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The role of muscle strength and voluntary activation on symptomatic fatigue in multiple sclerosis

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ABSTRACT

This study investigated the role of muscle strength and voluntary activation (VA) on symptomatic fatigue in individuals with multiple sclerosis (MS). Nine women with relapsing-remitting or secondary-progressive MS (mean age, 43yrs) were compared to nine healthy women (mean age, 37yrs). Symptomatic fatigue was assessed using the Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale, and Visual Analogue Fatigue Scale. Functional capacity was assessed with a 6-Minute Walk Test (6-MWT). Muscle strength and VA were determined using twitch interpolation applied to the right dorsiflexor muscles during maximal voluntary isometric contractions (MVIC). Muscle fatigue was assessed during a sustained submaximal contraction. Distance during the 6-MWT, muscle strength and VA were significantly lower in the MS group. MFIS scores were negatively associated with muscle strength and VA. The MS group was more easily fatigued, as measured by MVIC. In conclusion, symptomatic fatigue is associated with muscle fatigue and weakness in individuals with MS.

Keywords: Multiple Sclerosis (MS); Interpolated twitch technique (ITT); Voluntary activation (VA); Symptomatic fatigue; Muscle strength; Fatigue

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This thesis is dedicated to my grandma, Phyllis Lee, whom just turned 95!

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LIST OF ABBREVIATIONS

CNS- central nervous system

DF- dorsiflexor

DMTs- disease-modifying therapies

FSS- fatigue severity scale

ITT- interpolated twitch technique

LMN- lower motor neuron

M1- primary motor cortex

MFIS- modified fatigue impact scale

MS- multiple sclerosis

MVIC- maximal voluntary isometric contraction

NJM- neuromuscular junction

PNS- peripheral nervous system

RRMS- relapsing-remitting multiple sclerosis

SPMS- secondary progressive multiple sclerosis

UMN- upper motor neuron

VA- voluntary activation

VAFS- visual analogue fatigue scale

GLOSSARY OF TERMS

Central nervous system (CNS)- a portion of the nervous system which includes the brain and spinal cord

Kurtzke expanded disability status scale (EDSS)- clinical evaluation of quantifying disability in multiple sclerosis

Neuromuscular fatigue- a reduction in muscle force production following exertion

Fatigue- an overwhelming sense of exhaustion or tiredness that renders an individual from being able to initiate or complete an activity that he/she would normally be able to do

Fatigue severity scale (FSS)- a self-administered questionnaire used to assess the severity of fatigue and the impact on daily functioning during the past week

Interpolated twitch technique (ITT)- a technique used to assess the completeness of skeletal muscle activation

Maximal voluntary isometric contraction (MVIC)- maximal effort voluntary contraction where the joint angle remains constant during the contraction

Modified fatigue impact scale (MFIS)- a self-administered questionnaire used to assess the perceived impact of fatigue within the past four weeks

Multiple sclerosis (MS)- non-traumatic central nervous system (brain and spinal cord) disorder

Neuromuscular junction- a specialized synapse between a motor neuron and a muscle end-plate

Peak torque- the maximum production of force about a vector (the dynamometer arm) for a single contraction, measured in newton·meters (Nm)

Peripheral fatigue- a progressive reduction in force production resulting from fatigue occurring in the muscle distal to the neuromuscular junction

Voluntary activation (VA)- the level of central drive achieved during a voluntary isometric contraction at any target force

Visual analogue fatigue scale (VAFS)- a research instrument designed to measure an attribute that is best illustrated by a continuum of values versus discrete points

Weakness- loss of strength within a given muscle independent of previous work or activity

CHAPTER 1

FATIGUE IN THE NEUROMUSCULAR SYSTEM

1.0 GENERAL INTRODUCTION

1.01 Multiple Sclerosis

Multiple sclerosis (MS) is the most common non-traumatic central nervous system (brain and spinal cord) disorder of young adulthood, affecting approximately 100,000 people in Canada and 2.5 million people worldwide [1–4]. The diagnosis of MS most commonly occurs in the second or third decade of life, with a female:male ratio of 2:1 [2–5]. Although the etiology of MS has yet to be clearly established, interactions between environmental, infectious, and genetic factors are currently considered as possible causes [6–9]. MS involves unpredictable episodes of axonal demyelination, resulting in lesions along axons of nerve fibers in the central nervous system (CNS) pathways [7]. The demyelination of the nerve fibers interferes with the neuronal conduction from the CNS to effector organs [7,10–13]. This interference manifests as various symptoms such as sensory loss, cognitive impairment, gait disturbance, visual impairment, bladder and bowel control, spasticity, weakness and fatigue [7,12,14].
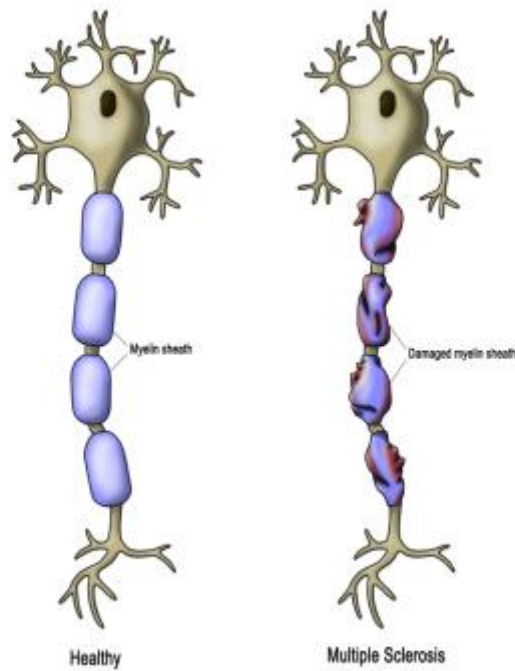
Figure 1.1. Nerve Fibre (neuron) from a healthy individual and person with MS (with permission from Alexandra Lynette-Krech, (2017))

The clinical course of MS is characterized by acute periods of worsening (relapses), progressive deterioration of neurological function, or combinations of both [15]. Relapsing-remitting MS (RRMS) is the most common disease course, affecting approximately 85% of individuals with MS [16]. This disease course manifests as a period of relapse followed by a period of remission, during which symptoms improve partially or completely [7,15]. Secondary-progressive MS (SPMS) follows the initial RRMS disease course with a steady progression, with or without relapses [2,15,17]. Sixty percent of people who are initially diagnosed with RRMS will transition to SPMS [2,15]. Primary-progressive MS occurs in approximately 10% of individuals with MS, and is characterized by steadily worsening neurological function from the

onset, with no distinct relapses or remission [2,7,15]. Lastly, progressive-relapsing MS is the least common of the four disease courses, occurring in approximately 5% of individuals with MS, and is characterized by steadily progressing disease from the beginning with occasional relapses along the way [2,7]. The disease continues to progress without remissions. The pattern of clinical symptoms and descriptors is complex; the types are displayed in Fig 1.2.
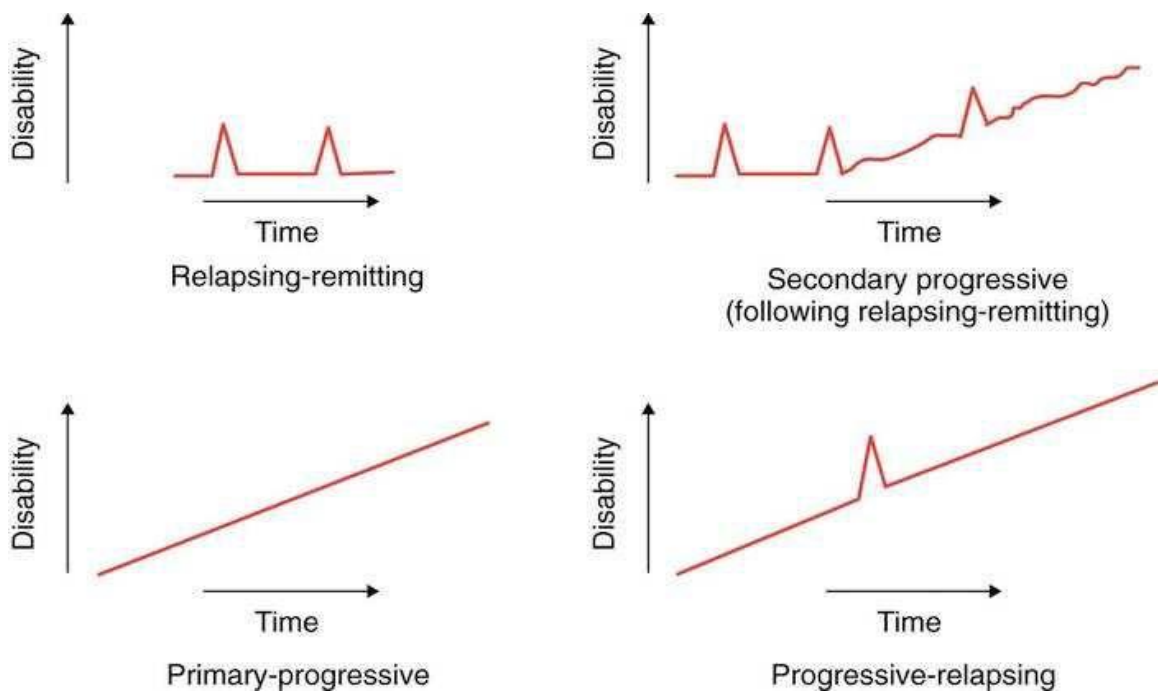
Figure 1.2. Clinical types of MS (with permission from Fred D. Lublin, M.D, (2016))

Therapies are a key component of MS care, along with treating symptoms and managing MS relapses. The approach to the treatment of MS is individualized to ones' relative disabilities, needs, and support system.

There are currently 12 disease-modifying therapies (DMTs) that have been approved by Health Canada; seven are injectable, three are oral, and two are infused [2]. These are currently the best approach available to slow the natural course of MS [2]. DMTs target some aspect of the inflammatory process of MS while reducing the severity and frequency of relapses, the development of new lesions, and the progression of disability [2]. Both clinical experience and clinical investigation have suggested that early intervention with DMTs may help to prevent permanent damage in the CNS, increasing ones' overall level of function and quality of life [2].

