Feb;86(2):224-229.

(3) Kos D, Nagels G, D'Hooghe MB, Duportail M, Kerckhofs E. A rapid screening tool for fatigue impact in multiple sclerosis. BMC Neurol 2006 Aug 17;6:27.

(4) Lapierre Y, Hum S. Treating fatigue. Int MS J 2007 Jun;14(2):64-71.

(5) Edwards RH. Human muscle function and fatigue. Ciba Found Symp 1981;82:1-18.

(6) Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. Muscle Nerve 1992 Oct;15(10):1123-1132.

(7) Ingram DA, Thompson AJ, Swash M. Central motor conduction in multiple sclerosis: evaluation of abnormalities revealed by transcutaneous magnetic stimulation of the brain. J Neurol Neurosurg Psychiatry 1988 Apr;51(4):487-494.

(8) Nielsen JF. Frequency-dependent conduction delay of motor-evoked potentials in multiple sclerosis. Muscle Nerve 1997 Oct;20(10):1264-1274.

(9) Kent-Braun JA, Walker CH, Weiner MW, Miller RG. Functional significance of upper and lower motor neuron impairment in amyotrophic lateral sclerosis. Muscle Nerve 1998 Jun;21(6):762-768.

(10) Kent-Braun JA, Sharma KR, Miller RG, Weiner MW. Postexercise phosphocreatine resynthesis is slowed in multiple sclerosis. Muscle Nerve 1994 Aug;17(8):835-841.

(11) Kent-Braun JA, Sharma KR, Weiner MW, Miller RG. Effects of exercise on muscle activation and metabolism in multiple sclerosis. Muscle Nerve 1994 Oct;17(10):1162-1169.

(12) Kent-Braun JA, Ng AV, Castro M, Weiner MW, Gelinas D, Dudley GA, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. J Appl Physiol 1997 Dec;83(6):1998-2004.

(13) Garner DJ, Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. Muscle Nerve 2003 Apr;27(4):456-464.

(14) Anema JR, Heijenbrok MW, Faes TJ, Heimans JJ, Lanting P, Polman CH. Cardiovascular autonomic function in multiple sclerosis. J Neurol Sci 1991 Aug;104(2):129-134.

(15) Cartlidge NE. Autonomic function in multiple sclerosis. Brain 1972;95(4):661-664.

(16) Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Jak AJ, et al. Use of the multiple sclerosis functional composite as an outcome measure in a phase 3 clinical trial. Arch Neurol 2001 Jun;58(6):961-967.

(17) Drory VE, Nisipeanu PF, Kroczyn AD. Tests of autonomic dysfunction in patients with multiple sclerosis. Acta Neurol Scand 1995 Nov;92(5):356-360.

(18) Nordenbo AM, Boesen F, Andersen EB. Cardiovascular autonomic function in multiple sclerosis. J Auton Nerv Syst 1989 Feb;26(1):77-84.

(19) Pepin EB, Hicks RW, Spencer MK, Tran ZV, Jackson CG. Pressor response to isometric exercise in patients with multiple sclerosis. Med Sci Sports Exerc 1996 Jun;28(6):656-660.

(20) Senaratne MP, Carroll D, Warren KG, Kappagoda T. Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. J Neurol Neurosurg Psychiatry 1984 Sep;47(9):947-952.

(21) Sterman AB, Coyle PK, Panasci DJ, Grimson R. Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. Neurology 1985 Nov;35(11):1665-1668.

(22) Thomaides TN, Zoukos Y, Chaudhuri KR, Mathias CJ. Physiological assessment of aspects of autonomic function in patients with secondary progressive multiple sclerosis. J Neurol 1993;240(3):139-143.

(23) Jones AM, Burnley M. Oxygen uptake kinetics: an underappreciated determinant of exercise performance. Int J Sports Physiol Perform 2009 Dec;4(4):524-532.

(24) Jones AM, Wilkerson DP, Vanhatalo A, Burnley M. Influence of pacing strategy on O2 uptake and exercise tolerance. Scand J Med Sci Sports 2008 Oct;18(5):615-626.

(25) Poole DC, Barstow TJ, McDonough P, Jones AM. Control of oxygen uptake during exercise. Med Sci Sports Exerc 2008 Mar;40(3):462-474.

(26) Bauer TA, Reusch JE, Levi M, Regensteiner JG. Skeletal muscle deoxygenation after the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes. Diabetes Care 2007 Nov;30(11):2880-2885.

(27) Regensteiner JG, Bauer TA, Reusch JE, Brandenburg SL, Sippel JM, Vogelsong AM, et al. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. J Appl Physiol 1998 Jul;85(1):310-317.

(28) Brandenburg SL, Reusch JE, Bauer TA, Jeffers BW, Hiatt WR, Regensteiner JG. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. Diabetes Care 1999 Oct;22(10):1640-1646.

(29) Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994 Feb;21(1):9-14.

(30) Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. Arch Phys Med Rehabil 1984 Mar;65(3):135-138.

(31) Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol 1988 Apr;45(4):435-437.

(32) Packer TL, Sauriol A, Brouwer B. Fatigue secondary to chronic illness: postpolio syndrome, chronic fatigue syndrome, and multiple sclerosis. Arch Phys Med Rehabil 1994 Oct;75(10):1122-1126.

(33) Lane RJ, Barrett MC, Taylor DJ, Kemp GJ, Lodi R. Heterogeneity in chronic fatigue syndrome: evidence from magnetic resonance spectroscopy of muscle. Neuromuscul Disord 1998 May;8(3-4):204-209.

(34) Sarelius I, Pohl U. Control of muscle blood flow during exercise: local factors and integrative mechanisms. Acta Physiol (Oxf) 2010 Mar 26.

(35) Ravits JM. AAEM minimonograph #48: autonomic nervous system testing. Muscle Nerve 1997 Aug;20(8):919-937.

(36) Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve 2004 Jun;29(6):843-852.

(37) Sharma KR, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. Muscle Nerve 1995 Dec;18(12):1403-1411.

(38) White LJ, Dressendorfer RH. Factors limiting maximal oxygen uptake in exertional monoparesis. Mult Scler 2005 Apr;11(2):240-241.

(39) Chung LH, Remelius JG, Van Emmerik RE, Kent-Braun JA. Leg power asymmetry and postural control in women with multiple sclerosis. Med Sci Sports Exerc 2008 Oct;40(10):1717-1724.

(40) Ng AV, Miller RG, Kent-Braun JA. Central motor drive is increased during voluntary muscle contractions in multiple sclerosis. Muscle Nerve 1997 Oct;20(10):1213-1218.

(41) Sobel RA. The pathology of multiple sclerosis. Neurol Clin 1995 Feb;13(1):1-21.

(42) Gutierrez-Ospina G, Gutierrez de la Barrera A, Larriva J, Giordano M. Insulin-like growth factor I partly prevents axon elimination in the neonate rat optic nerve. Neurosci Lett 2002 Jun 14;325(3):207-210.

(43) Goodkin DE, Hertsgaard D, Rudick RA. Exacerbation rates and adherence to disease type in a prospectively followed-up population with multiple sclerosis. Implications for clinical trials. Arch Neurol 1989 Oct;46(10):1107-1112.

(44) Moll C, Mourre C, Lazdunski M, Ulrich J. Increase of sodium channels in demyelinated lesions of multiple sclerosis. Brain Res 1991 Aug 16;556(2):311-316.

(45) Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998 Jan 29;338(5):278-285.

(46) Chen WY, Pierson FM, Burnett CN. Force-time measurements of knee muscle functions of subjects with multiple sclerosis. Phys Ther 1987 Jun;67(6):934-940.

(47) Ng AV, Dao HT, Miller RG, Gelinas DF, Kent-Braun JA. Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. J Appl Physiol 2000 Mar;88(3):871-880.

(48) Nielsen JF, Norgaard P. Increased post-exercise facilitation of motor evoked potentials in multiple sclerosis. Clin Neurophysiol 2002 Aug;113(8):1295-1300.

(49) Iriarte J, de Castro P. Correlation between symptom fatigue and muscular fatigue in multiple sclerosis. Eur J Neurol 1998 Nov;5(6):579-585.

(50) Lambert CP, Archer RL, Evans WJ. Muscle strength and fatigue during isokinetic exercise in individuals with multiple sclerosis. Med Sci Sports Exerc 2001 Oct;33(10):1613-1619.

(51) de Haan A, de Ruiter CJ, van Der Woude LH, Jongen PJ. Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. Muscle Nerve 2000 Oct;23(10):1534-1541.

(52) de Ruiter CJ, Jongen PJ, van der Woude LH, de Haan A. Contractile speed and fatigue of adductor pollicis muscle in multiple sclerosis. Muscle Nerve 2001 Sep;24(9):1173-1180.

(53) Kent-Braun JA, Le Blanc R. Quantitation of central activation failure during maximal voluntary contractions in humans. Muscle Nerve 1996 Jul;19(7):861-869.

(54) White LJ, McCoy SC, Castellano V, Gutierrez G, Stevens JE, Walter GA, et al. Resistance training improves strength and functional capacity in persons with multiple sclerosis. Mult Scler 2004 Dec;10(6):668-674.

(55) Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenberg Lecture. Neurology 1980 Dec;30(12):1303-1313.

(56) Barnes MP, Kent RM, Semlyen JK, McMullen KM. Spasticity in multiple sclerosis. Neurorehabil Neural Repair 2003 Mar;17(1):66-70.

(57) Foran JR, Steinman S, Barash I, Chambers HG, Lieber RL. Structural and mechanical alterations in spastic skeletal muscle. Dev Med Child Neurol 2005 Oct;47(10):713-717.

(58) Dietz V, Ketelsen UP, Berger W, Quintern J. Motor unit involvement in spastic paresis. Relationship between leg muscle activation and histochemistry. J Neurol Sci 1986 Aug;75(1):89-103.

(59) Booth CM, Cortina-Borja MJ, Theologis TN. Collagen accumulation in muscles of children with cerebral palsy and correlation with severity of spasticity. Dev Med Child Neurol 2001 May;43(5):314-320.

(60) Castle ME, Reyman TA, Schneider M. Pathology of spastic muscle in cerebral palsy. Clin Orthop Relat Res 1979 Jul-Aug;(142)(142):223-232.

(61) Romanini L, Villani C, Meloni C, Calvisi V. Histological and morphological aspects of muscle in infantile cerebral palsy. Ital J Orthop Traumatol 1989 Mar;15(1):87-93.

(62) Rose J, Haskell WL, Gamble JG, Hamilton RL, Brown DA, Rinsky L. Muscle pathology and clinical measures of disability in children with cerebral palsy. J Orthop Res 1994 Nov;12(6):758-768.

(63) Wang K, McCarter R, Wright J, Beverly J, Ramirez-Mitchell R. Viscoelasticity of the sarcomere matrix of skeletal muscles. The titin-myosin composite filament is a dual-stage molecular spring. Biophys J 1993 Apr;64(4):1161-1177.

(64) Lieber RL, Runesson E, Einarsson F, Friden J. Inferior mechanical properties of spastic muscle bundles due to hypertrophic but compromised extracellular matrix material. Muscle Nerve 2003 Oct;28(4):464-471.

(65) Bakshi R, Shaikh ZA, Miletich RS, Czarnecki D, Dmochowski J, Henschel K, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 2000 Jun;6(3):181-185.

(66) Bergamaschi R, Romani A, Versino M, Poli R, Cosi V. Clinical aspects of fatigue in multiple sclerosis. Funct Neurol 1997 Sep-Oct;12(5):247-251.

(67) Murray TJ. Amantadine therapy for fatigue in multiple sclerosis. Can J Neurol Sci 1985 Aug;12(3):251-254.

(68) Kopke S, Heesen C. Corticosteroids treatment of multiple sclerosis. J Neurol Sci 2005 Jul 15;234(1-2):117-8; author reply 119-20.

(69) Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity of interferons in cancer patients: a review. J Clin Oncol 1986 Feb;4(2):234-243.

(70) Schwid SR, Covington M, Segal BM, Goodman AD. Fatigue in multiple sclerosis: current understanding and future directions. J Rehabil Res Dev 2002 Mar-Apr;39(2):211-224.

(71) Colosimo C, Millefiorini E, Grasso MG, Vinci F, Fiorelli M, Koudriavtseva T, et al. Fatigue in MS is associated with specific clinical features. Acta Neurol Scand 1995 Nov;92(5):353-355.

(72) Schwartz CE, Coulthard-Morris L, Zeng Q. Psychosocial correlates of fatigue in multiple sclerosis. Arch Phys Med Rehabil 1996 Feb;77(2):165-170.

(73) Sheean GL, Murray NM, Rothwell JC, Miller DH, Thompson AJ. An electrophysiological study of the mechanism of fatigue in multiple sclerosis. Brain 1997 Feb;120 (Pt 2)(Pt 2):299-315.

(74) Marrie RA, Fisher E, Miller DM, Lee JC, Rudick RA. Association of fatigue and brain atrophy in multiple sclerosis. J Neurol Sci 2005 Feb 15;228(2):161-166.

(75) Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989 Oct;46(10):1121-1123.

(76) Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004 Mar 20;363(9413):978-988.

(77) Freeman R. Assessment of cardiovascular autonomic function. Clin Neurophysiol 2006 Apr;117(4):716-730.

(78) Shields RW,Jr. Functional anatomy of the autonomic nervous system. J Clin Neurophysiol 1993 Jan;10(1):2-13.

(79) Neubauer B, Gundersen HJ. Analysis of heart rate variations in patients with multiple sclerosis. A simple measure of autonomic nervous disturbances using an ordinary ECG. J Neurol Neurosurg Psychiatry 1978 May;41(5):417-419.

(80) Flachenecker P, Wolf A, Krauser M, Hartung HP, Reiners K. Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. J Neurol 1999 Jul;246(7):578-586.

(81) McDougall AJ, McLeod JG. Autonomic nervous system function in multiple sclerosis. J Neurol Sci 2003 Nov 15;215(1-2):79-85.

(82) Kodounis A, Stamboulis E, Constantinidis TS, Liolios A. Measurement of autonomic dysregulation in multiple sclerosis. Acta Neurol Scand 2005 Dec;112(6):403-408.

(83) Nasseri K, TenVoorde BJ, Ader HJ, Uitdehaag BM, Polman CH. Longitudinal follow-up of cardiovascular reflex tests in multiple sclerosis. J Neurol Sci 1998 Feb 18;155(1):50-54.

(84) Flachenecker P, Reiners K, Krauser M, Wolf A, Toyka KV. Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. Mult Scler 2001 Oct;7(5):327-334.

(85) Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. Acta Neurol Scand 2000 Feb;101(2):85-88.

(86) Saari A, Tolonen U, Paakko E, Suominen K, Pyhtinen J, Sotaniemi K, et al. Cardiovascular autonomic dysfunction correlates with brain MRI lesion load in MS. Clin Neurophysiol 2004 Jun;115(6):1473-1478.

(87) Keselbrener L, Akselrod S, Ahiron A, Eldar M, Barak Y, Rotstein Z. Is fatigue in patients with multiple sclerosis related to autonomic dysfunction? Clin Auton Res 2000 Aug;10(4):169-175.

(88) Merkelbach S, Dillmann U, Kolmel C, Holz I, Muller M. Cardiovascular autonomic dysregulation and fatigue in multiple sclerosis. Mult Scler 2001 Oct;7(5):320-326.

(89) Egg R, Hogl B, Glatzl S, Beer R, Berger T. Autonomic instability, as measured by pupillary unrest, is not associated with multiple sclerosis fatigue severity. Mult Scler 2002 May;8(3):256-260.

(90) Flachenecker P, Rufer A, Bihler I, Hippel C, Reiners K, Toyka KV, et al. Fatigue in MS is related to sympathetic vasomotor dysfunction. Neurology 2003 Sep 23;61(6):851-853.

(91) Ponichtera-Mulcare JA. Exercise and multiple sclerosis. Med Sci Sports Exerc 1993 Apr;25(4):451-465.

(92) Mitchell JH. J.B. Wolffe memorial lecture. Neural control of the circulation during exercise. Med Sci Sports Exerc 1990 Apr;22(2):141-154.

(93) Eldridge FL, Millhorn DE, Waldrop TG. Exercise hyperpnea and locomotion: parallel activation from the hypothalamus. Science 1981 Feb 20;211(4484):844-846.