The majority of current treatments for MS are pharmaceutical. However, due to the variability of MS symptoms, individuals often seek relief through rehabilitation and alternative medicine [2]. Rehabilitation specialists, such as physical therapy, occupational therapy, speech-language pathology, vocational rehabilitation and cognitive rehabilitation provide evaluation and treatment to improve and maintain function [2,18]. Alternative medicine includes a wide variety of interventions from naturopathy to stress management and acupuncture, and are instrumental in the management of the disease[18]. As well, assistive devices (e.g. walkers, scooters, wheelchairs) and appropriate orthoses (e.g. ankle foot orthoses) should be considered as they play a viable role in the management of mobility [18].

1.02 The Motor System

The motor systems in the CNS control a multitude of functional outputs, both voluntary and involuntary [19]. The motor systems are organized in hierarchy from the cerebral cortex, brainstem to spinal cord, to peripheral motor system. The spinal cord is the lowest level in the CNS hierarchical structure, and conduits information through neuronal circuits that control various reflexes and rhythmic movement [20]. The brainstem is the middle level in the hierarchical structure, and contains neuronal circuits that mediate locomotion and orofacial

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movement [20]. The cerebral cortex is the highest level in the hierarchical structure, housing the motor cortex [20]. The motor cortex consists of the primary motor cortex (M1), premotor area, and secondary motor areas, and are responsible for the planning, initiating, and execution of voluntary movement [20].

Movement is initiated through motor commands from the M1 and premotor areas. Commands are transmitted down the corticospinal tract to the spinal cord via upper motor neurons (UMNs) [19,20]. Axons of UMNs synapse in the ventral horn of the spinal cord with lower motor neurons (LMNs) either directly or indirectly, via spinal interneurons [19]. LMN axons exit as the ventral root, and combine with the dorsal root to form the peripheral nerve [19]. Axons of the LMNs leave the CNS, forming peripheral axons and eventually branch distally near their target muscle to form a terminal arborization [19]. Each of the terminal branches form a synapse-like junction, known as the neuromuscular junction (NMJ), innervating skeletal muscle and thus initiating movement [19].

Motor system dysfunction can result from damage or disease at any level of the motor system hierarchy. Damage to the UMNs of the descending motor pathways results in the upper motor neuron syndrome, and gives rise to a set of signs and symptoms such as weakness, fatigue, positive Babinski sign, spasticity, hyperreflexia of superficial reflexes, and loss of dexterity [21,22]. These acute manifestations tend to be most severe in the arms and legs and would be seen in conditions such as cerebral palsy, primary lateral sclerosis, and multiple sclerosis. Damage to the LMNs of the brainstem and spinal cord are referred to as the lower motor neuron syndrome, and would be characterized by weakness of the affected muscles, loss of reflexes, loss of muscle tone, and atrophy [21,22]. These signs would be seen in conditions such as spinal muscular atrophy, focal peripheral nerve injury, and generalized neuropathies. MS is a central

nervous system disorder and thus only results in impairment and disability secondary to UMN dysfunction.

1.03 Fatigue in the Neuromuscular System

The neuromuscular system is a complex system that provides humans with movement, from respiration and saccadic movements of the eye, to walking and standing [19,23]. The peripheral component of the neuromuscular system, also known as the lower motor neuron, is comprised of the alpha motor neurons and peripheral motor axons, which innervate and control skeletal muscle fibres. Motor neurons are responsible for relaying signals from the peripheral motor system, along the motor pathway, to the skeletal muscle which initiates contraction [24]. Muscle fibres are then responsible for contracting, thus generating the torque necessary for movement [24]. Muscular fatigue, or fatigability, results from a reduction in muscle torque production following exertion [25–27]. This may occur at various sites along the motor pathway from the brain and spinal cord to the muscle itself. Since multiple sites are involved in the development of neuromuscular fatigue, they can be divided into the CNS and peripheral nervous system (PNS). Changes in the CNS or the PNS both contribute to the reduction in muscle torque production [28,29].

Central fatigue results from the inability of the CNS to adequately drive the muscle to produce torque during a muscular contraction [30]. It can originate from various sites along the motor pathway, and can therefore result from either a reduction in central drive (central activation) or modulations to the central drive at the level of the spinal cord [26,31]. During a fatiguing task, the CNS increases its central drive to overcome fatigue [32]. Despite an increase in central drive, torque production decreases progressively with fatigue [33]. This is referred to as central fatigue, and can be identified using variants of the twitch interpolation technique

[25,34–36]. Central fatigue has been demonstrated in several muscle groups of both healthy and patient populations, including elbow flexors, quadriceps and ankle dorsi- and plantar-flexors for sustained, intermittent, maximal or submaximal voluntary contractions. Using electrical stimulation, an estimate that 12% and 20% of the loss of strength during maximal voluntary isometric contractions (MVIC) of the elbow flexors and of the ankle dorsiflexors are due to central fatigue, respectively [6,26,37]. Furthermore, several transcranial magnetic stimulation (TMS) studies have shown that central fatigue can account for over 25% of the reduced torque seen during sustained, maximal contractions [38–40]. However, central fatigue appears to contribute more significantly to the reduced torque during low-intensity exercise [38]. For example, it has been suggested that low-torque, long-duration contractions are more likely to lead to the development of central fatigue than high-torque, short-duration contractions performed by the same muscle group [41]. In fact, Sogaard et al [42] have indicated through the use of TMS, that 40% of fatigue can be attributed centrally during a submaximal (15% MVIC) contraction of the elbow flexors until exhaustion.

Peripheral fatigue, results from loss of muscular torque that occurs at or distal to the neuromuscular junction [30]. This can be thought of as fatigue within the peripheral nerve or muscle itself [30]. It is also referred to as peripheral fatigue because changes occur within the PNS as opposed to the CNS [31]. Schillings et al [43] demonstrated a significant difference in voluntary torque before and after a fatiguing task. Their findings suggest a large peripheral contribution to fatigue, accounting for 89% of the voluntary force loss after a 2-minute sustained MVC. Gandevia et al [33] and Kent-Braun and Le Blanc [6] reported a 26% and 80% loss of voluntary torque after a sustained voluntary contraction, respectively, attributing it to peripheral factors. Furthermore, Sharma et al [35] found excessive decline in tetanic torque during

peripheral nerve stimulation, along with the greater metabolic changes (reduction in phosphorus energy metabolites and pH) in individuals with MS. These findings indicate that the source of excessive fatigue was peripheral rather than central.

1.04 Fatigue in MS

Many of the tasks that we perform during our everyday activities, such as walking up a flight of stairs, shopping, or simply getting up from a chair, become increasingly difficult as a result of fatigue. In fact, adults with MS report fatigue as their most disabling symptom, affecting up to 90% of the MS population [44]. However, despite its high prevalence, fatigue in MS remains poorly understood [45]. The term fatigue has been used to describe a multitude of physical and cognitive complaints [27,34,46]. As reported by patients, fatigue typically refers to a state of exhaustion or tiredness [9,27,47–50]. Factors such as weakness, pain, sleep disturbance, and mental illness (depression) all potentially contribute to the increased level of fatigue [23,27,51–54]. Fatigue can also be manifested as muscular fatigue or fatigability, and can be described as the magnitude of change in the physical performance over a period of time [27,55–57]. Therefore, fatigue can be subjectively evaluated with self-report fatigue scales, or objectively evaluated with quantitative parameters, such as a reduction in peak torque [34,47].

Earlier studies that investigated the interrelationship between fatigability and the physical, cognitive and psychosocial complaints of fatigue in individuals with MS, reported no relation between symptomatic fatigue, central activation, muscle weakness, or any other clinical function measure, including fatigability [35,49,58,59]. Sharma et al [35] studied the extent to which fatigability was related to clinical status and symptomatic fatigue. Fatigue was examined in 42 participants by measuring muscle torque (MVIC), muscle activation (compound muscle action potential), and energy metabolism (phosphorus energy metabolites and pH) of the tibialis

anterior muscle, as well as a self-report fatigue questionnaire (FSS) [35]. The main findings of the study showed excessive decline in tetanic torque during peripheral nerve stimulation in individuals with MS, as well as a positive correlation between fatigability and UMN dysfunction and metabolic changes during exercise, but not with symptomatic fatigue ratings [35]. Van der Werf et al [59] studied the extent to which cerebral abnormalities, as indicated by white matter lesions on magnetic resonance imaging (MRI), had any relation with the severity of fatigue complaints of individuals with MS. Forty-five participants rated fatigue severity through a self-report fatigue questionnaire (Checklist Individual Strength-Fatigue) and the use of a 2-week diary, while the MRI provided measures for cerebral abnormalities (white matter lesion load, brain atrophy) [59]. These findings suggested no relation between symptomatic fatigue in individuals with MS and the extent of cerebral abnormalities, nor to the extent of MRI abnormalities in discrete cerebral areas [59].

Conversely, later studies using self-report fatigue scales and sustained maximal and submaximal contractions confirm a relation between symptomatic fatigue and fatigability [28,60]. These findings suggest that a combination of complaints is necessary to explain MS-related fatigue [28,60]. Steens et al [28] investigated associations between symptomatic fatigue and measure of fatigability, while correcting for muscle torque. Fatigue was examined in 40 participants by measuring muscle torque (MVIC), muscle activation (ITT), and corticospinal integrity (TMS) during electrical stimulation of the first dorsal interosseous muscle, as well as self-report fatigue questionnaires (FSS and HADS). The main results demonstrated a strong association between symptomatic fatigue in individuals with MS and the decline in torque during an MVIC, as well as measures of voluntary activation [28]. Wolkorte et al [60] took previous research one step further and evaluated the robustness of the association between symptomatic

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fatigue, depression scores, and muscle fatigability in individuals with MS [60]. Fatigue was examined in 100 participants by measuring muscle torque (MVIC) of the index finder abductor, as well as self-reported fatigue questionnaires (FSS, MFIS, and HADS) [60]. Wolkorte et al [60] reported a strong association between symptomatic fatigue and the combination of depression and muscle fatigability in individuals with MS [60].

1.05 Quantifying Fatigue in MS

A great deal of attention in the past 20 years has been focused on the accurate identification and measurement of fatigue [61]. Several methods have been developed to assess fatigue due to the broad range of underlying mechanisms and confounding factors associated with it [62]. A multidimensional approach incorporating both subjective evaluation and torque measurements is most useful for a comprehensive analysis when studying fatigue in individuals with MS [27,63,64].

Measurement of subjective evaluation typically requires the use of self-reported scales [1,65–67]. Both the Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS) have rapidly become the most widely used tools in MS, clinically [61,68]. Using a Likert-scale format, the MFIS is a 21 item questionnaire that quantifies the subjective experience of fatigue by addressing the constructs of physical, psychosocial and cognitive fatigue [1,61,66]. The FSS is a nine item questionnaire that quantifies the subjective impact and severity of fatigue [1,10,67]. In addition, the Visual Analogue Fatigue Scale (VAFS) is a one item questionnaire that evaluates the subjective perception of global fatigue experienced in MS [69].

Objective evaluation of fatigue typically requires the use of torque for its measurement. The most direct way of objectively quantifying fatigue involves measuring the change in torque

production through the use of a dynamometer [70–72]. This can be achieved by attempting a sustained maximal voluntary isometric contraction (MVIC), or a submaximal voluntary isometric contraction held to the limit of endurance [26,71,72]. Isometric contractions are defined by the production of increasing tension with a constant muscle length or joint angle. Measuring percentage drop of initial torque within a predetermined time has been used to facilitate group comparisons in special population studies [73,74]. Another way to objectively quantify fatigue involves measuring the extent of voluntary activation (VA) through twitch interpolation [26,39,75]. The underlying principle involves electrically stimulating the appropriate peripheral nerve or muscle at the point of maximal voluntary torque production [25]. If central activation is inadequate, the stimulation will evoke additional torque from the muscle [30]. The size of the additional torque is proportional to the central drive and number of inactive motor units that are not being maximally driven [25]. A decrease in activation, as can occur during a sustained contraction, can contribute to the development of fatigue [25]. Voluntary activation can be determined using the interpolated twitch technique and calculated according to Equation 1 [28].

$$VA\ (\%) = \left(1 - \left(\frac{Interpolated\ twitch}{Potentiated\ twitch} \right) \right) \times 100\ (1).$$

Interpolated twitch represents the maximal torque stimulated using a supramaximal stimulus during an MVIC. Potentiated twitch represents the torque using the same supramaximal stimulus following the MVIC, while the muscle is at rest [76].

Applying a fatigue protocol that incorporates changes in torque as the primary outcome measure provides a logical approach to objectively compare fatigue in individuals with MS.

Quantitative indicators of muscle weakness may provide direct evidence of neuromuscular fatigue in MS. Alternatively, objective measurements of fatigue might provide indirect evidence of subjective fatigue in individuals with MS.

1.06 Anatomy

When investigating fatigue and neuromuscular health, the physiology and function of the muscle must be considered. Flexors in the lower limbs, such as the ankle dorsiflexor muscles, tend to be more affected in MS due to the upper motor neuron patterns of weakness.

Literature studying muscle strength in MS reports an increase in muscle weakness and a reduction in muscle strength, specific to knee extensors [34,73,77,78], knee flexors [73,79], and ankle DF [58] muscle groups. Similarly, muscles of the lower extremities demonstrate a greater degree of muscle weakness compared to muscles of the upper extremities [74]. For the study of muscular fatigue in individuals with MS, muscles of the lower extremities that are particularly active during ambulation are most relevant. For the present investigation, the ankle DF muscles of the lower extremities have been selected due to their specific role in mobility and ankle stabilization during every day activities, such as walking or climbing up a flight of stairs [80].

The anterior compartment of the leg consists of muscles that dorsiflex the foot and extend the toes. These muscles include the tibialis anterior (TA), extensor hallucis longus, extensor digitorum longus and fibularis tertius. The TA is a long, thick muscle against the lateral surface of the tibia [81]. It originates on the lateral condyle and body of the tibia and interosseous membrane (sheet of fibrous tissue that holds shafts of tibia and fibula together) and inserts onto the first metatarsal and medial cuneiform [81,82]. The extensor hallucis longus is a thin muscle between the TA and extensor digitorum longus muscles [81]. It originates on the anterior surface of the fibula and interosseous membrane and inserts onto the distal phalanx of the great toe [81].

The extensor digitorum longus originates on the lateral condyle of the tibia, anterior surface of

the fibula, and interosseous membrane and inserts onto the middle and distal phalanges of toes 2-

5 [81]. Lastly, the fibularis tertius muscle is part of the extensor digitorum longus, with which it

shares a common origin, and inserts onto the base of the fifth metatarsal [81]. Innervated by the

peroneal nerve, the ankle DF muscles serve to dorsiflex the foot at the ankle joint, invert

(supination) and evert (pronation) the foot at the intertarsal joints, and extension of toes 1-5

[81,82]. The dorsiflexor muscles of the leg are displayed in figure 1.3.
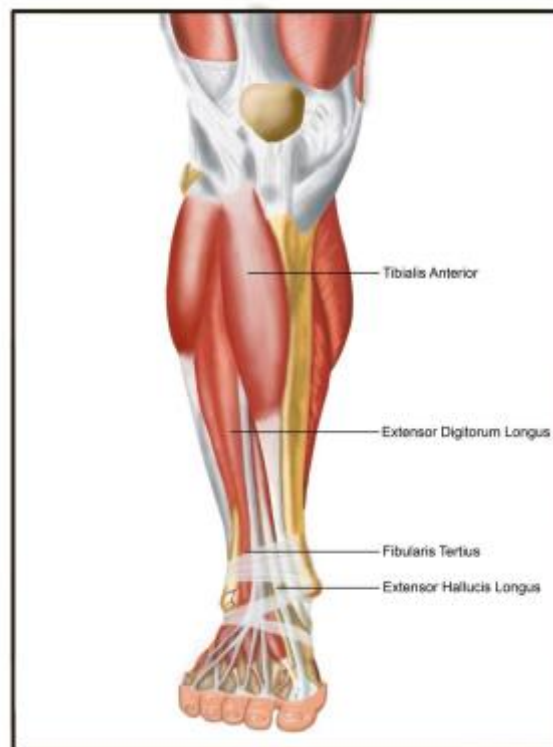
Figure 1.3. Dorsiflexor muscles of the leg (with permission from Alexandra Lynette-Krech, (2017))

The overall purpose of this thesis was to objectively evaluate the interrelationship between symptomatic fatigue and fatigability in individuals with MS.

Objectives

1. To compare dorsiflexor isometric strength in individuals with MS and healthy individuals

2. To compare voluntary activation in individuals with MS and healthy individuals

3. To compare fatigability in individuals with MS and healthy individuals

4. To compare 6-Minute Walk Times in individuals with MS and healthy individuals

5. To measure subjective perception of fatigue in individuals with MS and healthy individuals using the Modified Fatigue Impact Scale, Fatigue Severity Scale, and Visual Analogue Fatigue Scale

6. To measure fatigue severity and fatigability in individuals with MS and healthy individuals through the use of fatigue questionnaires and submaximal isometric testing

Hypotheses

1. Individuals with MS will show decreased dorsiflexor isometric strength in comparison to healthy individuals

2. Individuals with MS will show decreased voluntary activation in comparison to healthy individuals

3. Individuals with MS will exhibit greater fatigue in comparison to healthy individuals

4. Individuals with MS will have a reduced 6-Minute Walk time in comparison to healthy individuals

5. Individuals with MS will show higher subjective ratings of fatigue in comparison to healthy individuals

6. Individuals with a higher subjective rating of fatigue will experience greater muscle fatigue

7. The Modified Fatigue Impact Scale and the Fatigue Severity Scale scores will negatively correlate with muscle fatigue

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CHAPTER 2

QUANTITATIVE ASSESSMENT OF MUSCLE STRENGTH AND FATIGUE IN INDIVIDUALS WITH MS

2.0 INTRODUCTION

Individuals with multiple sclerosis (MS) characteristically present fatigue as one of their most prevalent and disabling symptoms [1–3]. It has been suggested that up to 95% of individuals with MS are affected by fatigue, and that it creates a major impact on quality of life and overall well-being [2,3]. The term fatigue can be expressed by various combinations of physical, emotional or cognitive complaints [1,4]. It can be described by individuals as a feeling of exhaustion [5–7] or lassitude, [8,9] or from a neuromuscular standpoint, it can be described as an inability to sustain a required or expected torque [8,10].

Fatigue remains a challenging symptom for individuals with MS and their care providers [11]. Due to its complexity, quantifying muscle fatigue is essential when attempting to fully understand the underlying causes. Self-report scales that can broadly be classified as measuring subjective fatigue, have emerged as preferred tools clinically [12,2,13]. In addition, objective measurements have been employed to quantify the decline in muscle torque during a fatigue-inducing task [8,12,14-18]. While it has been established that changes in both central and peripheral fatigue play a large role in the decline of muscle torque, it is possible to determine whether central fatigue or weakness is present during a fatigue-inducing task [8]. The simplest approach to determining this is to deliver a supramaximal electric stimulus to the motor nerve and to look for a twitch superimposed on the torque produced during a maximal voluntary isometric contraction (MVIC) [8,19,20]. Greater recruitment and central drive leaves fewer inactive motor units to be stimulated by the superimposed stimulus, yielding a smaller torque

recording, or a greater voluntary activation [21]. This commonly used technique is known as twitch interpolation and has been applied to various clinical and special populations such as knee osteoarthritis [21], chronic fatigue syndrome [22], amyotrophic lateral sclerosis [23], adult aging [24], and more.

Studies investigating voluntary activation (VA) [25–28,16,29] reported that individuals with MS have impaired central activation during both non-fatiguing and fatiguing motor tasks compared to healthy individuals. A study by Steens et al [25] reported that muscle fatigue was strongly associated with a decline in central activation during a fatiguing task of the first dorsal interosseous. Studies investigating direct muscle torque [25,30,27,29] reported that individuals with MS are significantly weaker than healthy individuals during a MVIC. Using surface EMG, van der Kamp et al [31] found MVICs of the thenar muscles were 40% weaker in individuals with various courses of MS.