(94) Eldridge FL, Millhorn DE, Kiley JP, Waldrop TG. Stimulation by central command of locomotion, respiration and circulation during exercise. Respir Physiol 1985 Mar;59(3):313-337.

(95) Blumenthal DK, Stull JT. Effects of pH, ionic strength, and temperature on activation by calmodulin an catalytic activity of myosin light chain kinase. Biochemistry 1982 May 11;21(10):2386-2391.

(96) Moussavi RS, Carson PJ, Boska MD, Weiner MW, Miller RG. Nonmetabolic fatigue in exercising human muscle. Neurology 1989 Sep;39(9):1222-1226.

(97) Dawson MJ, Gadian DG, Wilkie DR. Studies of the biochemistry of contracting and relaxing muscle by the use of 31P n.m.r. in conjunction with other techniques. Philos Trans R Soc Lond B Biol Sci 1980 Jun 25;289(1037):445-455.

(98) Kim DH, Witzmann FA, Fitts RH. Effect of disuse on sarcoplasmic reticulum in fast and slow skeletal muscle. Am J Physiol 1982 Sep;243(3):C156-60.

(99) Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler 2002 Apr;8(2):161-168.

(100) Tantucci C, Massucci M, Piperno R, Grassi V, Sorbini CA. Energy cost of exercise in multiple sclerosis patients with low degree of disability. Mult Scler 1996 Oct;2(3):161-167.

(101) Olgiati R, Jacquet J, Di Prampero PE. Energy cost of walking and exertional dyspnea in multiple sclerosis. Am Rev Respir Dis 1986 Nov;134(5):1005-1010.

(102) Olgiati R, di Prampero PE. Effect of physical exercise on adaptation to energy expenditure in multiple sclerosis. Schweiz Med Wochenschr 1986 Mar 22;116(12):374-377.

(103) O'Brien IA, O'Hare P, Corrall RJ. Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function. Br Heart J 1986 Apr;55(4):348-354.

(104) Grimby G, Nilsson NJ, Saltin B. Cardiac output during submaximal and maximal exercise in active middle-aged athletes. J Appl Physiol 1966 Jul;21(4):1150-1156.

(105) Ekblom B, Hermansen L. Cardiac output in athletes. J Appl Physiol 1968 Nov;25(5):619-625.

(106) Peronnet F, Ferguson RJ, Perrault H, Ricci G. Echocardiographic dimensions determined in normally active college women and in female athletes. Med Sci Sports Exerc 1982;14(3):181-182.

(107) Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. N Engl J Med 1991 Jan 31;324(5):295-301.

(108) Stolt A, Karjalainen J, Heinonen OJ, Kujala UM. Left ventricular mass, geometry and filling in elite female and male endurance athletes. Scand J Med Sci Sports 2000 Feb;10(1):28-32.

(109) McPhee JS, Williams AG, Stewart C, Baar K, Schindler JP, Aldred S, et al. The training stimulus experienced by the leg muscles during cycling in humans. Exp Physiol 2009 Jun;94(6):684-694.

(110) Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE family study. Aims, design, and measurement protocol. Med Sci Sports Exerc 1995 May;27(5):721-729.

(111) Teran-Garcia M, Rankinen T, Koza RA, Rao DC, Bouchard C. Endurance training-induced changes in insulin sensitivity and gene expression. Am J Physiol Endocrinol Metab 2005 Jun;288(6):E1168-78.

(112) Prior SJ, Hagberg JM, Phares DA, Brown MD, Fairfull L, Ferrell RE, et al. Sequence variation in hypoxia-inducible factor 1alpha (HIF1A): association with maximal oxygen consumption. Physiol Genomics 2003 Sep 29;15(1):20-26.

(113) Timmons JA, Jansson E, Fischer H, Gustafsson T, Greenhaff PL, Ridden J, et al. Modulation of extracellular matrix genes reflects the magnitude of physiological adaptation to aerobic exercise training in humans. BMC Biol 2005 Sep 2;3:19.

(114) Regensteiner JG, Sippel J, McFarling ET, Wolfel EE, Hiatt WR. Effects of non-insulin-dependent diabetes on oxygen consumption during treadmill exercise. Med Sci Sports Exerc 1995 Jun;27(6):875-881.

(115) Scheuermann-Freestone M, Madsen PL, Manners D, Blamire AM, Buckingham RE, Styles P, et al. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. Circulation 2003 Jun 24;107(24):3040-3046.

(116) Padilla DJ, McDonough P, Behnke BJ, Kano Y, Hageman KS, Musch TI, et al. Effects of Type II diabetes on capillary hemodynamics in skeletal muscle. Am J Physiol Heart Circ Physiol 2006 Nov;291(5):H2439-44.

(117) Behnke BJ, Kindig CA, McDonough P, Poole DC, Sexton WL. Dynamics of microvascular oxygen pressure during rest-contraction transition in skeletal muscle of diabetic rats. Am J Physiol Heart Circ Physiol 2002 Sep;283(3):H926-32.

(118) Arnold DL, Bore PJ, Radda GK, Styles P, Taylor DJ. Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a post-viral exhaustion/fatigue syndrome. A 31P nuclear magnetic resonance study. Lancet 1984 Jun 23;1(8391):1367-1369.

(119) Barnes PR, Taylor DJ, Kemp GJ, Radda GK. Skeletal muscle bioenergetics in the chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 1993 Jun;56(6):679-683.

(120) McCully KK, Natelson BH. Impaired oxygen delivery to muscle in chronic fatigue syndrome. Clin Sci (Lond) 1999 Nov;97(5):603-8; discussion 611-3.

(121) Cordero DL, Sisto SA, Tapp WN, LaManca JJ, Pareja JG, Natelson BH. Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome. Clin Auton Res 1996 Dec;6(6):329-333.

(122) Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? Am J Med 1997 Apr;102(4):357-364.

(123) Pagani M, Lucini D, Mela GS, Langewitz W, Malliani A. Sympathetic overactivity in subjects complaining of unexplained fatigue. Clin Sci (Lond) 1994 Dec;87(6):655-661.

(124) Wilke WS, Fouad-Tarazi FM, Cash JM, Calabrese LH. The connection between chronic fatigue syndrome and neurally mediated hypotension. Cleve Clin J Med 1998 May;65(5):261-266.

(125) Montague TJ, Marrie TJ, Bewick DJ, Spencer CA, Kornreich F, Horacek BM. Cardiac effects of common viral illnesses. Chest 1988 Nov;94(5):919-925.

(126) McCully KK, Natelson BH, Iotti S, Sisto S, Leigh JS,Jr. Reduced oxidative muscle metabolism in chronic fatigue syndrome. Muscle Nerve 1996 May;19(5):621-625.

(127) Chance B, Leigh JS,Jr, Kent J, McCully K. Metabolic control principles and 31P NMR. Fed Proc 1986 Dec;45(13):2915-2920.

(128) McCully KK, Smith S, Rajaei S, Leigh JS,Jr, Natelson BH. Blood flow and muscle metabolism in chronic fatigue syndrome. Clin Sci (Lond) 2003 Jun;104(6):641-647.

(129) Miyachi M, Tanaka H, Yamamoto K, Yoshioka A, Takahashi K, Onodera S. Effects of one-legged endurance training on femoral arterial and venous size in healthy humans. J Appl Physiol 2001 Jun;90(6):2439-2444.

(130) Kroese AJ. The effect of inactivity on reactive hyperaemia in the human calf: a study with strain gauge plethysmography. Scand J Clin Lab Invest 1977 Feb;37(1):53-58.

CHAPTER 3

BILATERAL DIFFERENCES IN LOWER EXTREMITY PERFORMANCE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS[1]

[1] Larson, R.L., Baumgartner, T.A., McCully, K.K., Pryor, W.M. and White, L.J. To be submitted to *Multiple Sclerosis*

Abstract

Introduction. In this study we assessed whether ambulatory individuals with mild Multiple Sclerosis (MS) display bilateral differences in lower extremity performance and metabolism during fixed load submaximal and incremental exercise. We also explored the relationship between limb asymmetry and function. **Methods.** Eight individuals (mean age = 51.6 ± 9.2 yrs) with relapsing remitting MS (Expanded Disability Status Scale (EDSS) score = 2.6 ± 1.6) and seven non-MS controls, similar in age, height, weight, and physical activity level, completed a series of four unilateral cycling tests. Stronger leg and weaker legs were identified based on single leg strength assessments. **Results.** Individuals with MS exhibited significant ($P < 0.05$) bilateral differences in leg extensor strength (stronger leg: 95.3 ± 27.9 (lbs) vs. weaker leg: 76.9 ± 19.6 (lbs)), duration of fixed load exercise (stronger leg: 4.8 min ± 0.3, weaker leg: 3.4 ± 1.5 min), peak oxygen uptake (VO_2) (stronger leg: 13.7 ± 3.2 ml/kg/min, weaker leg: 10.6 ± 3.0 ml/kg/min), and peak workload (watts) (stronger leg: 73.4 ± 22.3 watts, weaker leg: 56.3 ± 26.2 watts). No bilateral differences were observed in the control group ($P > 0.05$). Lower extremity asymmetry scores were significantly different between group ($P < 0.05$) for unilateral peak workload and leg extensor strength. Workload asymmetry was correlated (r = 0.62) with distance covered during the 6 minute walk. **Conclusion.** Ambulatory individuals with MS displayed statistically significant differences in leg performance during exercise which was related to physical function. These differences should be considered when developing intervention therapies and when designing studies that assess muscle function of individuals with MS.

Key Words: Multiple Sclerosis, bilateral, asymmetry.

Introduction

Multiple sclerosis (MS) is a chronic and progressive autoimmune disease of the central nervous system (CNS) characterized by nerve demyelination (1) and axonal deterioration (2). Common symptoms of MS include abnormal gait, deficient balance, muscle weakness, spasticity, and fatigue; all of which can reduce physical function and exercise capacity in a deleterious cycle that profoundly impacts health and quality of life (1). While symptoms vary widely across individuals, fatigue has been reported in as much as 85-95% of people with MS (3-9), with 40% identifying fatigue as their most disabling symptom (3,9).

General fatigue has been defined as, "a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with activities of daily living" (10,11). This type of fatigue is often referred to as symptomatic fatigue to distinguish it from muscular fatigue, and the relationship between symptomatic and muscular fatigue is complicated because of their overlapping influences. Greater relative muscle fatigue has been observed in individuals with MS. For example, previous reports have shown premature muscle fatigue using both electrical stimulation and voluntary isometric exercise protocols (12,13).

Skeletal muscle fatigue has been defined as, "a failure to maintain the required or expected force following repeated activity of the muscle" (14). Muscle fatigue in individuals with MS is often described as being related to central and/or peripheral impairments. The central component of muscular fatigue is represented by "higher" systems of control which could have either supraspinal or spinal contributions. Examples include decline in efferent motor outflow ("neural drive") to the muscle resulting in

activation failure, reduced muscle recruitment (15) and/or delayed neural transmission (16,17). The peripheral component of muscular fatigue reflects reduced force-generating mechanisms (18) within the skeletal muscle as a result of altered metabolic characteristics (19-21), and/or autonomic dysfunction (22-30). While skeletal muscle fatigue is a common problem that limits function in activities of daily living in people with MS, its pathophysiology remains unclear.

People with MS also often experience bilateral differences in lower extremity performance (31,32). For example, individuals experience some amount of strength or functional difference between limbs. As a result, one leg may perform a compensatory role which could contribute to early onset muscle fatigue and reduced exercise tolerance. A case study by White and Dressendorfer in 2005 reported bilateral differences in leg strength and maximal oxygen uptake in an individual with MS who exhibited left leg exercise induced monoparesis (33). Chung and colleagues in 2008 observed that lower knee extensor power asymmetry was greater in MS than controls (31). Unilateral leg weakness has also been observed in individuals with MS (34,35). In a recent study, Larson and White (2011) observed bilateral differences in hip bone density in ambulatory individuals with MS which may illustrate consequences of altered bilateral function (36).

Published reports suggest that people with MS exhibit compromised function compared to control subjects; (34,35) however there is limited published data formally describing interlimb differences in metabolism, and skeletal muscle physiological function in individuals with MS. Subsequently, there is a need for an enhanced understanding of possible physiological and functional disparities, as it might improve our understanding of functional limitations for people with MS. This new information

could advance the development of effective prevention and rehabilitation strategies to attenuate fatigue and premature disability.

Therefore, the purpose of this study was to determine whether ambulatory individuals with mild MS would display bilateral differences in physiological and functional measures during unilateral submaximal fixed load and incremental exercises, and whether the magnitude of any differences would correlate with function. We hypothesized that individuals with MS in our sample would exhibit statistically significant differences in strength, peak oxygen uptake, and maximal cycle workload, between legs during fixed load and incremental exercise.

Methods

Participants. Fifteen volunteers, eight individuals with MS (6 women and 2 men) and seven health individuals without MS, controls (5 women and 2 men) participated in the study. Individuals with MS were included in the study if they had a physician diagnosis of relapsing-remitting MS (37), and an Expanded Disability Status Scale (EDSS) of less than 6.5 (ambulatory without aid). Individuals with multiple risk factors for cardiovascular disease or orthopedic limitations according to ACSM guidelines were excluded from the study (38). Each subject has physician's clearance to participate and signed a consent form approved by the University Institutional Review Board prior to participation.

Study Design. The conducted study was a cross sectional design. Participants completed tests assessing leg extensor strength along with measurements of whole body and limb specific oxygen uptake (submaximal and maximal) with 48 hours separating each testing session.

Lower Extremity Strength. Leg extensor strength of each limb was assessed using a custom chair equipped with a force transducer. The knee angle was at a constant 70° and participants were stabilized using straps across the torso and thigh. The lever arm of the chair was connected to a force transducer and a digitized signal from the transducer was sent to a computer and recorded using MatLab. A brief warm-up was performed consisting of three submaximal contractions. Following a five minute rest period, participants performed three maximal isometric voluntary contractions (MVIC) using the highest value of the three trials. A stronger leg/less affected and a weaker leg/more affected were identified for each individual based on the MVIC results.

Whole Body Oxygen Uptake. A conventional incremental cycle (2-leg) ergometer (Lode, Groningen, Netherlands) test was used to measure peak oxygen uptake (VO_2peak) (Parvo Medics, Inc., Sandy, UT) with familiarization of testing procedures conducted during a previous visit. Participants performed a standard warm-up of cycling for 2-3 minutes at 25 W followed by a five minute rest period. The whole body incremental exercise test then began with a workload of 25 W which increased 15 W every minute until participants met one of our defined stopping criteria: 1) any symptom impairing the participant's ability to continue the test or indicating a risk to safety or health, 2) volitional exhaustion, or 3) pedaling rate below 40 revolutions per minute. These criteria were used for all subsequent tests. Expired gases were measured continuously using a calibrated metabolic cart (TrueMax 2400, Salt Lake city, Utah). Heart rate (HR) was recorded by telemetry (Polar RXS 800) and overall ratings of perceived exertion (RPE) using a Borg 10-point scale were obtained at the end of each stage (39). Blood lactate was measured by finger stick before and three minutes after exercise (Lactate Pro, BC,

Canada). Peak workload was defined as the highest workload sustained for at least 30 seconds into a workload stage.

Submaximal Fixed Load Cycling. Leg performance and oxygen onset kinetics were assessed using a single leg submaximal fixed load exercise test with familiarization of testing procedures done during a pervious visit. Following a standard warm-up of cycling for 2-3 minutes at 25 W, and a five minute rest period, participants performed a single leg five minute exercise bout at a fixed workload, which corresponded to 20% of peak whole body maximal workload. The workload was selected based on previous data suggesting that 20% of whole body peak workload would be submaximal (33,40). Oxygen consumption was recorded continuously to analyze the 1st phase of onset kinetics, (phase 1 reflects the fast increase in VO_2 that lasts approximately 15-20 seconds).

Unilateral Incremental Cycling. Limb specific peak oxygen uptake (one-legged cycling) was assessed using a continuous ramp protocol with familiarization of testing procedures done during a pervious visit. Following the standard warm-up, single leg cycling started at 0 W and increased 1 watt every 2. Metabolic measurements were recorded continuously and averaged over 30-second intervals. Heart rate and ratings of leg (RPE) using a Borg 10-point scale were obtained at the end of each stage. Blood lactate was measured by finger stick before and 3 minutes after the exercise test (Lactate Pro, BC, Canada).