Researchers continues to investigate the interrelationship between symptomatic fatigue and fatigability [5,32]. Earlier studies [5,7] showed no association between symptomatic fatigue in individuals with MS and objective measures of fatigability, while later studies [25] found a stronger association. The differences in these findings between symptomatic fatigue and fatigability might be specific to the methodology used. Therefore, a multidimensional approach used to study both the subjective (self-report scales) and objective (direct muscle torque) components of fatigue will provide a viable framework to study muscle strength and fatigue in individuals with MS [1].

The aim of this study was to objectively investigate the role of muscle strength and voluntary activation on symptomatic fatigue in individuals with MS. The muscle group chosen for this study was the ankle dorsiflexor (DF) muscles because of their specific role in mobility

and ankle stabilization when performing every day activities. Furthermore, weakness in the flexors of the lower limbs, such as DF muscles tend to be more common in individuals with MS due to upper motor neuron patterns of weakness. We hypothesize that individuals with MS who are experiencing fatigue will exhibit deficits in muscle strength and voluntary activation. Additionally, quantitative indicators of muscle weakness and fatigue may provide indirect evidence of symptomatic fatigue.

2.1 METHODS

2.1.1 Study Participants

A schematic representation of the study protocol is included in Figure 2.1. Eighteen participants (nine women with relapsing-remitting MS (RRMS) or secondary-progressive MS (SPMS) and nine healthy aged matched women; ages 20-60 years) were invited to participate in the study. Participants' health was determined through the inclusion/exclusion criteria of the study protocol as well as informal screening prior to commencement of the study. All participants were otherwise healthy with no self-reported neuromuscular or musculoskeletal disorders that would affect their gait or ability to perform strong muscle contractions in the lower leg. RRMS/SPMS participants were recruited and screened using an Expanded Disability Status Scale (EDSS) [33] (Appendix A) by Dr. S. Morrow, an experienced neurologist from the London Health Science Centre MS Clinic. Participants with an EDSS score between 2.0-6.5 were eligible to partake in the study. Healthy participants were recruited from the Western University student population, as well as the London community. All participants provided informed written consent and the study was approved by Western University, Health Sciences Research Ethics Board (Appendix F).
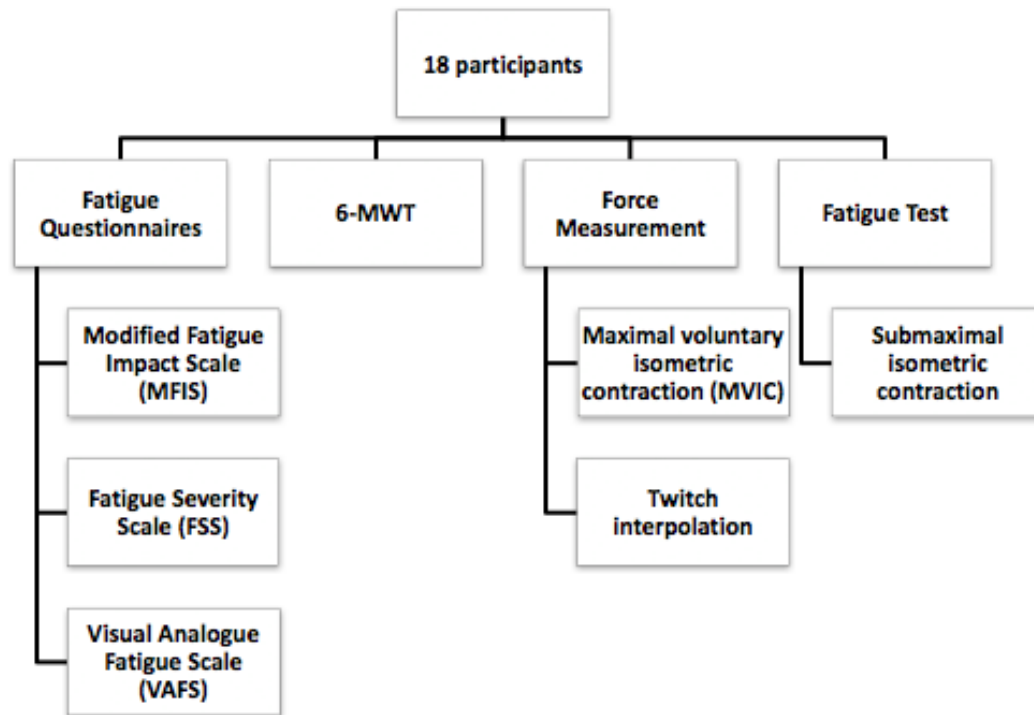
Figure 2.1. Schematic representation of the study protocol

2.1.2 Measures of Fatigue

All data was collected during a single visit to the Neuromuscular Performance Laboratory at Parkwood Institute (London, Ontario). At the beginning of the visit, participants completed the Modified Fatigue Impact Scale (MFIS) [34,36] (Appendix B), Fatigue Severity Scale (FSS) [34,35] (Appendix C), Visual Analogue Fatigue Scale (VAFS) [35] (Appendix D) and a 6-Minute Walk Test (6MWT) [37] (Appendix E).

The MFIS is a 21-item self-administered questionnaire used to assess the perceived impact of fatigue within the past four weeks, and is aggregated into physical, cognitive and psychosocial domains [34,38,12]. Participants rate on a 5-point Likert scale 0 being 'never' to 4

being 'almost always', the extent to which they feel the statement applies to them. A total sum score out of 84 is calculated, with higher scores indicating a greater impact of fatigue.

The FSS is a 9-item self-administered questionnaire used to assess the severity of fatigue and the impact on daily functioning during the past week [34,38,12,39]. Participants indicate on a 7-point Likert scale 1 being 'strongly disagree' to 7 being 'strongly agree', the extent to which they feel each statement applies to them. A total sum score out of 63 is calculated, with higher scores indicating a greater impact of fatigue.

The VAFS is a one-item questionnaire used to assess the participants' global fatigue. Participants rate on a 10-point Likert scale 0 being 'worst' to 10 being 'normal', the extent to which they feel the statement applies to them. A total sum score out of 10 is calculated, with lower scores indicating an increase in fatigue severity.

Following completion of the fatigue questionnaires, participants were required to complete a 6MWT. Procedures were adopted from the American Thoracic Society guidelines. Participants were able to use assistive devices if needed, while walking a 26 meter linear course, marked by 2 meter increments. Participants were instructed to walk as fast as possible along the marked course, turn around at the last marker, return to the start, and repeat this course as often as possible in six minutes. The time elapsed was measured with a stopwatch, and the distance walked per minute was measured and summed for total distance in meters. Verbal encouragement was provided and a scripted text was used to provide guidance before, during, and after the six minutes.

2.1.3 Measurement of Isometric Strength and Fatigue

Participants were seated upright in the ankle dynamometer (McComas and Belanger 1981) with their right ankle positioned at 30° plantar flexion and hip and knee angles of 90°. Velcro straps were fastened across the participant's foot (Figure 2.2). Additionally, during all contractions, participants were instructed to fold their arms across the chest to avoid extraneous movement.

The test protocol commenced with a series of submaximal isometric contractions for the purpose of warm-up and familiarization. Participants then performed repeated (3-5 repetitions), brief (~ 5s) MVICs of the ankle DF, each separated by 2 minutes of rest. Maximal torque was attained when two consecutive MVICs differed by less than 5%. Participants were provided with strong verbal encouragement. Torque was displayed in real-time on an online system using the Spike 2 software in attempt to obtain maximal effort.

The fatigue protocol consisted of a sustained submaximal voluntary isometric contraction (50% MVIC) held to the limit of endurance. Torque produced by each participant and two lines identifying the target torque (50% MVIC) and cut off torque level (40% MVIC) were displayed using Spike 2 software. Task termination resulted when the participants torque dropped below the 40% MVIC line twice and the time to task failure (TTF) in seconds was recorded. Immediately following task termination, participants completed one final MVIC of the ankle DF muscles, while the study examiner manually delivered an electrical stimulation ~ 1s prior, during maximal plateaued torque, and ~1s following their maximal contraction. To score global fatigue, the ratings of VAFS were requested from the participants following fatiguing task.

2.1.4 Measurement of Voluntary Activation

Voluntary activation

Participants were seated upright in the ankle dynamometer (McComas and Belanger 1981) with their right ankle positioned at 30° plantar flexion and hip and knee angles of 90°. Velcro straps were fastened across the participant's foot (Figure 2.2). Additionally, during all contractions, participants were instructed to fold their arms across the chest to avoid extraneous movement.

To obtain the maximal twitch torque, electrical stimulation was applied to the peroneal nerve around the fibular head with a constant current stimulator (DS7AH, Digitimer, UK). A series of incremental stimuli of increasing intensity were delivered to the resting muscle. Once the torque output reached a plateau, the stimulus was deemed maximal. The stimulus was then increased an additional ~10% to achieve supramaximal stimulation.

The test protocol commenced with a series of submaximal isometric contractions for the purpose of warm-up and familiarization. Participants then performed brief (~ 5s) MVICs of the ankle DF muscles. A single supramaximal stimulus was applied to the peroneal nerve prior to their MVIC. A second supramaximal stimulus was applied at the point of maximal voluntary torque, which was visually determined as the point of torque plateau. A third single supramaximal stimulus was delivered at rest ~1s following their MVIC to obtain the potentiated twitch. This procedure was repeated 3-4 times for each participant, followed by 2 minutes rest between trials.

A standard equation (VA (%) = (1 − (interpolated twitch /potentiated twitch)) x 100 was used to calculate the percent of VA. VA is considered maximal when there is no superimposed

twitch evoked at the peak of the MVIC in response to the supramaximal stimulation of the

peripheral nerve.

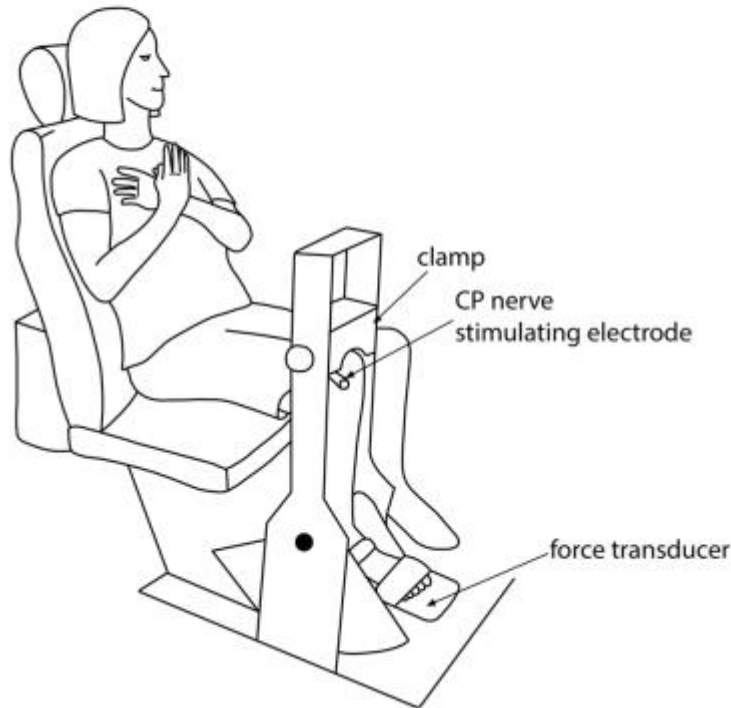**Figure 2.2. Schematic representation of the experimental setup** (with permission from
Alexandra Lynette-Krech, (2017))

2.1.5 Statistical Methods

All analyses were performed using Statistical Package for the Social Sciences (Version

24; IBM SPSS Inc., Chicago, IL). Data was testing for normal distribution using the Shapiro-

Wilk Test. A two-tailed independent samples t-test was used to identify any differences between

groups for demographic data, fatigue-scaled scores, 6-MWT, MVIC, VA, and TTF. The association between the dependent variables, such as the MFIS, FSS and VAFS, and the different measures of MVIC, VA, 6-MWT, and TTF as the independent variables were determined using Pearson's correlation analysis. A split-plot analysis of variance (group by time) was performed to investigate a potential interaction for MS participants versus healthy controls at baseline and post-fatigue on MVIC, VA and VAFS scores. If a significant interaction was detected, a Tukey post hoc analysis was performed to determine where the differences existed. A significance level of $p \leq 0.05$ was used for all statistical tests. All values are reported in mean ± standard deviation (SD).

2.2 RESULTS

2.2.1 Demographics

Subject characteristics are present in Table 1. Participants ranged in age from 22 to 60 years, with an average age of 39 years (SD= 10 years). No difference was observed in age between the MS group and healthy controls. The majority of participants were of Caucasian descent, with the exception of one African Canadian participant belonging to the MS group. According to international classification standards for body mass index (weight (kg) / height (m)^2), on average, both groups were slightly overweight (BMI $\geq$ 25). EDSS scores for the MS group ranged from 2.0 to 6.5 points, with an average of 4 points (SD= 2 points). The majority of MS participants were currently taking DMTs as a part of their MS treatment regime. A brief history of diagnosis date as well as current treatment are displayed in Table 2.

Table 1. Subject Characteristics

Group	n	Age (years) mean ± SD	BMI mean ± SD	EDSS mean ± SD
Control	9	35 ± 7	25 ± 3	n/a
MS	9	43 ± 11	27 ± 4	4 ± 2

BMI= body mass index, EDSS= expanded disability status scale.

Table 2. History of MS Participants

Code	Dx	Treatment
MS 01	2011	Rebif
MS 02	2012	None
MS 03	2009	None
MS 04	2017	Aubagio
MS 05	2004	Copaxone
MS 06	2009	Tysabi
MS 07	2011	None
MS 08	1994	None
MS 09	2010	Aubagio

Dx = date of diagnosis

2.2.2 Fatigue Questionnaires and 6-MWT

An overview of scores resulting from the MFIS, FSS and VAFS are included in Table 3. According to the MFIS, the MS group experienced more fatigue compared with healthy controls (p<0.05). Distance walked during the 6-MWT (r= -0.720, p= 0.001) (Figure 2.4), baseline MVIC torque (r= -0.689, p= 0.002), post-fatigue MVIC torque (r= -0.666, p= 0.003), and baseline VA (r= -0.589, p= 0.010) scores were all negatively associated with MFIS scores. No association was found between MFIS scores and post-fatigue VA and TTF scores.

The MS group experienced more physical fatigue compared with healthy controls (p<0.05). A negative association was observed between MFIS physical scores and distance walked during the 6-MWT (r = -0.659, p= 0.003), baseline MVIC torque (r = -0.641, p = 0.004), post-fatigue MVIC torque (r = -0.541, p = 0.020), and baseline VA (r = -0.609, p = 0.007) scores. These findings suggest that the higher ratings of perceived physical fatigue were associated with lower activation and strength of the DF muscles. No association was found between MFIS physical scores and post-fatigue VA and TTF scores.

Like physical fatigue scores, the MS group experienced more cognitive fatigue compared with healthy controls (p<0.05). Distance walked during the 6-MWT (r = -0.477, p = 0.045), baseline MVIC torque (r = -0.498, p = 0.036), post-fatigue MVIC torque (r = -0.596, p = 0.009), and post-fatigue VA (r = -0.504, p = 0.033) scores were all negatively associated with MFIS cognitive scores. No correlation was found between MFIS cognitive scores and baseline VA and TTF scores.

MFIS psychosocial scores did not differ between groups (p>0.05). However, MFIS psychosocial scores were negatively associated with distance walked during the 6-MWT (r = -0

.628, p = 0.005). No association was found between MFIS psychosocial scores and MVIC, VA, and TTF scores.

No difference was observed in FSS scores between the MS group and healthy controls (p>0.05). However, the FSS was negatively associated with distance walked during the 6-MWT (r = -0.731, p = 0.001), indicating higher ratings of perceived fatigue were accompanied by shorter distance walked. No association was found between FSS scores and MVIC torque, VA, and TTF scores.

Results from the 2-item VAFS indicated no difference between groups or scores (p>0.05). In addition, disability status (EDSS) showed a significant association with FSS (r = 0.687, p = 0.041) scores but not with MFIS scores.

Table 3. Fatigue Scales

Group	MFIS Total mean ± SD range	MFIS physical mean ± SD range	MFIS cognitive mean ± SD range	MFIS psychosocial mean ± SD range	FSS Total mean ± SD range	Baseline VAFS mean ± SD range	Post-fatigue VAFS mean ± SD range
Control	31 ± 9 22 to 49	13 ± 4 7 to 20	15 ± 4 11 to 24	3 ± 2 1 to 6	31 ± 12 14 to 49	8 ± 1 6 to 9	8 ± 1 7 to 9
MS	51 ± 14* 32 to 79	26 ± 12* 10 to 35	21 ± 6* 9 to 30	4 ± 2 2 to 7	42 ± 11 18 to 53	7 ± 2 4 to 10	7 ± 2 4 to 10

MFIS = modified fatigue impact scale, FSS = fatigue severity scale, VAFS = visual analogue fatigue scale. * Indicates a significant difference between controls and MS.

2.2.3 Force Measurement and Fatigue Test

As shown in figure 2.3, the MS group walked a shorter distance compared with healthy controls during the 6-MWT ($p<0.001$). A positive relation was found between distance walked and baseline MVIC torque ($r = 0.547$, $p = 0.019$) scores, indicating that increased distance walked was associated with increased MVIC torque.

Baseline and post-fatigue scores on MVIC, VA, 6-MWT, and TTF are outlined in Table 4 and Table 5, respectively. The average strength (MVIC) for healthy controls was 26.06 ± 3.33 Nm, which was significantly stronger than the MS group who had an average MVIC of 18.61 ± 7.33 Nm ($p<0.05$). As shown in Figure 2.5, when normalized to participants' body mass (BM), healthy controls had greater MVIC torque scores compared with the MS group at baseline and post-fatigue testing ($p<0.05$). Both groups MVIC torque decreased post-fatigue ($p<0.05$). There was no interaction between participants (MS and healthy controls) and MVIC torque ($F(1,16) = 0.94$, $p>0.05$) at baseline and post-fatigue testing. There was a main effect on MVIC torque within participants ($F(1,16) = 37.60$), $p<0.001$), as well as between groups ($F(1,16) = 18.97$, $p<0.001$). As shown in figure 2.6, healthy controls had greater VA scores compared with the MS group at baseline and post-fatigue testing ($p<0.05$). There was no interaction between participants (MS and healthy controls) and VA ($F(1,16) = 9.34$, $p>0.05$) scores at baseline and post-fatigue testing. There was a main effect on VA scores between groups ($F(1,16) = 9.34$, $p<0.05$). A positive association was observed between MVIC torque and VA scores at baseline, indicating that lower MVIC torque was accompanied by lower VA levels ($r = 0.607$, $p = 0.008$; $r = 0.743$, $p = 0.001$, respectively).

As shown in Figure 2.7, no difference was found in average TTF scores between the MS group and healthy controls ($p > 0.05$).

Table 4. Baseline Quantitative Parameters

Group	Baseline MVIC (Nm) mean ± SD	Baseline MVIC (Nm/kg BM) mean ± SD	6-MWT (m) mean ± SD	Baseline VA (%) mean ± SD
Control	26.0 ± 3.33	0.39 ± 0.06	458 ± 63	95 ± 2
MS	18.6 ± 7.33*	0.25 ± 0.07*	312 ± 85*	76 ± 23*

* Indicates a significant difference between healthy controls and MS participants.