Single Leg Max Test Reliability. The unilateral incremental cycling test was repeated in all participants for test reliability. The interclass correlation for peak oxygen uptake was 0.96 (CI: 0.84 to 0.99) and for peak workload was 0.96 (CI: 0.89 to 0.99).

Leg Position-Single Leg Cycling. During all single leg cycling tests, the foot was securely fastened to the pedal with straps and adhesive (duct) tape and the non exercising leg was positioned to ensure it did not contribute to the cycling action. The exercising leg was positioned so that the leg was all most fully extended when the pedal crank was at the lowest position (Figure 1). The same position was used for all trials.

6 minute walk: The six minute walking test was used as a measure of exercise tolerance and overall functional limitation (41). This test was conducted according to McGavin et al (42) and has been previously used in studies with MS patients.

Body Composition. Body composition and limb specific composition were measured by dual-energy x-ray absorptiometry (iDXA, GE Healthcare-Lunar, Madison, WI). Total body fat free mass was used to normalize oxygen uptake during the whole body exercise test.

Control Variables. Participants were asked to abstain from exercise, alcohol, caffeine and smoking 12 hrs prior to the visit. Since the stronger and weaker legs were tested on different days, separated by 48 hrs, participants filled out two questionnaires related to feelings of fatigue which included the profile of moods state brief version (POMS-B) and the physical subscale for the modified fatigue impact scale (MFIS). This was implemented to strengthen the study design and minimize a possible confounding influence fatigue could have on outcome variables. Hydration status was determined by urine measuring specific gravity (USG < 1.030). If the urine specific gravity was low (USP > 1.030), the participant was asked to hydrate and return to the lab the next day for testing. Self reported physical activity level was measured using a questionnaire which

asked about frequency, duration, and intensity of physical activity during a typical week. Each participant completed their testing at the same time of day throughout the study.

Statistical Analysis. All analyses were performed using SPS software v. 16.0 (SPSS, Inc., Chicago, IL). Independent t-tests were used to detect across-group differences. Dependent t-tests were used to compare across-limb differences for strength, fixed load time cycled, peak oxygen uptake, and peak workload; the primary aims of this study. Linear correlations were used to examine the relationship between the 6 minute walk (a measure of exercise tolerance and overall functional limitation) and asymmetry. Data are expressed as mean ± SD. An alpha of 0.05 was our criteria to establish statistically significant differences. Precise *P* values, Cohen's d, and confidence intervals (CI) are reported, where appropriate.

Results

Participant characteristics. Eight ambulatory (no assisted devices) individuals (6 women and 2 men) with physicians diagnosed relapsing remitting MS and seven healthy controls (5 women and 2 men) completed the study. The mean Expanded Disability Status Scale (EDSS) score of 2.6 ± 1.6 indicated a mild to moderate impairment in the MS participants. Duration of the disease was 12.6 ± 8.1 yr (ranging from 6 to 31 yr.). Anthropometric data are shown in Table 3.1. No statistically significant differences existed between the groups for age, height, weight, body mass index, percent body fat and self reports of physical activity.

Leg Composition. Lean and fat mass of the legs were not statistically different between legs for both groups (Table 3.2). Across group comparisons showed no

differences in lean or fat mass for the stronger (P = 0.52 and 0.93, respectively) and the weaker legs (P = 0.33, and 0.91, respectively).

Leg Strength. Maximal voluntary isometric quadriceps strength was statistically lower in the weaker leg within the MS group (stronger leg: 95.3 ± 27.9 (lbs) vs. weaker leg: 76.9 ± 19.6 (lbs), P = 0.004). The MS group's leg mean difference in strength was 18.3 (lbs) with a 95% CI of (7.9 to 28.8). The effect size for leg difference corresponded to a Cohen's d = 1.20 (43) which is considered large. No statistically significant differences were observed in strength between legs for the control group (stronger leg: 87.5 ± 26.5 (lbs) vs. weaker leg: 82.9 ± 33.5 (lbs), P = 0.40). There were no statistically significant differences when comparing the stronger leg or weaker legs across groups (P > 0.05).

Leg Strength Asymmetry Ratio. A WL/SL (ND/D) ratio was calculated for our sample using quadriceps strength from the MVIC. The asymmetry mean ratio for the MS group (0.82 ± 0.09) was statistically lower than the control group's mean ratio (0.93 ± 0.14; P = 0.03, Cohen's d = .93, Figure 3.2).

Cardiporespiratory Fitness. Cardiorespiratory fitness was assessed during the whole body oxygen uptake test. No statistically significant differences were observed across groups for VO_2peak (ml/kg/min), peak workload (watts), respiratory exchange ratio (RER), peak lactate, maximal heart rate (HR max, beats per minute (bpm)), ventilation (VE (L/min)) and overall ratings of perceived exertion (RPE) (P > 0.05). However, the groups were statistically different when normalizing peak oxygen uptake with the individuals' total body fat free mass (VO_2peak ml/kgFFM/min, P < 0.05) (Table 3.3).

Submaximal Unilateral Fixed Load Cycling. The difference in workloads between groups did not reach the level of statistical significance (MS: 22.3 ± 5.5 watts and controls: 31.1 ± 10.4 watts $P = 0.07$). An estimation of oxygen onset kinetics was calculated by summing the first 30 seconds of exercise and comparing the values between legs. The differences in oxygen consumption during the first 30 seconds of exercise were not statistically different between legs for either group ($P > 0.05$).

The duration of time completed was also compared between legs. The stronger leg in the MS group completed a statistically greater amount of the five minute test when compared to the time completed by the weaker leg (stronger leg: 4.8 ± 0.3 min, weaker leg: 3.4 ± 1.5 min, $P = 0.03$, Figure 3.2). The effect size for leg differences was considered large (Cohen's d = 1.1) (43). The control group displayed no statistical differences in their ability to complete the fixed load cycling trial ($P > 0.05$).

Unilateral Incremental Exercise. Table 3.4 summarizes the data from the unilateral incremental exercise test to volitional fatigue for both groups. VO_2peak (ml/kg/min) and peak workload (watts) were statistically different between legs for the individuals with MS ($P < 0.05$) (VO_2peak: Cohen's d = 1.8; Workload: Cohen's d = 1.2) with no statistical differences observed between legs for RER, peak lactate, maximal HR, VE, and RPE. The mean between leg differences for VO_2peak was 3.1 ml/kg/min with a 95% CI of (1.5 to 4.6) and 18.1 watts for peak workload with a 95% CI of (6.4 to 29.9). No statistical differences were observed between legs in the control group for VO_2peak, peak workload, maximal HR, VE, and RPE. Comparing across the groups (MS vs. controls), the stronger leg was not statistically different for either VO_2peak or peak workload ($P = 0.09$ and 0.08, respectively) whereas the weaker leg was statistically

different ($P < 0.05$ for both variables). There were no statistically significant differences for RER, peak lactate, HR max, and VE between MS and controls subject in stronger or weaker limbs. However, RPE was different between the groups when comparing the weaker legs. The RPE for the weaker leg in the MS group was 8.3 ± 2.1 which was statistically higher than the controls groups' RPE of 5.7 ± 2.1 ($P < 0.05$). There was no statistically significant difference in RPE of the stronger leg across the groups.

Unilateral Incremental Asymmetry Ratio. Asymmetry ratios for peak workload (watts) presented in Figure 3.4. The ratios for the MS group was 0.73 ± 0.23 which was statistically lower when compared control group's ratio (1.01 ± 0.05, $P = 0.01$, d = 1.67).

Comparison between Whole Body and Unilateral Exercise. Peak performance for the stronger leg in the MS group was 72.0 ± 12.7% of double leg VO_2peak and 65.6 ± 14.6% of peak workload. The weaker leg in the MS group performed at 55.9 ± 13.2% and 48.4 ± 19.9% of the double leg max test for VO_2peak and peak workload respectively, which was statistically lower than the performance of the stronger leg ($P = 0.003$, Cohen's d = 2.3 and $P = 0.02$, Cohen's d = 1.6, respectively). In the control group, the stronger leg attainted 69.5 ± 16.1% of the group's double leg VO_2peak and 65.5 ± 15.3% of peak workload. The control group's weaker leg performed at 66.3 ± 14.1% and 65.7 ± 14.3% respectively, which was also not statistically different from the group's stronger leg ($P = 0.32$, Cohen's d = 0.37 and 0.88, Cohen's d = 0.02, respectively, Figure 3.5).

Unilateral Comparison (submaximal fixed load vs. incremental). The subjects' set workloads during the 5-minute fixed load submaximal ride were compared to peak workloads achieved during the single leg max test (Figure 3.6). Retrospectively, the

weaker leg of the MS group was performing at a statistically higher relative intensity compared to the stronger leg (stronger leg: 31.7 ± 11.1%, weaker leg: 48.9 ± 27.5%, $P < 0.05$, Cohen's d = 0.91). Both legs in the control group performed at 32% of maximal workload.

6 Minute Walk: The distance covered during the 6 minute walk was statistically different between groups (MS: 474.3 ± 93.1 vs controls: 626.9 ± 94.0 meters, $P < 0.05$) and was highly correlated to the peak workload asymmetry ratio (r = 0.62).

Study Control Variables: No differences in pre-test physical fatigue scores were observed between sets of single leg visits in either group as measured by the MFIS physical domain ($P > 0.05$). No differences in pre-test POMS-B scores for vigor and fatigue were observed between sets of single leg visits in either group ($P > 0.05$). During the study, two participants (one from each study group) were asked to return on a later date due to elevated MFIS physical scores that were greater than 2.5 standard deviations higher than previous scores. They were re-tested at a later date once fatigue levels returned to their normal levels. The elevated levels of fatigue reported by participants were due to seasonal colds and were unrelated to the current study procedures.

Discussion

The major findings of this study were that ambulatory individuals with relapsing remitting MS, with relatively low disability scores, exhibited statistically significant interlimb differences in strength, oxidative capacity (VO_2peak), and work performed. The magnitude of the asymmetry was related to reductions in exercise tolerance and functional capacity. These findings indicate that despite being ambulatory and having

low disability, our sample of participants exhibited significant interlimb differences not observed in the control group

People with MS often experience decrements in motor drive which often affects the lower limbs disproportionally (32). Despite this knowledge, a majority of previous findings on muscle physiology, function, and fatigue in individuals with MS are based on results conducted on a single leg or with a single muscle group. For example, some studies only test the left leg (44), while other test the right leg (45). Some investigators did not even report which leg was tested (12,20,46), making data interpretation and drawing comparisons across study findings challenging. A select few investigators have tested the weaker/more affected side of the body (18,47) but to date, limited published reports describe interlimb differences in individuals with MS (33).

Activities of daily living such as walking require sufficient synchronization of bilateral motor unit recruitment and discharge rates. Typically, the legs are recruited bilaterally and limb preference may switch depending on the complexity and conditions during the movement (48). Individuals with MS can be limited in their ability to activate motor units during bilateral movements which may result in the development of compensatory strategies in recruitment patterns to their stronger/less affected limb (49). Therefore, the stronger/less affected leg might actually become stronger because of a greater overload stimulus during compensation. Our data might support the possibility of a compensatory recruitment shift, in that the stronger leg in the MS groups produced slightly more isometric force compared to the control group however they were not statistically higher. The inability to bilaterally modulate and produce motor discharge rates appropriately during exercise could result in further interlimb differences

contributing to reductions in exercise capacity and increased levels of premature muscle failure.

The inability of the weaker leg in the MS group to complete the 5 minute submaximal fixed load cycling test may be further evidence of a compensatory motor recruitment switching to the stronger/less affected leg. Comparing workloads during the fixed load ride to the unilateral incremental test, the weaker leg was actually exercising at approximately 49% (range: 24% - 104%) of maximal workloads while the group's stronger leg was exercising at only 32% (range: 25% - 58%). In comparison, the control group was exercising at approximately the same relative intensity for both legs (32%). The inability of the weaker leg to maintain the effort indicates a premature muscle fatigue/task failure not observed in the stronger leg or in either leg of the control group. The premature failure observed in the weaker leg of the MS group may, in part, be explained because it was exercising at a higher relative intensity as a result of altered neurological function.

Previous reports of single leg cycling have shown no differences between legs at constant and incremental loads in both athletic and non-athletic groups for both peak oxygen uptake(50,51) and in the magnitude of muscle activation (recruitment patterns) as measured by electromyography (EMG) (50,51). Data from these studies suggests that each leg produces work and functions aerobically at approximately the same level (50). In participants with MS we found that the stronger limb performed at ~72% of VO_2peak while the weaker limb reached only ~56% of VO_2peak. Similar results have been observed in a case report by White and Dressendorfer who found that in an aerobically trained person with MS the weaker leg was performing at approximately 70% of the

stronger leg (33) and that the weaker leg was not limited by cardiorespiratory mechanisms, but was limited by motor recruitment and/or muscle oxidative capacity. Although no EMG data was collected in the present study, our observations may indicate a possible dissimilar neural activation pattern in the weaker leg in those with MS as indicated by the leg's premature task failure as evidence by the poorer performance during both incremental and fixed load cycling tests.

Further support of the weaker leg in the MS group being susceptible to premature failure was observed in the possible associations between the legs in the MS group for lactate, peak ventilation, and max heart rate. These physiological variables were on average lower (not statistically) for the group's weaker leg relative to the stronger leg during the incremental cycling test, suggesting that the weaker leg might be limited by motor unit recruitment causing premature fatigue/task failure. Additionally the MS group's stronger leg performed similar to the controls group's stronger leg whereas the across group differences comparing the weaker legs showed that the MS group's weaker leg performed at a statistically lower peak oxygen uptake, and peak workload but at a higher leg RPE. The observation that the MS group's stronger legs were comparable to the control group legs suggests that the weaker leg might be a limiting factor in exercise tolerance and performance. Additionally, the increased effort (RPE) during significantly lower exercise performance may show that our sample of individuals with MS lack the ability to achieve cardiorespiratory overload which potentially influences the acute response to exercise as evidence by the differences observed between groups in VO_2peak (ml/kg FFM/min). It is also important to note that our study participants were considered to have relatively low aerobic fitness based on oxygen uptake normative values (52).

The MS participants on average were considered to have “very poor” aerobic fitness and the control participants were of “fair” fitness levels (52). A similar investigation with subjects of higher fitness levels might have produced different results.

Changes in muscle fiber type occur after hemiparetic stroke and other neurological conditions such that myosin heavy chain (MHC) type I are decreased with concomittent increases in MHC type IIx within the weaker limb (53). Additionally, people with MS have displayed an altered ratio of type IIx to type I fibers than non-MS controls (20). Decreased central motor drive and altered muscle fiber phenotypes may help explain the bilateral differences that were found in our research participants. However, our study was not able to separate central and peripheral influences on the observation of premature failure in the weaker leg. However a combination of these factors might play an important role in augmenting the asymmetry observed in this group of individuals with MS.

Rehabilitation specialists have reported using 80% or a ratio of 0.8 between non dominant and dominant leg as an index of a potential pathological imbalance (54). The asymmetry peak workload (WL/SL) ratio in the MS group was 0.73 which was statistically lower in comparison to ratio in our control group 1.01. To gain some insight into the potential consequences of asymmetry we correlated the peak workload asymmetry ratio with the six minute walking test, which is a measure of exercise tolerance and overall functional limitation (42). The high correlation observed between peak workload and the distance covered during the six minute walk further suggests that interlimb differences impacts function and exercise tolerance.

Study Limitations. Our study is one of the first studies to quantify lower extremity bilateral physiological and functional differences during submaximal fixed workload and incremental exercises in individuals with MS. Considering limited published literature, our small sample size and lack of metabolic measurements warrants further research to fully understand these differences. Additionally, this study involved ambulatory individuals with relapsing remitting MS, therefore larger studies with various levels of disease severity would be of interest to further quantify asymmetry and whether the magnitude of the differences in performance between legs changes or can be altered in individuals with MS. It is important to note that; based on our sample of people with mild MS there still was a wide variability in asymmetry. For example, some individuals had legs that are relatively similar in strength and function whereas others had severe asymmetry that was not related to leg dominance (left vs. right). Future studies might attempt to uncover the mechanism of this variability in the MS population.