Table 5. Post-fatigue Quantitative Parameters

Group	TTF (s) mean ± SD	Post-fatigue MVIC (Nm/kg BM) mean ± SD	Post-fatigue VA (%) mean ± SD
Control	149 ± 69	0.30 ± 0.06	95 ± 4
MS	118 ± 31	0.19 ± 0.07*	78 ± 17*

* Indicates a significant difference between healthy controls and MS participants.
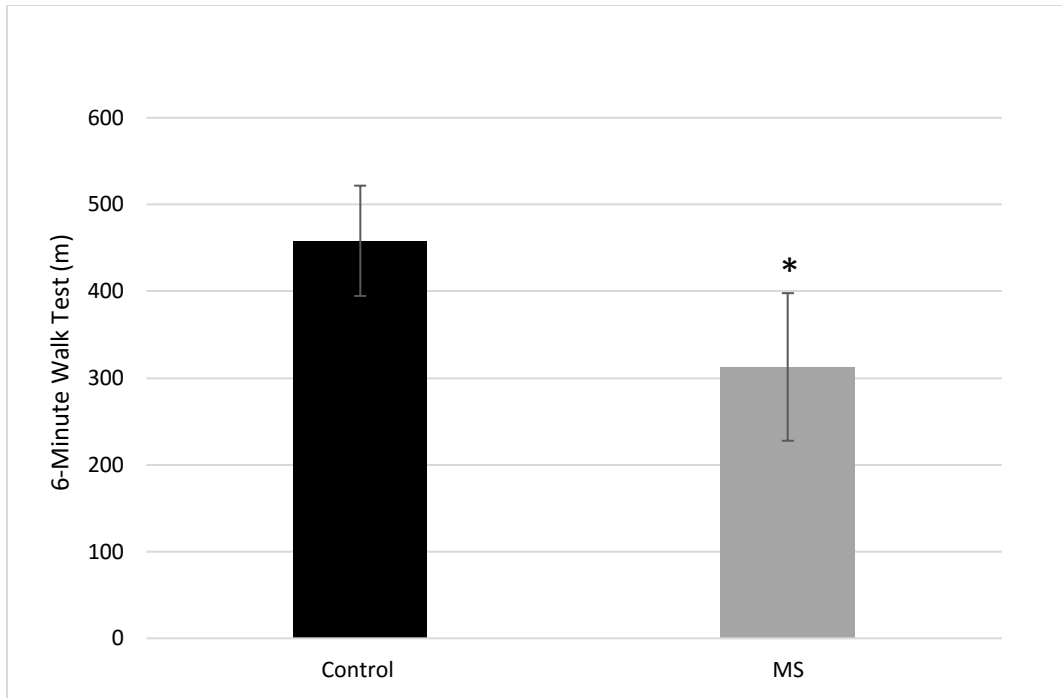
Figure 2.3. Distance walked during the 6-minute walk test

Distance walked (m) during the 6-MWT for healthy controls (black) and MS participants (grey). Distance walked was significantly shorter in the MS group (p<0.05). Values are presented as means ± SD. * Represents a significant difference between healthy controls and MS participants.
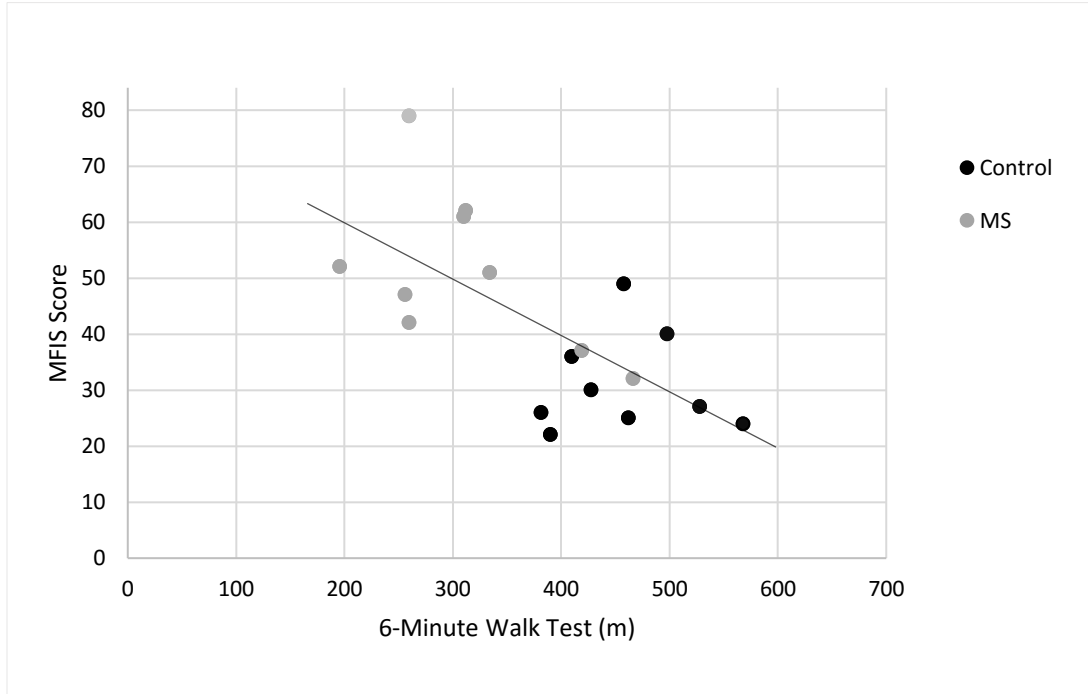
Figure 2.4. Correlation between 6-minute walk times and MFIS scores

A strong correlation exists between distance walked during the 6-minute walk test and MFIS scores (r = 0.720, p = 0.001) in healthy controls (black) and MS participants (grey).
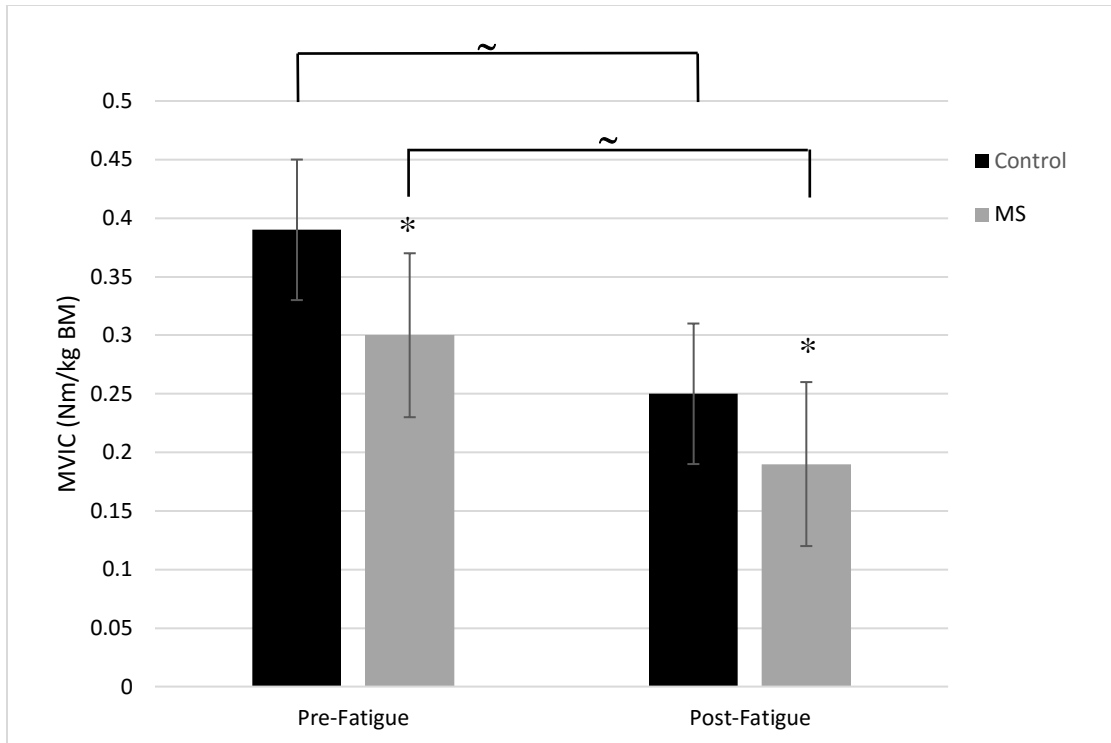
Figure 2.5. Strength of the DF muscles

Peak torque (Nm/kgBM) of the DF muscles normalized to subjects' BM of healthy controls (black) and MS participants (grey). MS participants were significantly weaker than healthy controls (p<0.05). Both groups decreased torque post-fatigue (p<0.05). Values are presented as means ± SD. **~** Represents a significant effect within healthy controls and MS participants. **∗** Represents a significant effect between healthy controls and MS participants.
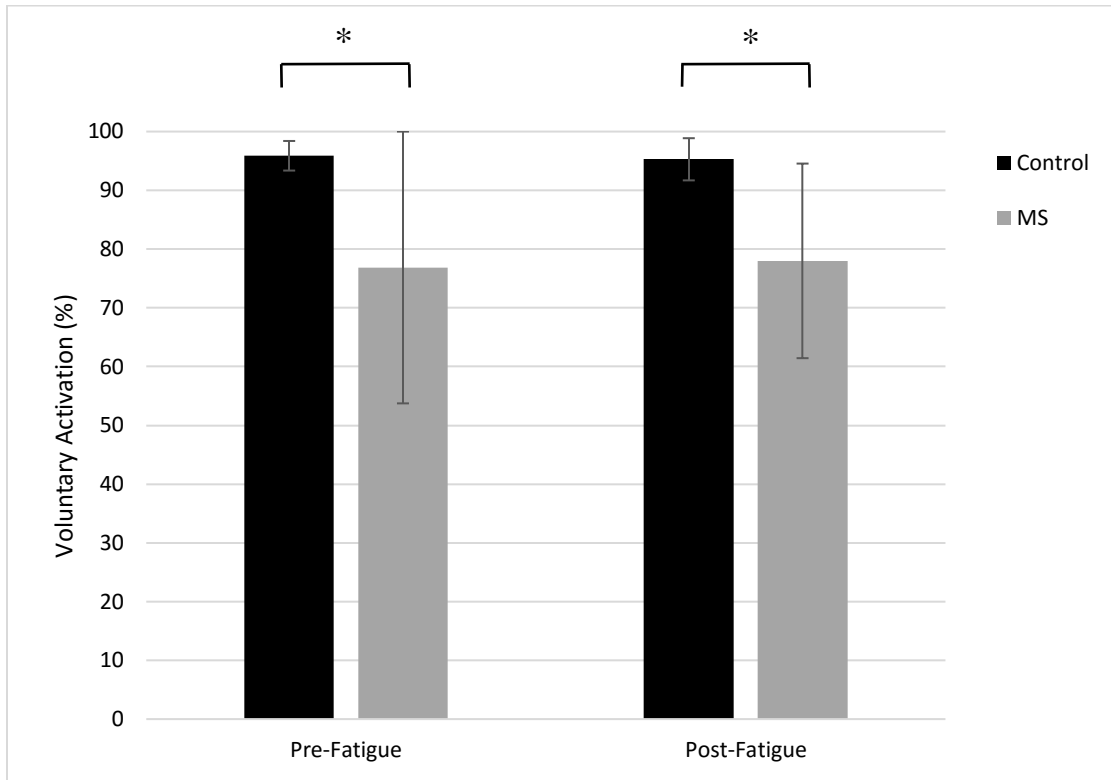
Figure 2.6. Voluntary activation of the DF muscles

Voluntary activation (%) of the DF muscles for healthy controls (black) and MS participants (grey). Voluntary activation was significantly lower in MS participants at baseline and post-fatigue testing (p<0.05). Values are presented as means ± SD. * Represents a significant effect between healthy controls and the MS participants.
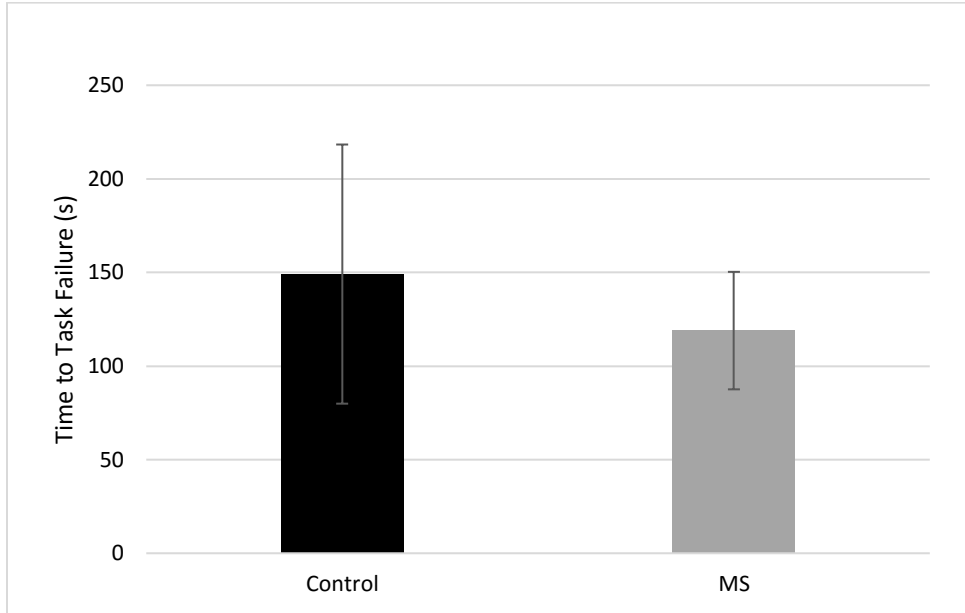
Figure 2.7. Time to task failure

Time to task failure (s) during submaximal contraction of the DF muscles held to the limit of endurance for healthy controls (black) and MS participants (grey). No difference was observed between groups ($p>0.05$). Values are presented as means $\pm$ SD.

2.3 DISCUSSION

The study assessed the impact of muscle strength and voluntary activation on symptomatic fatigue in individuals with MS. It was hypothesized that individuals with MS would exhibit 1) reduced muscle strength and voluntary activation, which would correlate to 2) a higher symptomatic fatigue rating, 3) greater fatigability on an objective test of neuromuscular fatigue and 4) a reduced 6-minute walk time. The main findings demonstrated that individuals with MS have reduced muscle strength, voluntary activation, and 6-minute walk times compared with healthy controls. Individuals with MS reported higher levels of symptomatic fatigue, which were strongly associated with normalized peak torque and voluntary activation for DF muscles. No relation exists between symptomatic fatigue and fatigability.

As fatigue is a predominant characteristic of MS, the observation that individuals with MS report greater fatigue than healthy controls is well supported by previous research [7,44,20]. In the present study, individuals with MS subjectively reported themselves significantly more fatigued on the MFIS, FSS and VAFS than healthy controls. A difference in the total MFIS score was observed between groups. Furthermore, a significant difference in MFIS physical and cognitive scores was observed between groups. However, no difference was observed in psychosocial scores. Previous research using self-report scales have indicated a strong correlation between total MFIS and FSS scores [34,45]. Consistent with the findings, a strong relation existed between MFIS and FSS scores in the present study, however, no difference was observed in FSS scores between groups. One possible explanation for the non-significant finding in the FSS may be due to the relatively small sample size (N=18), and large group variance in the present study. Studies that have reported significant findings incorporated a larger sample size (N>100), increasing the power to detect a statistically significant relationship [34,36,46]. In

addition, previous studies have shown a stronger relation with depression scores and total MFIS scores, compared with FSS scores [34,45,36]. Thus, the MFIS may have been more sensitive to the psychological variables that presented in the healthy control group.

The relationship between decreased muscle strength and a subsequent increase in physical inactivity and psychological factors has been determined in individuals with MS [34,47]. Despite the well-known benefits of physical activity, it has been established that individuals with MS report being less physically active than healthy controls [48,49,38]. Engaging in physical activity may further improve cognitive function, fatigue, and quality of life. In a study by Trojan et al [51], researchers compared symptomatic fatigue and biopsychosocial correlates of fatigue (disease course, physical inactivity, and depression) in 53 individuals with MS. One main finding was the association between physical inactivity and increased symptomatic fatigue in individuals with MS. The majority of participants in Trojan's study were slightly overweight (B.M.I ≥ 25) or obese, potentially contributing to the indirect cause of physical activity and subsequently leading to an increased perception of fatigue [51]. Further, studies have found significant associations between psychological variables, such as depression and fatigue in individuals with MS [3,52]. A longitudinal study by Kinsinger et al [3] examined the influence of depression and fatigue on symptomatic cognitive fatigue and neuropsychological impairment in a clinical trial. Self-report scales and structured interviews were conducted over 127 participants with MS. Findings suggest that the treatment of depression and fatigue symptoms can influence an individual's ability to accurately perceive their cognitive performance. This study supports previous findings [53–56] by demonstrating the impact of depression and symptomatic fatigue on cognitive function [3]. In the present study however, behavioural or psychosocial variables were not measured. Through structured conversations,

38% of participants in the present study (17% controls, 21% MS) presented a mental illness (depression and or anxiety), potentially contributing to the increased symptomatic fatigue experienced in both groups. Therefore, the interaction between symptomatic fatigue and muscle fatigue merits further investigation. Determining the impact of biopsychosocial variables on symptomatic fatigue will offer the opportunity to implement new treatments to reduce experienced fatigue in the MS population.

A primary objective of this investigation was to determine if there were differences in muscle strength and activation between individuals with MS and healthy controls. After accounting for differences in body mass and age, we found that overall, absolute peak torque was 36% lower in the MS group than healthy controls. This finding is slightly lower than previous research studying similar parameters [25,15,29,30]. A difference in peak torque was observed between groups at baseline (pre-fatigue) and immediately following the fatigue task. Following the fatigue task, both groups exhibited decreased torque. One explanation for lower torque-generation in the MS group is the impaired central drive from the CNS to the LMNs of specific muscles, such as the DF muscles [57]. It has been reported that when a supramaximal electrical stimulus is imposed on the working muscle during a MVIC, there is a large increase in torque in individuals with MS. This suggests that individuals with MS have a reduced ability to fully activate their muscles [15]. Rice et al [26] have reported that motor neuron firing rates during a MVIC are significantly lower in individuals with MS which may indicate reduced central drive. In the present study, a strong association was demonstrated between MVIC torque and voluntary activation levels, indicating that higher MVIC torques were accompanied by higher voluntary activation levels. Furthermore, we used interpolated twitch to measure voluntary activation of the DF muscles between the MS group and healthy controls. Complete voluntary activation

represents a state in which all motor units are recruited and firing at their optimal rate [58]. Several muscles, including muscles of the lower limbs, have demonstrated a reduction in voluntary activation following prolonged activity [26,58,59,40]. This decrease in voluntary activation has been defined as central fatigue [26,58,59,40]. The mean non-fatigued level of voluntary activation in lower limb muscles ranges from 94%-100% in healthy controls. In comparison, the mean non-fatigued level of voluntary activation in individuals with MS is quite variable, ranging from 47%-93% [60]. Consistent with these findings, in the present study, a significantly lower activation was demonstrated in the MS group. The MS group produced a mean activation level of 77% versus 96% in healthy controls. This difference could account for almost all of the difference observed in MVIC torque scores between groups. The remaining difference could be attributed to the changes within the muscle, such as muscle mass or intrinsic strength. However, no difference was observed between groups following the fatigue task. One possible explanation relates to central and peripheral adaptions during the fatigue task. Following prolonged muscle activity, lower limb muscles have demonstrated that the extent to which central fatigue develops may be dependent on the task performed [26]. Studies suggest that low-torque, long-duration contractions are more likely to lead to the development of central fatigue than high-torque, short-duration contractions performed by the same muscle group [59]. In a study by Behm and St-Pierre [59], two intermittent fatigue tasks were used to examine central fatigue in the quadriceps muscle. The contraction intensity largely influences the duration of the fatiguing task [59]. The high-torque, short duration fatiguing task consisted of a 50% MVIC intensity, while the low-torque, long duration fatiguing task consisted of a 25% MVIC intensity. A greater decline in voluntary activation was observed following the low-torque (25%), long duration MVIC compared to the high-torque (50%), short duration MVIC. Therefore, the similar

times to fatigue in the current study may be dependent on the similar 50% contraction intensity of the fatiguing task performed. Further, sample size and variability are two important factors that influence the power of a study, such that the greater the sample size and the lower the variance, the greater the power. In the present study, a relatively small sample size in addition with high variability was observed during the fatiguing task, potentially contributing to a greater type II error.