Conclusion and Future Directions. The major findings of this study were the statistically significant asymmetry in lower extremity strength and performance in a group of individuals with MS. Theses differences appear to affect mobility in individuals with MS as distance covered in the 6 minute walk was highly correlated to the level of asymmetry. The need for early screening and therapeutic interventions targeted at minimizing limb differences could play an important role in maximizing function, minimizing fatigue and attenuating injury risk. These data also highlight that exercise prescription based on heart rate and workload might under overestimate the actually intensity experienced by individuals with MS. Ratings of perceived exertion s should be considered for prescriptions particularly for unilateral exercises. Finally, these leg

differences should be considered when designing future research study protocols. These observations might indicate the need for individually tailored therapeutic interventions designed to target muscle asymmetries. More research is needed to specifically assess muscle quality and function in those individuals susceptible to developing bilateral differences, e.g. MS.

References

(1) Romberg A, Virtanen A, Aunola S, Karppi SL, Karanko H, Ruutiainen J. Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. Mult Scler 2004 Apr;10(2):212-218.

(2) Carroll CC, Gallagher PM, Seidle ME, Trappe SW. Skeletal muscle characteristics of people with multiple sclerosis. Arch Phys Med Rehabil 2005 Feb;86(2):224-229.

(3) Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. Arch Phys Med Rehabil 1984 Mar;65(3):135-138.

(4) Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol 1988 Apr;45(4):435-437.

(5) Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. Mult Scler 2003 Jun;9(3):219-227.

(6) Bakshi R, Shaikh ZA, Miletich RS, Czarnecki D, Dmochowski J, Henschel K, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 2000 Jun;6(3):181-185.

(7) Bergamaschi R, Romani A, Versino M, Poli R, Cosi V. Clinical aspects of fatigue in multiple sclerosis. Funct Neurol 1997 Sep-Oct;12(5):247-251.

(8) Murray TJ. Amantadine therapy for fatigue in multiple sclerosis. Can J Neurol Sci 1985 Aug;12(3):251-254.

(9) Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994 Feb;21(1):9-14.

(10) Kos D, Nagels G, D'Hooghe MB, Duportail M, Kerckhofs E. A rapid screening tool for fatigue impact in multiple sclerosis. BMC Neurol 2006 Aug 17;6:27.

(11) Kos D, Duportail M, D'hooghe M, Nagels G, Kerckhofs E. Multidisciplinary fatigue management programme in multiple sclerosis: a randomized clinical trial. Mult Scler 2007 Sep;13(8):996-1003.

(12) Sharma KR, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. Muscle Nerve 1995 Dec;18(12):1403-1411.

(13) Kent-Braun JA, Sharma KR, Weiner MW, Miller RG. Effects of exercise on muscle activation and metabolism in multiple sclerosis. Muscle Nerve 1994 Oct;17(10):1162-1169.

(14) Edwards RH. Human muscle function and fatigue. Ciba Found Symp 1981;82:1-18.

(15) Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. Muscle Nerve 1992 Oct;15(10):1123-1132.

(16) Ingram DA, Thompson AJ, Swash M. Central motor conduction in multiple sclerosis: evaluation of abnormalities revealed by transcutaneous magnetic stimulation of the brain. J Neurol Neurosurg Psychiatry 1988 Apr;51(4):487-494.

(17) Nielsen JF. Frequency-dependent conduction delay of motor-evoked potentials in multiple sclerosis. Muscle Nerve 1997 Oct;20(10):1264-1274.

(18) Garner DJ, Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. Muscle Nerve 2003 Apr;27(4):456-464.

(19) Kent-Braun JA, Sharma KR, Miller RG, Weiner MW. Postexercise phosphocreatine resynthesis is slowed in multiple sclerosis. Muscle Nerve 1994 Aug;17(8):835-841.

(20) Kent-Braun JA, Ng AV, Castro M, Weiner MW, Gelinas D, Dudley GA, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. J Appl Physiol 1997 Dec;83(6):1998-2004.

(21) Kent-Braun JA, Walker CH, Weiner MW, Miller RG. Functional significance of upper and lower motor neuron impairment in amyotrophic lateral sclerosis. Muscle Nerve 1998 Jun;21(6):762-768.

(22) Anema JR, Heijenbrok MW, Faes TJ, Heimans JJ, Lanting P, Polman CH. Cardiovascular autonomic function in multiple sclerosis. J Neurol Sci 1991 Aug;104(2):129-134.

(23) Cartlidge NE. Autonomic function in multiple sclerosis. Brain 1972;95(4):661-664.

(24) Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Jak AJ, et al. Use of the multiple sclerosis functional composite as an outcome measure in a phase 3 clinical trial. Arch Neurol 2001 Jun;58(6):961-967.

(25) Drory VE, Nisipeanu PF, Kroczyn AD. Tests of autonomic dysfunction in patients with multiple sclerosis. Acta Neurol Scand 1995 Nov;92(5):356-360.

(26) Nordenbo AM, Boesen F, Andersen EB. Cardiovascular autonomic function in multiple sclerosis. J Auton Nerv Syst 1989 Feb;26(1):77-84.

(27) Pepin EB, Hicks RW, Spencer MK, Tran ZV, Jackson CG. Pressor response to isometric exercise in patients with multiple sclerosis. Med Sci Sports Exerc 1996 Jun;28(6):656-660.

(28) Senaratne MP, Carroll D, Warren KG, Kappagoda T. Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. J Neurol Neurosurg Psychiatry 1984 Sep;47(9):947-952.

(29) Sterman AB, Coyle PK, Panasci DJ, Grimson R. Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. Neurology 1985 Nov;35(11):1665-1668.

(30) Thomaides TN, Zoukos Y, Chaudhuri KR, Mathias CJ. Physiological assessment of aspects of autonomic function in patients with secondary progressive multiple sclerosis. J Neurol 1993;240(3):139-143.

(31) Chung LH, Remelius JG, Van Emmerik RE, Kent-Braun JA. Leg power asymmetry and postural control in women with multiple sclerosis. Med Sci Sports Exerc 2008 Oct;40(10):1717-1724.

(32) DeMyer WE. *Technique of the Neurological Examination*. 5th ed. 5th ed. U.S.: McGraw Hill; 2004.

(33) White LJ, Dressendorfer RH. Factors limiting maximal oxygen uptake in exertional monoparesis. Mult Scler 2005 Apr;11(2):240-241.

(34) Thoumie P, Lamotte D, Cantalloube S, Faucher M, Amarenco G. Motor determinants of gait in 100 ambulatory patients with multiple sclerosis. Mult Scler 2005 Aug;11(4):485-491.

(35) Lambert CP, Archer RL, Evans WJ. Muscle strength and fatigue during isokinetic exercise in individuals with multiple sclerosis. Med Sci Sports Exerc 2001 Oct;33(10):1613-1619.

(36) Larson RL, White LJ. Asymmetrical Hip Bone Density in Multiple Sclerosis. IJMSC 2011;13(1):43-47.

(37) Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983 Nov;33(11):1444-1452.

(38) Whaley MH. ACSM's guidelines for exercise testing and prescription. 7th ed. New York: Lippincott Williams & Wilkins; 2006.

(39) Borg GA. Perceived exertion. Exerc Sport Sci Rev 1974;2:131-153.

(40) McPhee JS, Williams AG, Stewart C, Baar K, Schindler JP, Aldred S, et al. The training stimulus experienced by the leg muscles during cycling in humans. Exp Physiol 2009 Jun;94(6):684-694.

(41) Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985 Apr 15;132(8):919-923.

(42) McGavin CR, Gupta SP, McHardy GJ. Twelve-minute walking test for assessing disability in chronic bronchitis. Br Med J 1976 Apr 3;1(6013):822-823.

(43) Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* : Lawrence Erlbaum Associates; 1988.

(44) de Haan A, de Ruiter CJ, van Der Woude LH, Jongen PJ. Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. Muscle Nerve 2000 Oct;23(10):1534-1541.

(45) Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve 2004 Jun;29(6):843-852.

(46) Ng AV, Dao HT, Miller RG, Gelinas DF, Kent-Braun JA. Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. J Appl Physiol 2000 Mar;88(3):871-880.

(47) Ng AV, Miller RG, Kent-Braun JA. Central motor drive is increased during voluntary muscle contractions in multiple sclerosis. Muscle Nerve 1997 Oct;20(10):1213-1218.

(48) Hart S, Gabbard C. Brief communication: bilateral footedness and task complexity. Int J Neurosci 1996 Nov;88(1-2):141-146.

(49) Teixeira MC, Teixeira LA. Leg preference and interlateral performance asymmetry in soccer player children. Dev Psychobiol 2008 Dec;50(8):799-806.

(50) Carpes FP, Diefenthaeler F, Bini RR, Stefanyshyn D, Faria IE, Mota CB. Does leg preference affect muscle activation and efficiency? J Electromyogr Kinesiol 2010 Dec;20(6):1230-1236.

(51) Sargeant AJ, Davies CT. Forces applied to cranks of a bicycle ergometer during one- and two-leg cycling. J Appl Physiol 1977 Apr;42(4):514-518.

(52) Heyward VH. Advance Fitness Assessment & Exercise Prescription. 5th ed.: Burgess Publishing Company; 1998.

(53) McKenzie MJ, Yu S, Prior SJ, Macko RF, Hafer-Macko CE. Hemiparetic stroke alters vastus lateralis myosin heavy chain profiles between the paretic and nonparetic muscles. Res Sports Med 2009 Jan-Mar;17(1):17-27.

(54) Wyatt MP, Edwards AM. Comparison of Quadriceps and Hamstring Torque Values during lsokinetic Exercise. J Orthop Sports Phys Ther 1981;3(2):48-56.

Table 3.1. *Participant characteristics*

	MS (n = 8)	Controls (n = 7)	*P*
Age (yrs)	51.6 ± 9.2	49.4 ± 14.3	0.74
Height (cm)	167.5 ± 7.5	169.1 ± 9.0	0.72
Body Mass (kg)	70.4 ± 13.8	75.4 ± 30.4	0.74
Body Mass Index (kg/m^2)	25.0 ± 3.9	26.0 ± 8.3	0.77
Fat Mass (%)	39.4 ± 6.1	36.9 ± 8.7	0.52
Frequency of exercise (day/wk)	2.8 ± 2.5	3.8 ± 1.9	0.58
Duration of exercise sessions (min)	30 ± 11.3	42.9 ± 25.1	0.25

Data are mean ± SD. MS, Multiple Sclerosis. *$P < 0.05$ represents a statistically significant difference in group means.

Table 3.2. *Lean and fat mass of lower leg*

	MS (n = 8)			Controls (n = 7)		
	Stronger Leg	Weaker Leg	*P*	Stronger Leg	Weaker Leg	*P*
Lean Mass (Kg)	7.5 ± 1.4	7.3 ± 1.4	0.20	8.1 ± 2.2	8.2 ± 2.1	0.31
Fat Mass (Kg)	5.3 ± 1.1	5.3 ± 1.2	0.95	5.3 ± 2.0	5.2 ± 2.0	0.66

Data are mean ± SD. MS, Multiple Sclerosis. *$P < 0.05$ represents a statistically significant difference between legs and across groups.

Table 3.3. *Metabolic and associated measures during whole body GXT*

Variable	MS	Controls	*P*
VO_2peak (ml/kg/min)	19.3 ± 4.9	26.1 ± 8.4	0.07
VO_2peak (ml/kgFFM/min)	32.9 ± 4.7	41.7 ± 8.7	0.04*
Peak Workload (watts)	115.0 ± 28.9	155.0 ± 51.8	0.10
RER (VCO_2/VO_2)	1.18 ± 0.17	1.17 ± 0.1	0.96
Peak Lactate (mmol/L)	5.7 ± 2.5	6.7 ± 1.8	0.38
HR max (beats/min)	138.0 ± 15.7	159.4 ± 21.7	0.06
VE (L/min)	50.5 ± 17.9	59.4 ± 17.1	0.32
RPE (whole body)	7.9 ± 2.2	7.7 ± 1.7	0.88

Data are mean ± SD. MS, Multiple Sclerosis; FFM, fat free mass, RER respiratory exchange ratio; HR max, maximal heart rate; VE, ventilation; RPE, rate of perceived exertion. *$P < 0.05$ represents statistically significant differences in group means.

Table 3.4. *Metabolic and associated measures during single leg GXT*

	MS			Controls		
Variable	Stronger Leg	Weaker Leg	*P*	Stronger Leg	Weaker Leg	*P*
VO_2peak (ml/kg/min)	13.7 ± 3.2	10.6 ± 3.0	0.002*	18.1 ± 5.8	17.24 ± 5.3	0.31
Peak Workload (watts)	73.4 ± 22.3	56.3 ± 26.2	0.01*	98.7 ± 26.7	99.29 ± 27.1	0.78
RER peak	1.2 ± 0.2	1.1 ± 2.1	0.26	1.2 ± 0.1	1.1 ± 0.13	0.35
Lactate (mmol/L)	5.1 ± 2.6	4.2 ± 1.9	0.26	4.67 ± 1.2	4.64 ± 1.5	0.92
HR max (beats/min)	130.9 ± 19.2	121.8 ± 22.3	0.09	138.7 ± 17	141.1 ± 19.1	0.25
VE (L/min)	35.4 ± 14.8	27.1± 13.7	0.07	36.3 ± 11.2	36.0 ± 10.5	0.90
RPE (exercising leg)	7.6 ± 2.4	8.3 ± 2.1	0.22	5 ± 2	5.7 ± 2.1	0.36
Pain	2.5 ± 2.9	1.1 ± 2.1	0.15	3 ± 3	2.9 ± 3.0	1.0

Data are mean ± SD. MS, Multiple Sclerosis; RER, respiratory exchange ratio; HR max, maximal heart rate; VE, ventilation; RPE, rate of perceived exertion of exercising leg. *$P < 0.05$ represents statistically significant differences in group means.

a)

b)

Figure 3.1. Single leg cycling position (a-b).

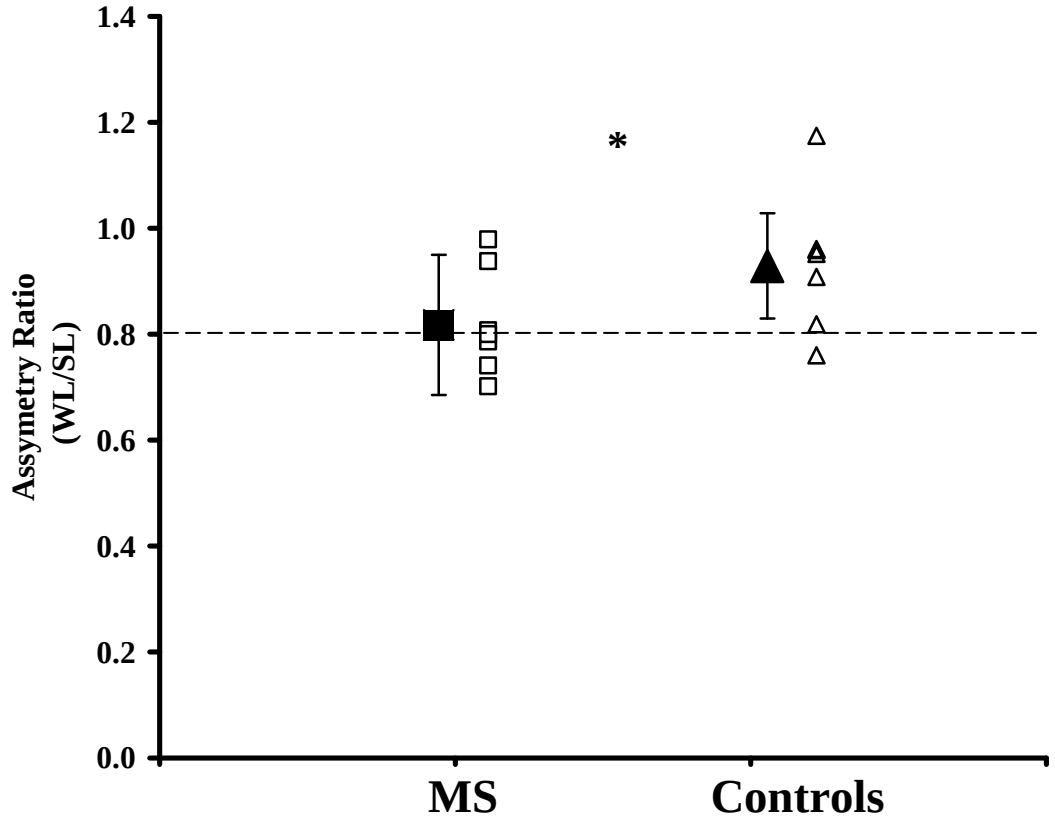


Figure 3.2. Leg asymmetry ratios for maximal isometric strength of the quadriceps. Values are means ± SD. MS, Multiple Sclerosis; WL, weaker leg; SL, stronger leg. *$P < 0.05$ represents statistically significant differences in group means. Dashed line indicates pathological imbalance.

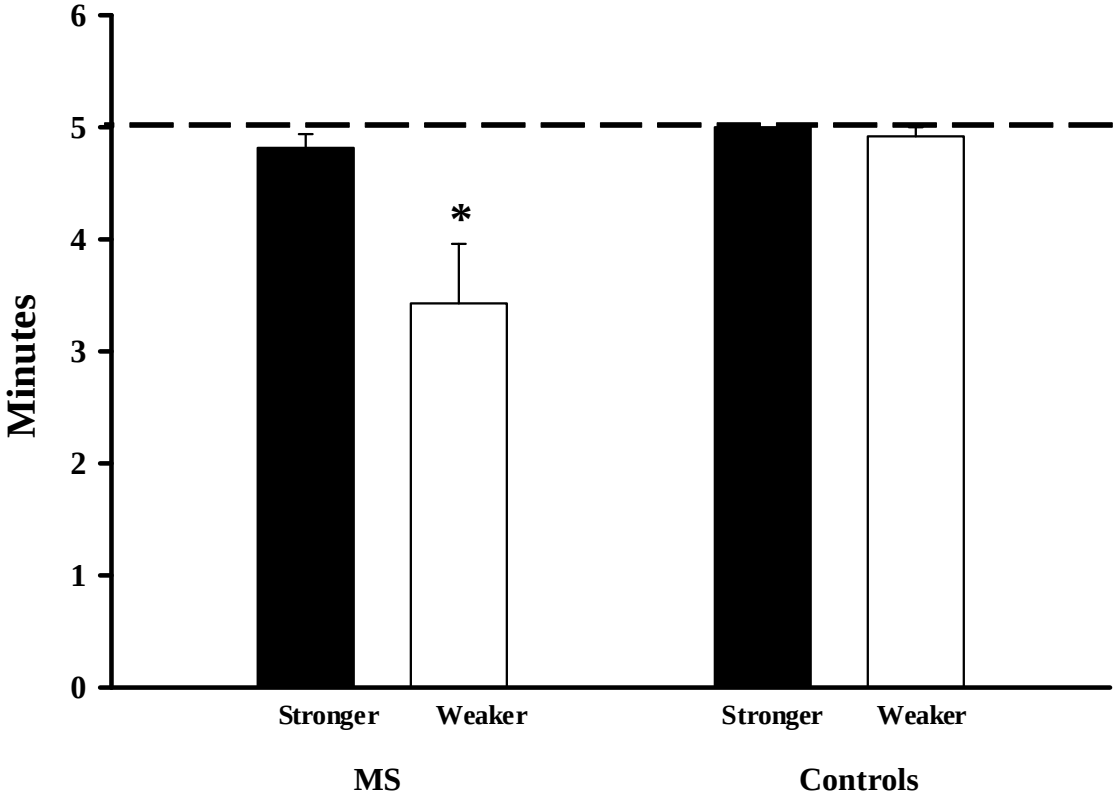


Figure 3.3. Time completed of the submaximal fixed workload ride (5 minute). Values are means ± SE. MS, Multiple Sclerosis. *P < 0.05 represents statistically significant differences in group means. Dashed line indicates maximum ride time.

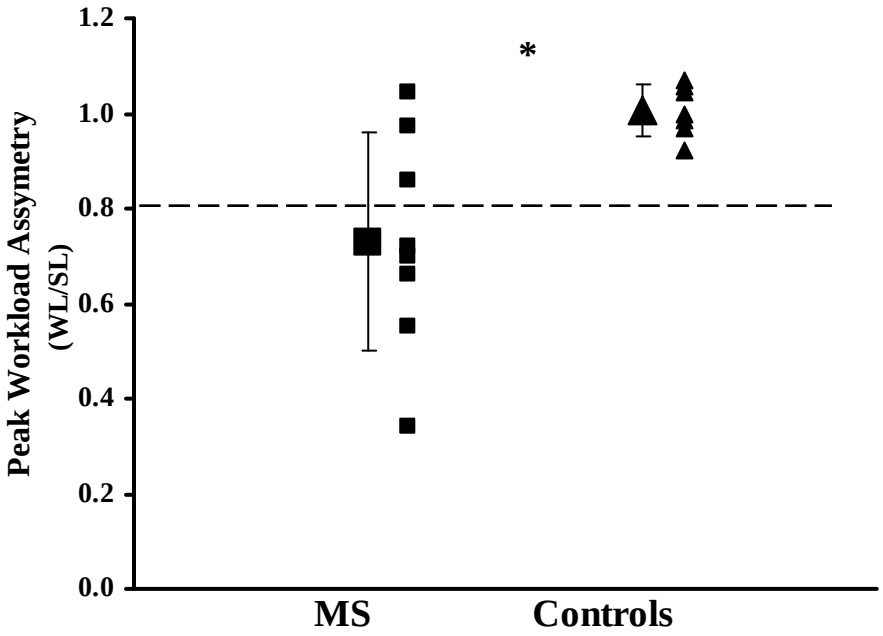


Figure 3.4. Leg asymmetry ratios for peak workload. Values are means ± SD. MS, Multiple Sclerosis; WL, weaker leg; SL, stronger leg. * Significant difference between groups ($P < 0.05$). Dashed line indicates pathological imbalance.

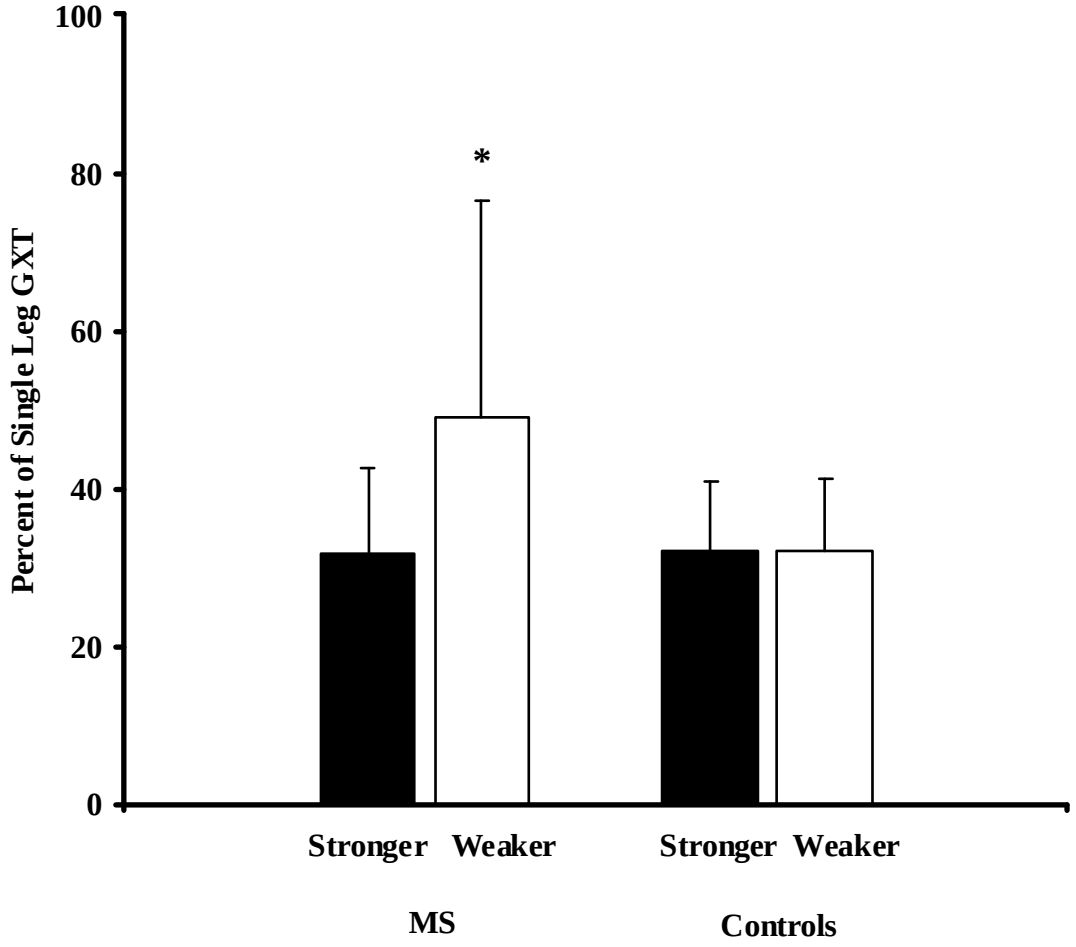


Figure 3.5. Submaximal single leg workload as a percent of single leg maximal workload. Values are means ± SD. MS, Multiple Sclerosis. * Significant difference between limbs ($P < 0.05$).

CHAPTER 4

DIFFERENCES IN MUSCLE FUNCTION AND MOBILITY FOLLOWING UNILATERAL EXERCISE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS[2]

[2] Larson, R.L., Baumgartner, T.A., McCully, K.K., Pryor, W.M. and White, L.J. To be submitted to *Multiple Sclerosis*

Abstract

Introduction. The purpose of this study was to determine whether unilateral exercise would affect bilateral asymmetry in individuals with mild Multiple Sclerosis (MS) relative to non-MS controls. **Methods.** Eight individuals (mean age = 51.6 ± 9.2 yrs) with relapsing remitting MS and an Expanded Disability Status Scale score (EDSS) = 2.6 ± 1.6 and 7 controls (49.4 ± 14.3 yrs) completed unilateral cycling tests with pre and post measures of lower extremity muscle performance and gait. **Results.** Prior to exercise the groups had significantly different strength asymmetry ratios (MS: 0.82 ± 0.09 vs. control: 0.93 ± 0.14 (P <0.05)) and following unilateral exercise, the magnitude of asymmetry was no longer statistically different between groups (P > 0.05). Both groups displayed non significant (P > 0.05) interlimb differences in stride velocity and foot tap speed. Stride velocity and foot tap speed were significantly reduced (P < 0.05) following both bouts of unilateral exercise (stronger leg: 156.3 ± 30.6 to 141.5 ± 20.9 cm/sec and weaker leg: 157.8 ± 30.9 to 140.8 ± 20.1 cm/sec; stronger leg: 32.13 ± 6.58 to 24.50 ± 6.37 taps/10sec, and weaker leg: 26.88 ± 7.00 to 19.00 ± 6.93 taps/10sec, respectively) in the MS but not the control group. **Conclusion.** These findings provide possible insight into the consequences of fatigue on lower extremity asymmetry and function and the need for new therapeutic interventions.

Key Words: Multiple Sclerosis, bilateral, unilateral, fatigue, strength, gait.

Introduction

Fatigue (symptomatic and/or muscular) is often expressed as the most disabling symptom in individuals with Multiple Sclerosis (MS) (1,2). Muscular fatigue has been associated with reduced exercise performance and function (3,4). However, the exact mechanisms of muscular fatigue in MS patients remain relatively elusive despite its prevalence. Individuals with MS are known to exhibit reduced skeletal muscle neural drive (motor fatigue) during exercise which contributes to premature fatigue and subsequent impact on muscle function and performance (5-9). One area of muscle fatigue research that remains relatively unexplored is whether exercise impacts function similarly between legs.

Some evidence of bilateral differences in strength and function have been indentified in individuals with MS (4,10-12). The inability to equally activate lower body musculature could contribute to different rates of fatigue between legs causing a compensatory role in one limb (13). Magnified unilateral symptoms of the lower extremities may heighten muscle fatigue because of poor efficiency or other adaptive mechanisms related to asymmetry. Therefore, the purpose of this study was to determine whether unilateral exercise would affect bilateral differences in individuals with mild Multiple Sclerosis compared to controls. We hypothesized that individuals with MS would exhibit greater leg differences in performance and function as measured by foot tap speed, strength, and ambulation speed following unilateral exercise relative to controls.

Methods

Participants. Fifteen volunteers, eight individuals with MS (6 women and 2 men) and 7 non-MS healthy controls (5 women and 2 men) participated in the study. Participants with MS were included in the study if they had a physician diagnosis of relapsing-remitting MS (14) and an Expanded Disability Status Scale (EDSS) score (as determined by a physician) of less than 6.5 (ambulatory without aid). Individuals with multiple risk factors for cardiovascular disease or orthopedic limitations established by ACSM were excluded from the study (15). Prior to enrollment, each individual received physician's clearance to ensure safe participation and signed a consent form approved by the University's Institutional Review Board.

Experimental Design. This study was part of a larger study and involved participation in five days of testing separated by at least two days (48 hours, to provide full recovery), with subject testing conducted at approximately the same time of day. All participants had a defined stronger leg (less affected) and a weaker leg (more affected) based on leg extensor strength assessments and self reports. The first day consisted of familiarization of all testing procedures, and during subsequent visits, participants completed a series of four (2 sets) unilateral incremental cycling tests to induce muscle fatigue and measure outcomes.

Set 1: Participants performed gait and strength assessments from rested (pre) and post unilateral exercise states. Participants walked across a specialized mat, one time, and then performed a maximal leg extensor isometric force test. The time between the gait and strength assessments was approximately 30 seconds. Following the exercise treatment, the gait and strength assessments were both administered again. The time

between the end of the exercise test and the start of the gait assessment was approximately 30 seconds which was directly followed by the strength assessment which was administered within 30 seconds after the gait assessment, approximately one minute following exercise.

Set 2: A lower body neuroperformance foot tap test was performed before and within 15 seconds following the unilateral incremental exercise test (10,16).

Gait Assessment. Ambulation speed was assessed using a special computerized electronic walkway (GAITRite (Havertown, PA). The GAITRite has been validated for healthy adults (17-19) and has also been used as a research tool in clinical studies using individuals with MS (20). The selected gait parameter used for this study was stride velocity to measure ambulation speed. To ensure participant safety, a gait belt was worn along with research staff acting as spotters. Prior to unilateral exercise, participants were asked to walk one time across the gait mat "as quickly, but as safely as possible".

Lower Extremity Strength. A stronger/less affected leg and a weaker/more affected leg were identified for each individual based on an initial strength assessment. Leg extensor strength of each limb was assessed using a custom chair equipped with a force transducer. The knee angle was at a constant 70 degrees and participant's torso and testing leg were secured with straps for stabilization. The lever arm of the chair was connected to a force transducer and a digitized signal from the transducer was sent to a computer and recorded using MatLab. A standardized warm-up of three submaximal contractions was performed. Following a five minutes of rest period, participants performed three maximal voluntary isometric contractions (MVIC) using the highest of

the three trials. The strength assessments during Set 1 visits used the same equipment and procedures with the exception of the warm-up and the repeated trials.

Unilateral Incremental Exercise Protocol. Unilateral cycling protocols have been previously used in healthy individuals to detect differences between limbs (21-23) and responses to training (24). A single leg continuous ramp protocol was used to induce muscle fatigue. Prior to the start of exercise, participants performed a standard two legged warm-up which included cycling for 2-3 minutes at 25 W followed by a five minute rest period. For testing, the foot of the leg being tested was securely fastened to the pedal and the non-exercising leg was positioned to minimize its use while keeping the overall body position similar to two legged cycling (Figure 4.1. depicts leg this position). The seat height was positioned so that the exercising leg was almost fully extended when the pedal crank was at the lowest position. The exercise trial started at 0 W and increased the workload in a continuous manner of 1 watt every 2 seconds until participants met one of the following criteria: 1) any symptoms that impaired the participants ability to continue the test or indicated a risk to safety or health, 2) volitional exhaustion, and/or 3) the pedaling rate fell below 40 revolutions per minute. Metabolic measurements were recorded continuously and averaged over 30-second intervals.

Foot Tap Test: Foot tap speed was measured as the number of foot taps performed in 10 seconds with the knee and hips at 90º of flexion with the participant's leg place on a chair next to the bike. Participants were instructed to keep their heel on the chair and to tap the chair with the ball of their foot as quickly as possible. The number of taps was counted by the same investigator (10,16).

Study Control Variables. Since legs were tested on different days, separated by 48 hrs, participants filled out two questionnaires related to feelings of fatigue prior to testing, which included the, Modified Fatigue Impact Scale (MFIS) physical subscale and, the profile moods state brief version (POMS-B). This was done to guard against possible confounding influences baseline fatigue could have on outcome variables. Hydration status was determined by urine measuring specific gravity (USG < 1.030). If the urine specific gravity was low (USG > 1.030), the participant was asked to hydrate and return to the lab the next day for testing. Body composition and limb specific tissue composition were measured by dual-energy x-ray absorptiometry (iDXA, GE Healthcare-Lunar, Madison, WI). Self reported physical activity level was measured using a questionnaire which asked about frequency, duration, and intensity of physical activity during a typical week.

Statistics analyses. All analyses were performed using SPSS software v. 16.0 (SPSS, Inc., Chicago, IL). Independent t-tests were used to detect any across group differences. Dependent t-tests were used to compare across-limb differences for strength, stride velocity, and foot tap speed before and after exercise. Data are expressed as mean ± SD. An alpha of 0.05 was our criteria to establish statistically significant differences. Precise *P* values, Cohen's d, and confidence intervals (CI) are reported, as appropriate.

Results

Participant characteristics. Eight individuals in the MS group (6 women and 2 men, without assisted devices) and seven healthy individuals (5 women and 2 men) in the control group completed the study. MS disease classification was relapsing remitting and the mean Expanded Disability Status Scale (EDSS) score of 2.6 ± 1.6 indicated a mild to

moderate impairment. Duration of the disease was 12.6 ± 8.1 yr (ranging from 6 to 31 yr.). Anthropometric data are shown in Table 4.1. No statistically significant differences existed between the groups for age, height, weight, body mass, body mass index, total percent body fat, and self reports of physical activity ($P > 0.05$).

Leg Composition. Lean and fat mass of the legs were not different between legs for both groups (Table 4.2). Neither lean nor fat mass were significantly different across the groups for the strong ($P = 0.52$ and 0.93, respectively) and the weak legs ($P = 0.33$, and 0.91, respectively).

Unilateral Incremental Exercise. VO_2peak (ml/kg/min) and peak workload (watts) were significantly different between the stronger and weaker legs for the individuals with MS ($P < 0.05$). The control group demonstrated no statistically significant differences between legs for both variables. The two sets of unilateral exercise tests were compared to assure test-retest reliability. Interclass correlation for peak oxygen uptake was 0.96 with a 95% CI of (0.84, 0.99) and for peak workload was 0.96 with a 95% CI of (0.89, 0.99).

Leg Strength before and after Exercise. Prior to exercise leg extensor strength was statistically different between legs in the MS group (stronger leg: 95.3 ± 27.9 (lbs) vs. weaker leg: 76.9 ± 19.6 (lbs), $P = 0.004$). The effect size for leg differences was (d = 1.2) considered large (25). The mean strength difference between legs in the MS group was 18.3 (lbs) with a 95% CI of (7.9 to 28.8). No statistical differences were observed between legs in the control group (stronger leg: 87.5 ± 26.5 (lbs) vs. weaker leg: 82.9 ± 33.5 (lbs), $P = 0.40$). Following unilateral exercise, maximal isometric strength of the leg extensors was not statistically different for either leg in either group ($P > 0.05$).

Normalizing strength to the fat free mass of the legs did not produce different results (Figure 4.2).

Leg Strength Asymmetry Ratio Before and After Exercise. A WL/SL (ND/D) ratio was calculated using maximal leg extensor strength. The ratio for the MS group was 0.82 ± 0.09 which was statistically lower compared to the control group's ratio of 0.93 ± 0.14 (P = 0.03, Cohen's d = .93). Following unilateral exercise, the MS group's asymmetry ratio was 0.89 ± 0.13 which was no longer statistically different when compared to the controls group post exercise asymmetry ratio which was 0.90 ± 0.17 (P = 0.42, Cohen's d = 0.11, Figure 4.3).

Stride Velocity Before and After Exercise: There were no significant differences in stride velocity between legs before or after unilateral exercise in either group (P > 0.05). Following unilateral cycling, significant reductions in stride velocity were observed for both the stronger and weaker legs in participants with MS (stronger leg: 156.3 ± 30.6 to 141.5 ± 20.9 cm/sec, P = 0.03; and weaker leg: 157.8 ± 30.9 to 140.8 ± 20.1 cm/sec, P = 0.02, See Figure 4.4). Whereas we observed no statistical differences for the control group following the exercise bout (stronger leg: 215.6 ± 21.6 to 210.8 ± 19.3 cm/sec, P = 0.38 and weaker leg: 203.7 ± 19.4 to 209.0 ± 23.3 cm/sec, P = 0.28, See Figure 4.4). Comparing across the groups, stride velocity was statistically slower before and after unilateral exercise (fatigued and non-fatigued, P < 0.05) for MS participants.

Foot-Tap Speed. The foot tap speed was not statistically different between legs in either group prior to exercise (P > 0.05). Unilateral foot tap speed was statistically slower following the unilateral exercise for both the stronger and weaker legs in the MS group (stronger leg: 32.1 ± 6.6 to 24.5 ± 6.4 tap/10sec, P = 0.009, Cohen's d = 2.05 and

weaker leg: 26.9 ± 7.0 to 19.0 ± 6.9, P = 0.005, Cohen's d = 2.06). The control group showed no statistical differences in foot tap speed following exercise for either leg (stronger leg: 35.3 ± 4.2 to 32.4 ± 7.0 taps/10sec; P = 0.41 and weaker leg: 36.0 ± 5.3 to 34.6 ± 4.8, P = 0.22). Comparing foot tap speed between groups at rest, no statistical differences were observed between the stronger legs (P = 0.21) whereas the weaker legs were statically different (P = 0.02). Following exercise both the stronger and weaker legs were statistically different ($P < 0.05$) across the groups (Figure 4.5).

Discussion

The major findings of this study were that ambulatory individuals with Relapsing Remitting MS 1) did not exhibit statistically significant differences in gait and foot tap speed but were different in strength bilaterally and 2) did not exhibit magnified asymmetry in pre to post assessments of strength, stride velocity, or foot tap speed, following unilateral exercise, and 3) exhibited a significantly slower gait speed and foot tap speed before and after unilateral exercise compared to controls. Our original hypothesis was that unilateral exercise would magnify differences between legs for MS participants and that we would observe no differences in our control group. Our results do not totally support our original hypothesis as we observed similar reductions in performance in both legs.

It has been repeatedly shown that individuals with MS have muscle weakness (4,5,7,9) and elevated levels of muscle fatigue, especially in their lower extremities compared to controls (6,26,27). Our study focused on asymmetry as a potential mechanism for premature muscle fatigue by unilaterally fatiguing the lower leg and assessing maximal voluntary isometric strength (MVIC), ambulation speed, and foot tap

speed. We designed our study to assess differences between the stronger /less affected and the weaker /more affected limbs based on the knowledge that MS can affect one side more than the other (28). A majority of previous findings on muscle function and fatigue in individuals with MS are based on results from studies conducted on one leg or with a single muscle group. For example, some studies only use the left leg (29) while others use the right leg (5) for experimentation. Some investigators did not even report which leg was tested (5,26,30). A select few investigators have tested the weaker/more affected side of the body (7,31) but to date, limited published reports describe between leg differences in individuals with MS (10,12).

Significant skeletal muscle weakness has been observed before and following both voluntary exercise and electrical stimulation in individuals with MS (26,30,32). These results are not consistent across all studies, with some investigators observing no difference in quadriceps force production between MS and controls following exercise (7). These conflicting findings could be explained as being a result of motor unit recruitment variability between and within groups of individuals with MS (9,26). Additionally, these disparate observations across studies may reflect a multitude of confounding factors which include, but are not limited to, the type of exercise (voluntary vs. electrically stimulation), exercise intensity (maximal vs. submaximal), disease severity and duration, and/or the muscle group tested.

In the current study, we observed differences in strength between legs in the MS group that were not observed in the control group. Maximal leg extensor strength was not statistically reduced in either leg following unilateral exercise in either group. However, the group's asymmetry ratios following exercise were altered. The leg

extensor asymmetry ratio prior to unilateral exercise was 12% lower in the MS group compared to the control group (0.82 and 0.92, respectively). Following unilateral exercise, the MS group's asymmetry ratio increased about 8% (0.89) whereas the control group's ratio decreased about 3% (0.90), negating the statistically significant difference between the groups before exercise. These results are contrary to our original hypothesis that unilateral exercise would increase the magnitude of bilateral differences for individuals with MS.

Our observations of post exercise improvement in the asymmetry ratio such that the groups were no longer statistically different may appear to be contradictory to investigators who observe decrements in force production following exercise. However, previous literature assessing muscle fatigue in individuals with MS have primarily used isometric electrical stimulation (26,29,29,33) to induce isolated muscle fatigue, whereas we used whole leg voluntary concentric exercise and then measured force production in the quadriceps. Voluntary and electrical stimulated exercises clearly place the muscle under different physiological conditions. Motor unit recruitment order is one of the main contributors to these physiological differences. With electrical stimulation, the fast-twitch fibers (larger axons) can be activated at lower force levels in a random/nonselective pattern, resulting in a greater reduction in muscle force production (34-37), greater increases in oxygen consumption, and greater changes in blood lactate; when compared to voluntary exercise at the same intensity (38-42). During voluntary muscle contractions, motor unit recruitment follows a different sequence, purportedly governed by the "size principle," which states that at low muscle force levels, motor units

with small axons are recruited first and as force increases the larger axons are recruited (43).

Additionally, the order of the tests might have influenced the outcome of our results. Since leg extensor strength test was performed up to approximately one minute following unilateral exercise, the leg could have started to recover slightly from the fatiguing ride. However, the observation of non statistical differences in asymmetry following exercise may suggest that the legs in the MS group might respond to task failure differently.

To our knowledge, we are the first to examine ambulation speed following unilateral exercise in any population. Similar to previous studies, we observed a statistically slower stride velocity in the group of individuals with MS compared to our control group (20,44,45). The participants were asked to try and walk as "quickly but as safely as possible" following unilateral exercise. Increasing stride velocity requires a person to decrease the amount of time in the stance phase of the gait cycle (46). Following unilateral exercise, a greater reliance of support had to come from the opposite limb. In a response to the instability, the speed of movement slowed in the individuals with MS (a 9% reduction), whereas these differences were not observed in the control group (a 1.3% reduction). Exercising the one limb in the MS group could have disturbed neural drive on that side, thus slowing the speed of contraction which has been previously reported by other investigators (5-9,27). Our original hypothesis was that unilateral exercise would cause a more pronounced asymmetry following the weaker leg treatment, resulting in a slower ambulation speed. Instead, we observed relatively similar responses for both leg treatments.

The ability to perform movements that require rapid succession, such as the number of foot taps in a short period of time, is dependent on the effective modulation of both motor unit recruitment and rate coding (47). Loss of upper motor neuron function can result in slower contraction speeds, muscle weakness and decreases in the ability to activate muscles (47-49). The number of foot taps performed in 10 seconds has been used as a clinical tool to assess central motor function and has been previously used by other investigators assessing upper motor neuron function in individuals with MS (16,26,33). The significant slowing in foot-tap speed in both legs following unilateral exercise in individuals with MS might indicate that muscle function and performance could be limited by the ability to rapidly develop high motor discharge rates as the muscles become fatigued (49). Functionally, the inability to modulate motor discharge rates might result in greater magnitudes and rates of fatigability. These seemed to be slightly amplified in the weaker leg (reduced by 29%) compared to the stronger leg (reduced by 23%) in our MS sample. Comparatively, the control group showed no statistical slowing in foot tap speed following unilateral exercise for either leg. We did not observe bilateral differences in foot tap speed in either group before or after exercise. When comparing across the groups, the weaker leg was statistically slower in the MS group prior to unilateral exercise. Following unilateral exercise, both the stronger and weaker legs in the MS group displayed slower toe tap speed compared to controls ($P < 0.05$).

The ability to perform repeated rapid movements is important in activities of daily living. If this ability is compromised because of premature task failure and lower extremity muscle asymmetry, therapeutic interventions effective in minimizing such

differences may enhance or preserve daily activity performance. Thus, the present observations of reduced ability to produced rapid movements following exercise maybe more clinically relevant due to its impact on mobility and on safe physical functioning especially in those individuals with MS who exhibit foot drop (a symptom of MS).

Study Limitations. Our study is one of the first to examine the effects of unilateral leg exercise on indices of bilateral strength, ambulation speed, and foot tap speed. Due to the limited published literature and our small sample size of only ambulatory individuals with relapsing remitting MS, further research is warranted to fully understand these differences. Additionally, this study involved ambulatory individuals with relapsing remitting MS, therefore larger studies with various levels of disease severity would be of interest to further quantify the differences in performance following unilateral leg exercise in individuals with MS. Another study limitation is the lack of a muscle activation test. A commonly used protocol to asses muscle activation requires high levels of electrical stimulation to a muscle or muscle group during a voluntary muscle contraction. Our study was limited by the lack of participant tolerance to stimulation rates high enough to induce maximal activation of motor units. Despite study limitations, our findings provide valuable information regarding the non uniform performance effects between limbs both before and following exercise compared to controls. It is important to note that; based on our sample of people with mild MS there still is a wide variability in asymmetry. For example, some individuals had legs that are relatively similar in strength and function whereas others had severe asymmetry that was not related to leg dominance (left vs. right). Future studies might attempt to uncover the mechanism of this variability in the MS population.

Conclusion and Future Directions. The major findings of this study were the statistically significant asymmetry in quadriceps strength observed in a group of ambulatory individuals with MS not observed in a similar group of individuals without MS. Following unilateral exercise, the strength asymmetry ratio improved and was primarily from the augmented improvement in the strength from the weaker leg in the individuals with MS, which might suggest differences in potentation characteristics between legs. This information could lead to novel interventions to reduce skeletal muscle asymmetry. The reduction in stride velocity and foot tap speed suggests that contraction speed (speed of movement) was compromised in people with MS which could potentially lead to instability and heightened fall risk. This study represents an important step in understanding how exercise may influence indices of leg strength and gait characteristics in people with mild MS. Anecdotally, some of the participants with MS noted that this study validated personal experiences they have had regarding their function. When trying to walk during a fatigued state and feeling unable to increase their speed of movement in spite of their increased effort and being told by other to "just try harder", this study offered if not a defense then solace.

References

(1) Kos D, Duportail M, D'hooghe M, Nagels G, Kerckhofs E. Multidisciplinary fatigue management programme in multiple sclerosis: a randomized clinical trial. Mult Scler 2007 Sep;13(8):996-1003.

(2) Romberg A, Virtanen A, Aunola S, Karppi SL, Karanko H, Ruutiainen J. Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. Mult Scler 2004 Apr;10(2):212-218.

(3) Iriarte J, de Castro P. Correlation between symptom fatigue and muscular fatigue in multiple sclerosis. Eur J Neurol 1998 Nov;5(6):579-585.

(4) Lambert CP, Archer RL, Evans WJ. Muscle strength and fatigue during isokinetic exercise in individuals with multiple sclerosis. Med Sci Sports Exerc 2001 Oct;33(10):1613-1619.

(5) Kent-Braun JA, Ng AV, Castro M, Weiner MW, Gelinas D, Dudley GA, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. J Appl Physiol 1997 Dec;83(6):1998-2004.

(6) Kent-Braun JA, Sharma KR, Miller RG, Weiner MW. Postexercise phosphocreatine resynthesis is slowed in multiple sclerosis. Muscle Nerve 1994 Aug;17(8):835-841.

(7) Ng AV, Miller RG, Kent-Braun JA. Central motor drive is increased during voluntary muscle contractions in multiple sclerosis. Muscle Nerve 1997 Oct;20(10):1213-1218.

(8) Latash M, Kalugina E, Nicholas J, Orpett C, Stefoski D, Davis F. Myogenic and central neurogenic factors in fatigue in multiple sclerosis. Mult Scler 1996 Feb;1(4):236-241.

(9) Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. Muscle Nerve 1992 Oct;15(10):1123-1132.

(10) Chung LH, Remelius JG, Van Emmerik RE, Kent-Braun JA. Leg power asymmetry and postural control in women with multiple sclerosis. Med Sci Sports Exerc 2008 Oct;40(10):1717-1724.

(11) Thoumie P, Lamotte D, Cantalloube S, Faucher M, Amarenco G. Motor determinants of gait in 100 ambulatory patients with multiple sclerosis. Mult Scler 2005 Aug;11(4):485-491.

(12) White LJ, Dressendorfer RH. Factors limiting maximal oxygen uptake in exertional monoparesis. Mult Scler 2005 Apr;11(2):240-241.

(13) Teixeira MC, Teixeira LA. Leg preference and interlateral performance asymmetry in soccer player children. Dev Psychobiol 2008 Dec;50(8):799-806.

(14) Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983 Nov;33(11):1444-1452.

(15) Whaley MH. ACSM's guidelines for exercise testing and prescription. 7th ed. New York: Lippincott Williams & Wilkins; 2006.

(16) Kent-Braun JA, Walker CH, Weiner MW, Miller RG. Functional significance of upper and lower motor neuron impairment in amyotrophic lateral sclerosis. Muscle Nerve 1998 Jun;21(6):762-768.

(17) McDonough AL, Batavia M, Chen FC, Kwon S, Ziai J. The validity and reliability of the GAITRite system's measurements: A preliminary evaluation. Arch Phys Med Rehabil 2001 Mar;82(3):419-425.

(18) Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. Gait Posture 2003 Feb;17(1):68-74.

(19) Sacco R, Bussman R, Oesch P, Kesselring J, Beer S. Assessment of gait parameters and fatigue in MS patients during inpatient rehabilitation: a pilot trial. J Neurol 2011 May;258(5):889-894.

(20) Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: characterization of temporal-spatial parameters using GAITRite functional ambulation system. Gait Posture 2009 Jan;29(1):138-142.

(21) McPhee JS, Williams AG, Stewart C, Baar K, Schindler JP, Aldred S, et al. The training stimulus experienced by the leg muscles during cycling in humans. Exp Physiol 2009 Jun;94(6):684-694.

(22) Carpes FP, Diefenthaeler F, Bini RR, Stefanyshyn D, Faria IE, Mota CB. Does leg preference affect muscle activation and efficiency? J Electromyogr Kinesiol 2010 Dec;20(6):1230-1236.

(23) Sargeant AJ, Davies CT. Forces applied to cranks of a bicycle ergometer during one- and two-leg cycling. J Appl Physiol 1977 Apr;42(4):514-518.

(24) Davies CT, Sargeant AJ. Effects of training on the physiological responses to one- and two-leg work. J Appl Physiol 1975 Mar;38(3):377-375.

(25) Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* : Lawrence Erlbaum Associates; 1988.

(26) Sharma KR, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. Muscle Nerve 1995 Dec;18(12):1403-1411.

(27) Kent-Braun JA, Sharma KR, Weiner MW, Miller RG. Effects of exercise on muscle activation and metabolism in multiple sclerosis. Muscle Nerve 1994 Oct;17(10):1162-1169.

(28) DeMyer WE. *Technique of the Neurological Examination*. 5th ed. 5th ed. U.S.: McGraw Hill; 2004.

(29) de Haan A, de Ruiter CJ, van Der Woude LH, Jongen PJ. Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. Muscle Nerve 2000 Oct;23(10):1534-1541.

(30) Ng AV, Dao HT, Miller RG, Gelinas DF, Kent-Braun JA. Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. J Appl Physiol 2000 Mar;88(3):871-880.

(31) Garner DJ, Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. Muscle Nerve 2003 Apr;27(4):456-464.

(32) Andreasen AK, Jakobsen J, Petersen T, Andersen H. Fatigued patients with multiple sclerosis have impaired central muscle activation. Mult Scler 2009 Jul;15(7):818-827.

(33) Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve 2004 Jun;29(6):843-852.

(34) Hamada T, Kimura T, Moritani T. Selective fatigue of fast motor units after electrically elicited muscle contractions. J Electromyogr Kinesiol 2004 Oct;14(5):531-538.

(35) Foran JR, Steinman S, Barash I, Chambers HG, Lieber RL. Structural and mechanical alterations in spastic skeletal muscle. Dev Med Child Neurol 2005 Oct;47(10):713-717.

(36) Jubeau M, Gondin J, Martin A, Sartorio A, Maffiuletti NA. Random motor unit activation by electrostimulation. Int J Sports Med 2007 Nov;28(11):901-904.

(37) Moritani T, Muro M, Kijima A. Electromechanical changes during electrically induced and maximal voluntary contractions: electrophysiologic responses of different muscle fiber types during stimulated contractions. Exp Neurol 1985 Jun;88(3):471-483.

(38) Hamada T, Hayashi T, Kimura T, Nakao K, Moritani T. Electrical stimulation of human lower extremities enhances energy consumption, carbohydrate oxidation, and whole body glucose uptake. J Appl Physiol 2004 Mar;96(3):911-916.

(39) McNeil CJ, Murray BJ, Rice CL. Differential changes in muscle oxygenation between voluntary and stimulated isometric fatigue of human dorsiflexors. J Appl Physiol 2006 Mar;100(3):890-895.

(40) Ratkevicius A, Mizuno M, Povilonis E, Quistorff B. Energy metabolism of the gastrocnemius and soleus muscles during isometric voluntary and electrically induced contractions in man. J Physiol 1998 Mar 1;507 (Pt 2)(Pt 2):593-602.

(41) Theurel J, Lepers R, Pardon L, Maffiuletti NA. Differences in cardiorespiratory and neuromuscular responses between voluntary and stimulated contractions of the quadriceps femoris muscle. Respir Physiol Neurobiol 2007 Aug 1;157(2-3):341-347.

(42) Vanderthommen M, Duteil S, Wary C, Raynaud JS, Leroy-Willig A, Crielaard JM, et al. A comparison of voluntary and electrically induced contractions by interleaved 1H- and 31P-NMRS in humans. J Appl Physiol 2003 Mar;94(3):1012-1024.

(43) HENNEMAN E, SOMJEN G, CARPENTER DO. Functional Significance of Cell Size in Spinal Motoneurons. J Neurophysiol 1965 May;28:560-580.

(44) Gehlsen G, Beekman K, Assmann N, Winant D, Seidle M, Carter A. Gait characteristics in multiple sclerosis: progressive changes and effects of exercise on parameters. Arch Phys Med Rehabil 1986 Aug;67(8):536-539.

(45) Orsnes GB, Sorensen PS, Larsen TK, Ravnborg M. Effect of baclofen on gait in spastic MS patients. Acta Neurol Scand 2000 Apr;101(4):244-248.

(46) Goslow GE,Jr, Stauffer EK, Nemeth WC, Stuart DG. The cat step cycle; responses of muscle spindles and tendon organs to passive stretch within the locomotor range. Brain Res 1973 Sep 28;60(1):35-54.

(47) Miller RG, Moussavi RS, Green AT, Carson PJ, Weiner MW. The fatigue of rapid repetitive movements. Neurology 1993 Apr;43(4):755-761.

(48) Logigian EL, Hefter HH, Reiners K, Freund HJ. Neurophysiology of fastest voluntary muscle contraction in hereditary neuropathy. Ann Neurol 1990 Jan;27(1):3-11.

(49) Desmedt JE, Godaux E. Ballistic contractions in man: characteristic recruitment pattern of single motor units of the tibialis anterior muscle. J Physiol 1977 Jan;264(3):673-693.

Table 4.1. *Participant characteristics*

	MS (n = 8)	Controls (n = 7)	*P*
Age (y)	51.6 ± 9.2	49.4 ± 14.3	0.74
Height (cm)	167.5 ± 7.5	169.1 ± 9.0	0.72
Body Mass (kg)	70.4 ± 13.8	75.4 ± 30.4	0.74
Body Mass Index (kg/m^2)	25.0 ± 3.9	26.0 ± 8.3	0.77
Fat Mass (%)	39.4 ± 6.1	36.9 ± 8.7	0.52
Frequency of exercise (wk)	2.8 ± 2.5	3.8 ± 1.9	0.58
Duration of exercise (min)	30 ± 11.3	42.9 ± 25.1	0.25

Data are mean ± SD. *$P < 0.05$ represents a statistically significant difference in group means.

Table 4.2. *Composition of lower leg (means ± SD)*

	MS			Controls		
	Stronger leg	Weaker leg	*P*	Stronger leg	Weaker leg	*P*
Lean Mass (Kg)	7.5 ± 1.4	7.3 ± 1.4	0.20	8.1 ± 2.2	8.2 ± 2.1	0.31
Fat Mass (Kg)	5.3 ± 1.1	5.3 ± 1.2	0.95	5.3 ± 2.0	5.2 ± 2.0	0.66

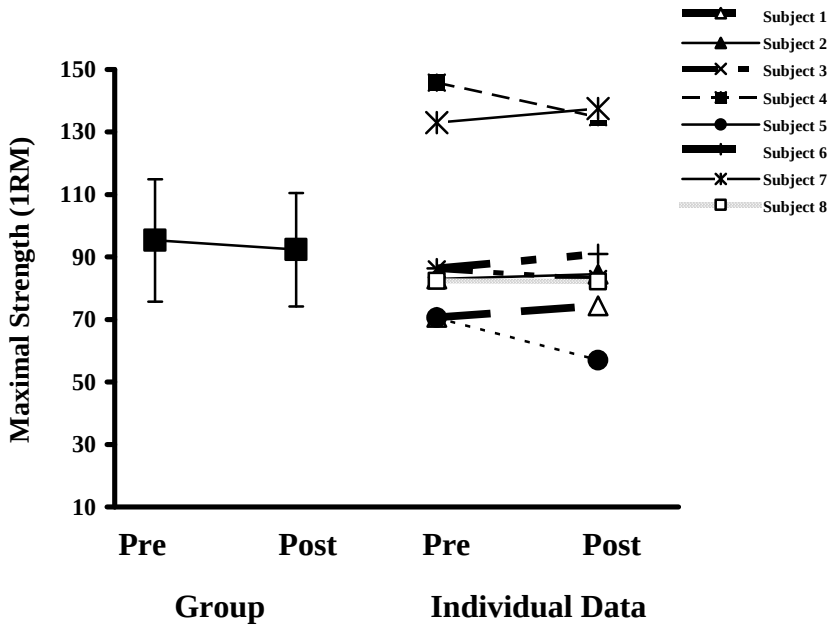
Data are mean ± SD. MS, Multiple Sclerosis. *$P < 0.05$ represents a statistically significant difference in between legs.

a)

b)

Figure 4.1. Single leg cycling position (a-b).

a)



b)

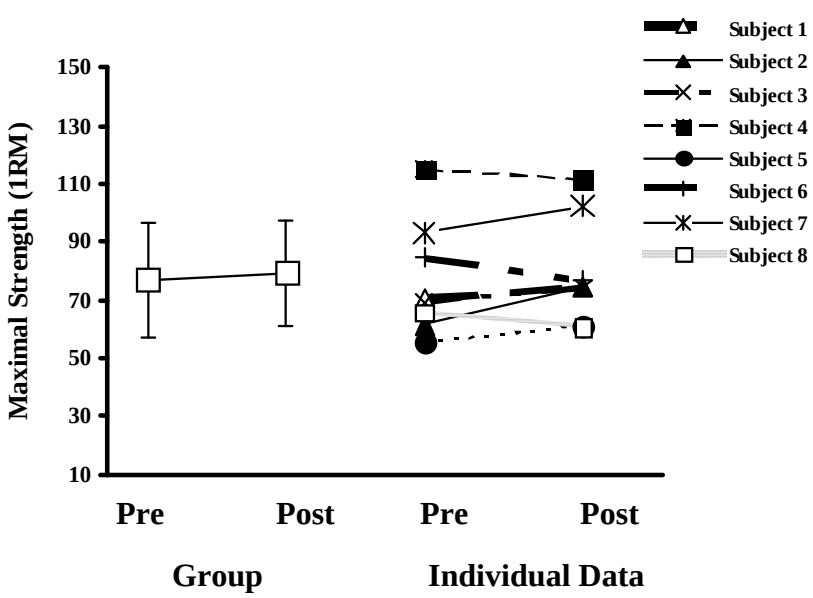


Figure 4.2. Multiple Sclerosis group and individual maximal isometric quadriceps strength before and after single leg exercise (means ± SD) a) stronger leg and b) weaker leg. *$P < 0.05$ represents a statistically significant difference from pre to post.

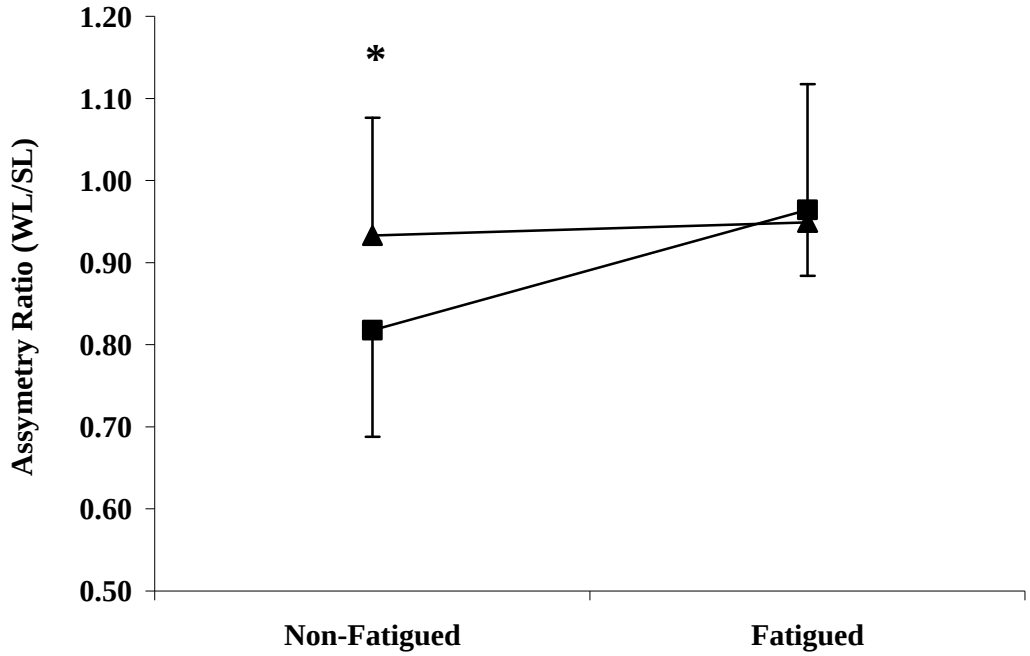


Figure 4.3. Strength symmetry ratios for groups (MS compared to controls) before and after exercise. (means ± SD). MS = squares and control = triangles. * Represents a statistically significant difference in between groups $P < 0.05$.

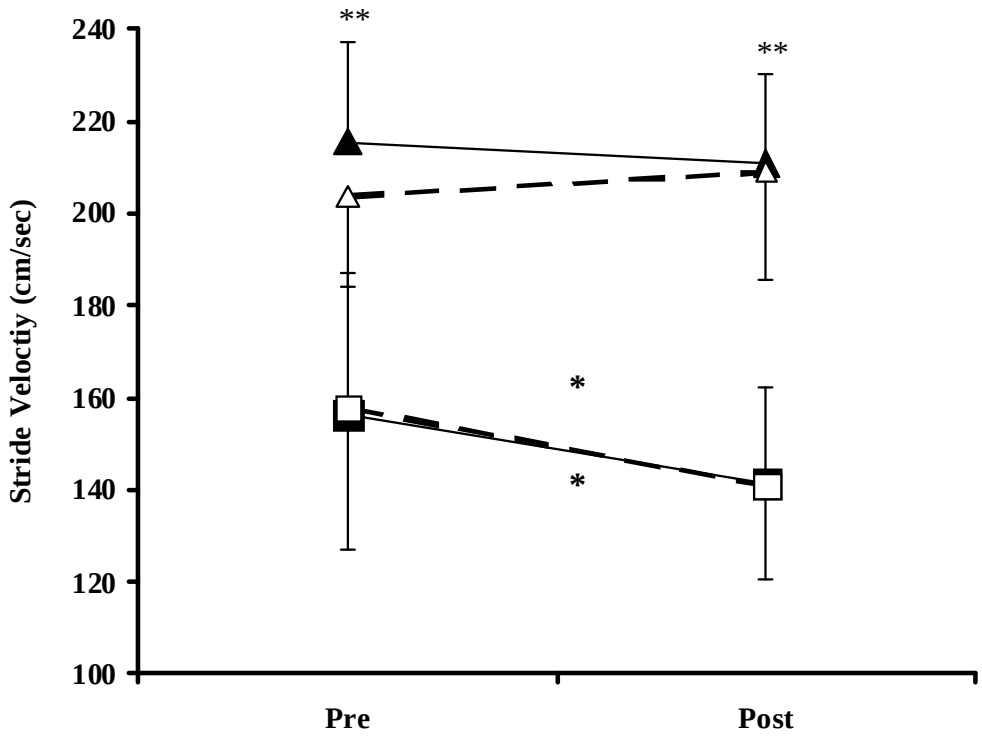


Figure 4.4. Changes in stride velocity following unilateral exercise (means ± SD). * Significant difference from pre to post $P < 0.05$. ** Significant difference between groups $P < 0.05$. MS: stronger leg = closed squares, MS weaker leg = open squares and controls: stronger leg = closed triangles, controls weaker leg = open triangles.

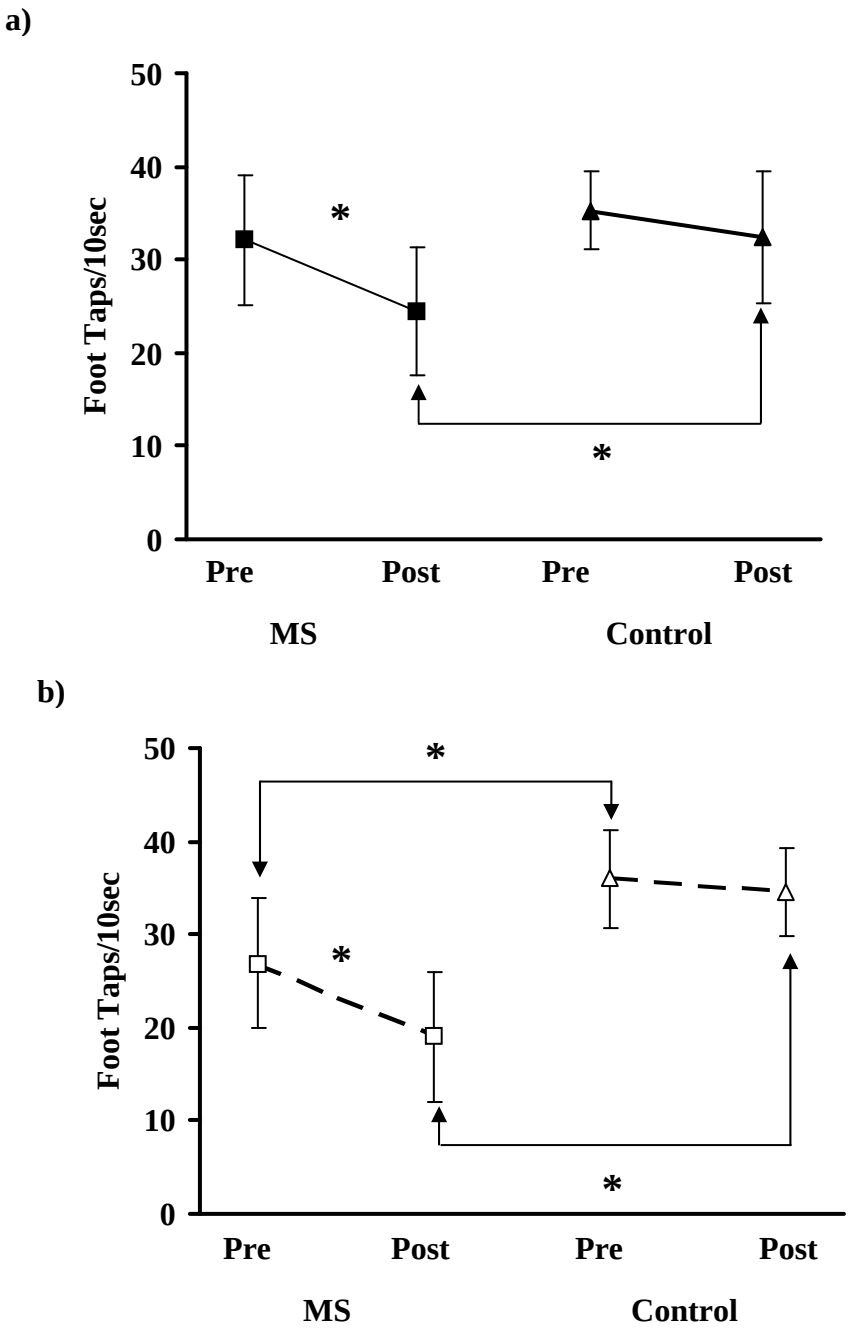


Figure 4.5. Foot tap speed before and after exercise (means ± SD) a) stronger leg and b) weaker Leg. * Represents a statistically significant difference, $P < 0.05$.

CHAPTER 5

SUMMARY AND CONCLUSIONS

The primary purposes of these investigations were to investigate bilateral differences among ambulatory individuals with mild MS. Uniquely, these inquiries were conducted using bouts of single leg exercise to not only measure exercise response, but to also produce conditions of muscle fatigue prior to functional testing.

The significance of this study is that it is one of the first to formally quantify differences in leg function in people with mild MS. Leg asymmetry in this population has been recognized clinically and has been presented in a few previous research studies. Our participants displayed few outwards signs of asymmetry, but under the demands of exercise bilateral differences became pronounced. Our results also demonstrate that people with mild MS have leg differences that can vary in magnitude and severity. For example, some individuals might have two legs that are similar in strength and function whereas others have a 'weak' leg that is up to 70% weaker than their stronger leg and was not related to leg dominance (left vs. right). This study strongly suggests that limb selection is important for future studies of exercise capacity or function in people with MS, and new research designs should address the issue of potential leg differences. Additionally the bilateral assessments such as walking or two legged strength measures may mask interlimb differences and should be considered prior to evaluation.

Because of previous reports of increased muscle fatigue in individuals with MS, we also wanted to address the question of whether the magnitude of muscle fatigue might

occur to a greater extent in the weaker leg compared to the stronger leg. This would result in greater asymmetry during a 'fatigued' state compared to resting conditions in people with MS. Our study did not support this idea, as both the stronger and weaker legs demonstrated similar responses to exercise-related fatigue as evidenced by changes in strength, foot tap speed, and gait speed following maximal unilateral exercise tasks. However, based on the observed differences during the fixed workload and incremental workload tests, using a threshold model of function might push the weaker leg closer to 'task failure' which could limit function. It appears that despite similar responses following task failure during cycling, the weaker leg should still be considered more vulnerable and susceptible to earlier failure and has less performance capacity. The reduced performance combined with higher vulnerability may be a limiting factor during bilateral movements such as walking.

Additionally, using traditional means of exercise prescription, e.g. heart rate targets, rating of perceived exertion, and even bilateral modes of exercise, might not be appropriate for individuals with these bilateral differences. Further research is warranted to develop more information regarding leg asymmetry and how it contributes to the observed premature fatigue in the current study. The next logical step for this research would be to determine if differences between legs can be minimized through an intervention such as resistance training and adaptations to aerobic training to answer the question of whether the weaker legs adapt in similar manners to the stronger legs.

One of the original aims of this study was to use electrical stimulation to evaluate muscle activation. However, this data was not included in our results because we were unable to use a high enough current to stimulate our participants to perform the

superimposed twitch measurements. This was in contrast to previous studies which have successfully used these measurements on participants with MS (1-5). It is possible that we were less 'aggressive' and used lower stimulation currents than previous studies. We used an individualized stimulation rate by increasing the stimulation intensity until the participants reported a rating of 4 on a 0-10 pain scale. The aim was to minimize discomfort in the protocol, while most previous research used a "one size fits all" stimulation rate. One possible reason for the success of other investigators was that their superimposed twitch was administered during the maximal muscle contraction. The subjective discomfort using this method seems to be much lower than the titration technique we employed. Retrospectively, we observed that that stimulation was tolerated better during the muscle contraction than during the stimulation alone. Conduction stimulation titration during muscle contraction might yield better results, i.e. higher stimulation rates with the same subjective discomfort. One alternative to avoid these issues entirely would be to use a different method to assess muscle activity. Assessment of neural activity through the use of electromyography (EMG) could provide valuable information pertaining to activation patterns between legs. However, like many testing procedures EMG has its own limitations.

One of our other original goals was to evaluate potential leg differences in metabolic capacity using measurements of exercise onset kinetics and local muscle oxygen balance (delivery versus utilization) using near infrared spectroscopy during single leg cycling. This data was also not reported because during the fixed workload single leg cycling test, many of the participants with MS were unable to perform the exercise long enough when using their weaker leg to obtain complete onset kinetics. This

does remain a viable goal and would add further insight into the metabolic differences between legs, but the relative intensity should be based on the apparently reduced capacity of the weaker leg.

During the planning of this study we were aware that the NIRS measurements might not have worked for all of our participants. We used an NIRS device that had a fixed separation distance between light source and detectors of 3 cm. The light path from the source follows a "banana-shaped" curve in that the penetration depth into the tissue is approximately half the distance between the light source and the detector (6). This means that for our device the penetration depth would be 1 to 2 cm. Subcutaneous fat greatly impacts the NIRS signal because fat is metabolically inactive it absorbs less light resulting in less of a signal change during experimentation and during the physiological calibration (cuff occlusion for 5 minutes to obtain maximal and minimum saturation levels for each participant). Due to the unanticipated levels of subcutaneous leg fat among many of the participants, we were only able to collect a subset of data using NIRS. As shown in Figure 5.1, the individuals with MS had more subcutaneous fat (measure via ultrasound) which disrupted the signal reducing the change in optical density, making signal differences harder to detect. Even though the 3 cm device should have a penetration depth close to 2cm Figure 5.1 shows that once the thickness of subcutaneous fat was above 13mm the signal during cuff occlusion (physiological calibration which gives us the minimum saturation (ischemia) and the maximal (reactive hyperemic response)) showed a high signal to noise ratio and small changes in optical density. This made measurement and interpretations of saturation levels practically impossible. Assessment of differences in oxidative capacity between legs is still a viable

goal and could be accomplished through different techniques, like magnetic resonance spectroscopy measurement of phosphocreatine recovery kinetics.

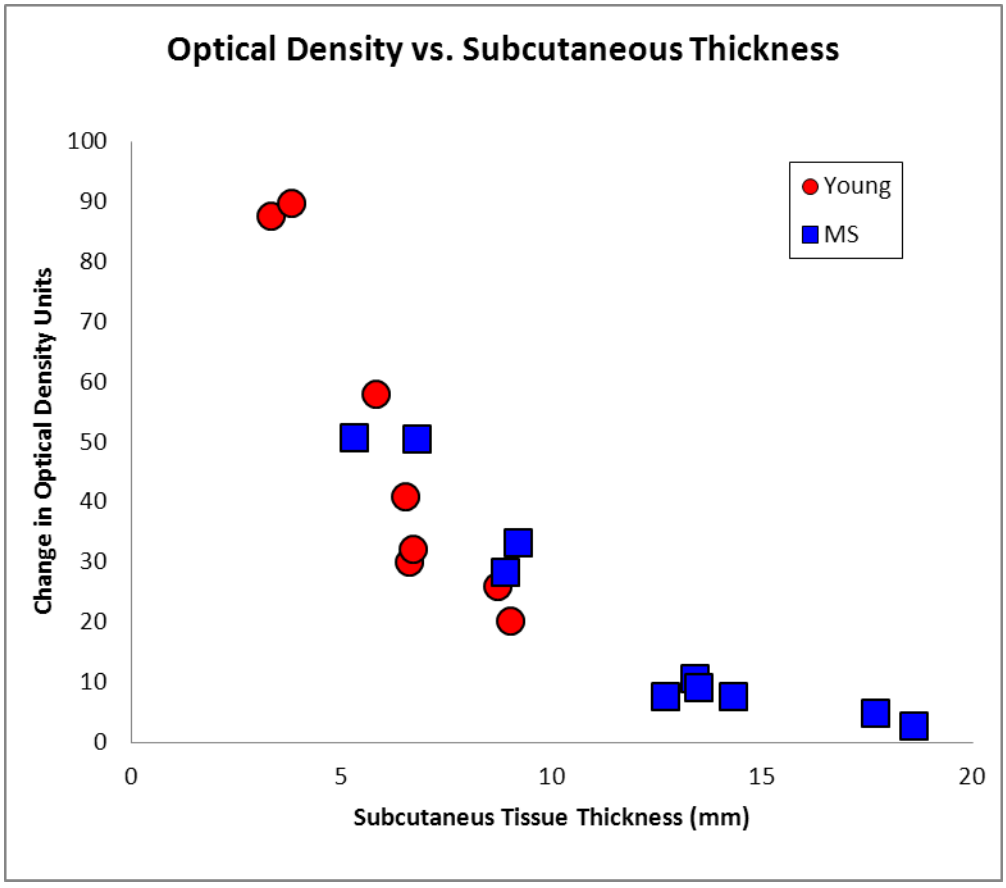


Figure 5.1 This figure shows the relationship between subcutaneous fat thickness and changes in optical density during a 5 minute cuff occlusion. The physiological range was assessed by inducing muscle ischemia (cuff occlusion) to obtain the minimal saturation (0%) and then releasing the cuff and using the highest saturation during the reactive hyperemic response (100%). For this comparison subcutaneous fat of the vastus lateralis was measured using ultrasound techniques. The individuals with MS had about 1/10 the change in optical density during cuff occlusion compared to a group young healthy subjects.

Our study also incorporated autonomic nervous system (ANS) testing to identify dysfunction in blood pressure and heart rate responses. We included this assessment because 1) our subjects with MS might have a high incidence of ANS dysfunction, and 2) the possibility it could help explain any unanticipated response to exercise. Unfortunately the results from the ANS testing did not help explain our study outcomes and our sample size limited our ability to account for these differences statistically. The efforts made to conduct the battery of ANS tests with each subject may have not have been time well spent. However, this is only said because it did not help explain our results, but if in fact an individual had an abnormally blunted heart rate and/or blood pressure response to exercise, ANS testing would have been useful. Due to the high incidence of autonomic dysfunction in individuals with MS I would still recommend performing ANS testing as a possible explanatory variable that could be accounted for statistically if the sample size is large enough.

Our study had a relatively small sample size. While this is a limitation, the main aims of the study were still achieved. Small sample sizes are a reoccurring problem for studies on people with neurological diseases. It is not unusual to see studies with sample sizes in the 6-15 range, similar to ours. Future studies might need to be organized across multiple sites, which would allow more successful recruitment. However, the limitations of such studies are that they limit the ability of to use laboratory measurements that require breakable and hard to move instruments. Additionally, large multicenter studies potentially introduce more error into the measurements taken with multiple raters, equipment, and laboratory environments.

Despite some limitations, these studies provide valuable insight regarding premature muscle fatigue/failure in individuals with MS and the need for further research and the implementation of therapeutic interventions.

References

(1) Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve 2004 Jun;29(6):843-852.

(2) Sharma KR, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. Muscle Nerve 1995 Dec;18(12):1403-1411.

(3) Andreasen AK, Jakobsen J, Petersen T, Andersen H. Fatigued patients with multiple sclerosis have impaired central muscle activation. Mult Scler 2009 Jul;15(7):818-827.

(4) Kent-Braun JA, Le Blanc R. Quantitation of central activation failure during maximal voluntary contractions in humans. Muscle Nerve 1996 Jul;19(7):861-869.

(5) Ng AV, Dao HT, Miller RG, Gelinas DF, Kent-Braun JA. Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. J Appl Physiol 2000 Mar;88(3):871-880.

(6) Chance B, Dait MT, Zhang C, Hamaoka T, Hagerman F. Recovery from exercise-induced desaturation in the quadriceps muscles of elite competitive rowers. Am J Physiol 1992 Mar;262(3 Pt 1):C766-75.