Significant differences between symptomatic fatigue and measures of fatigability have been demonstrated in previous research [29,27,61]. In the present study however, no association was observed between symptomatic fatigue and fatigability, as measured by time to task failure. Thus, higher MFIS and FSS scores were not correlated to higher muscle fatigability at a submaximal intensity. A study by Romani et al [62] examined the relationship between symptomatic fatigue and measures of fatigability in individuals with MS. A multidimensional assessment tool was used to categorize individuals who experienced high (75th percentile) fatigue versus low (25th percentile) fatigue. Fatigability was measured through sustained MVICs of the thumb adductors. Results indicated no difference in fatigability between individuals who reported experiencing high fatigue versus low fatigue. Similar findings were presented in individuals with Chronic Fatigue Syndrome (CFS) [63]. Individuals with CFS reported high levels of effort associated with physical activity with no apparent difference in fatigability compared with healthy controls [63]. It has been suggested that fatigue in individuals with CFS is central in origin resulting from disrupted signaling between normal firing frequency upon motor units [64]. Thus, the underlying pathophysiology of fatigue could provide a framework for fatigue perceived by individuals with MS.

A study by McKenzie and Gandevia [65] provides evidence of a relationship between absolute muscle torque and fatigability, suggesting that the greater the absolute torque the more quickly the muscle fatigues [65]. In the present study, a lower absolute torque was observed in the MS group compared with healthy controls and thus, potentially contributing to greater fatigue resistance experienced. The underlying pathophysiology of fatigue in MS may be curtailed by a significantly lower absolute torque. Furthermore, studies have reported a greater decline in distance walked during the 6-minute walk test in individuals with MS compared to healthy controls [66]. The decline in distance walked correlated with greater symptomatic physical fatigue and poorer physical function [66]. In the present study, distance walked during a 6-minute walk test was shorter in the MS group compared with healthy controls. A strong association was demonstrated in the 6-minute walk time and MVIC torque, indicating that stronger MVIC torques were accompanied by greater distances walked. The 6-minute walk test distance also distinguished a relationship between various disability scores on the EDSS and distance walked. A higher disability score was associated with a reduced distance walked during the 6-minutes compared to lower disability scores in the MS group. These findings were not surprising as higher EDSS (4.0-6.5) scores are primarily based upon walking ability. However, this observation was not significant. Due to the large difference in distance covered on the 6-MWT between the MS group and healthy controls, it would be interesting to quantify VA after a fatiguing task similar to the 6-MWT. In the present study, fatigability, as measured by time to task failure, did not produce a significant difference between the MS group and healthy controls but distanced covered on the 6-MWT did.

In summary, individuals with MS reported higher levels of symptomatic fatigue on the MFIS, FSS and VAFS, while demonstrating reduced muscle strength, voluntary activation and

distanced covered on the 6-MWT compared with healthy controls. Symptomatic fatigue assessed by the MFIS was associated with fatigability, as measured by MVIC torque but not time to task failure.

2.4 LIMITATIONS

It is important to consider the limitations of the present study before applying the findings to a broader population of individuals with MS. One limitation of the study was that the sample size of each group was relatively small, decreasing the overall power of the study. Although previous literature has been able to identify a significant difference between symptomatic fatigue and fatigability, a sample size of eighteen participants used in the present study in addition with high variability may have contributed to the non-significant results observed in the FSS and TTF scores.

Another limitation in the present study was that MS participants were not severely affected by the disease. The study targeted individuals with relapsing-remitting or secondary-progressive MS, at a moderate level of disability (EDSS= 4 ± 2). Therefore, it is unknown whether similar results may be obtained in a more progressive stage of MS or disabled population.

Other variables may distort the relationship between symptomatic fatigue and fatigability. For example, mental illness, such as depression, is positively associated with fatigue. Through structured interview, 38% of participants (17% controls, 21% MS) in the present study reported a history of mental illness, possibly contributing to the non-significant result. A more definitive study could examine symptomatic variability and consider excluding confounding variables including mental illness.

Lastly, fatigue is a broad and multidimensional construct. Despite the good psychometric properties of the MFIS and FSS, self-reported questionnaires have their acknowledged limitations, such as retrospective bias. Therefore, the ability to directly link symptomatic fatigue to muscle fatigability in the present study is somewhat limited. A multidisciplinary approach was used in the present study to limit this problem, however in a clinical population it is challenging to avoid all potentially confounding variables.

2.5 CONCLUSIONS AND FUTURE DIRECTIONS

In summary, the data presented here demonstrate that individuals with MS have significant reductions in distance walked during 6-minutes, peak torque, and voluntary activation of the DF muscles compared with healthy controls. Symptomatic fatigue, established from the MFIS, was associated with fatigability, as measured by MVIC but not time to task failure. Overall our findings provided an introductory contribution to research in quantifying muscle strength and fatigue in individuals with MS. Further, MRIs directly measuring muscle mass may contribute to greater understanding of mechanisms for muscle weakness and fatigue. Future research in quantifying muscle strength and fatigue should emphasize more functionally relevant fatiguing tasks, such as the 6-minute walk test or sit to stand tasks. This would allow studies to determine how muscle strength and fatigue may impact activities of daily living in individuals with MS. In addition, repeating the present study that establishes a sub-group analysis based on disease severity, may also yield unique findings.

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Kurtzke Expanded Disability Status Scale (EDSS)

❑ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).

❑ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).

❑ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).

❑ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).

❑ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).

❑ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.

❑ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).

❑ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.

❑ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.

❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).

❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).

❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

❏ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

❏ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

❏ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

❏ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

❏ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

❏ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

❏ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).

❏ 10.0 - Death due to MS.

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*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

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Modified Fatigue Impact Scale (MFIS)

Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. But people who have medical conditions like MS experience stronger feelings of fatigue more often and with greater impact than others.

Following is a list of statements that describe the effects of fatigue. Please read each statement carefully, the circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select choose the one answer that comes closest to describing you. Ask the interviewer to explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost Always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8.	I have been less motivated to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have trouble maintaining physical effort for long periods.	0	1	2	3	4
11.	I have had difficulty making decisions.	0	1	2	3	4
12.	I have been less motivated to do anything that requires thinking	0	1	2	3	4
13.	My muscles have felt weak	0	1	2	3	4
14.	I have been physically uncomfortable.	0	1	2	3	4
15.	I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16.	I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17.	I have been less able to complete tasks that require physical effort.	0	1	2	3	4

	Never	Rarely	Sometimes	Often	Almost Always
18. My thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Instructions for Scoring the MFIS

Items on the MFIS can be aggregated into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on a person's activities.

Physical Subscale

This scale can range from 0 to 36. It is computed by adding raw scores on the following items: 4+6+7+10+13+14+17+20+21.   0

Cognitive Subscale

This scale can range from 0 to 40. It is computed by adding raw scores on the following items: 1+2+3+5+11+12+15+16+18+19.   0

Psychosocial Subscale

This scale can range from 0 to 8. It is computed by adding raw scores on the following items: 8+9.   0

Total MFIS Score

The total MFIS score can range from 0 to 84. It is computed by adding scores on the physical, cognitive, and psychosocial subscales.   0

Fatigue Severity Scale (FSS)

Your Name_____

Date:_____Date of birth: _____

This questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

***A low value (e.g. 1) indicates strong disagreement with the statement, whereas a high value (e.g. 7) indicates strong agreement.

During the past week, I have found that:	Disagree ⟷ Agree
1. My motivation is lower when I am fatigued	1 2 3 4 5 6 7
2. Exercise brings on my fatigue.	1 2 3 4 5 6 7
3. I am easily fatigued.	1 2 3 4 5 6 7
4. Fatigue interferes with my physical functioning.	1 2 3 4 5 6 7
5. Fatigue causes frequent problems for me.	1 2 3 4 5 6 7
6. My fatigue prevents sustained physical functioning.	1 2 3 4 5 6 7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1 2 3 4 5 6 7
8. Fatigue is among my three most disabling symptoms.	1 2 3 4 5 6 7
9. Fatigue interferes with my work, family or social life.	1 2 3 4 5 6 7

Total Score: _____

APPENDIX D

VISUAL ANALOGUE FATIGUE SCALE (VAFS)

Please mark an "X" on the number line which describes your global fatigue with 0 being worst and 10 being normal.

0	1	2	3	4	5	6	7	8	9	10

American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS MARCH 2002

CONTENTS

PURPOSE AND SCOPE

This statement provides practical guidelines for the 6-minute walk test (6MWT). Specifically, it reviews indications, details factors that influence results, presents a brief step-by-step protocol, outlines safety measures, describes proper patient preparation and procedures, and offers guidelines for clinical interpretation of results. These recommendations are not intended to limit the use of alternative protocols for research studies. We do not discuss the general topic of clinical exercise testing.

As with other American Thoracic Society statements on pulmonary function testing, these guidelines come out of a consensus conference. Drafts were prepared by two members (P.L.E. and R.J.Z.) and were based on a comprehensive Medline literature search from 1970 through 2001, augmented by suggestions from other committee members. Each draft responded to comments from the working committee. The guidelines follow previously published methods as closely as possible and provide a rationale for each specific recommendation. The final recommendations represent a consensus of the committee. The committee recommends that these guidelines be reviewed in five years and in the meantime encourages further research in areas of controversy.

BACKGROUND

There are several modalities available for the objective evaluation of functional exercise capacity. Some provide a very complete assessment of all systems involved in exercise performance (high tech), whereas others provide basic information but are low tech and are simpler to perform. The modality used should be chosen based on the clinical question to be addressed and on available resources. The most popular clinical exercise tests in order of increasing complexity are stair climbing, a 6MWT, a shuttle-walk test, detection of exercise-induced asthma, a cardiac stress test (e.g., Bruce protocol), and a cardio-

pulmonary exercise test (1, 2). Other professional organizations have published standards for cardiac stress testing (3, 4).

Assessment of functional capacity has traditionally been done by merely asking patients the following: "How many flights of stairs can you climb or how many blocks can you walk?" However, patients vary in their recollection and may report overestimations or underestimations of their true functional capacity. Objective measurements are usually better than self-reports. In the early 1960s, Balke developed a simple test to evaluate the functional capacity by measuring the distance walked during a defined period of time (5). A 12-minute field performance test was then developed to evaluate the level of physical fitness of healthy individuals (6). The walking test was also adapted to assess disability in patients with chronic bronchitis (7). In an attempt to accommodate patients with respiratory disease for whom walking 12 minutes was too exhausting, a 6-minute walk was found to perform as well as the 12-minute walk (8). A recent review of functional walking tests concluded that "the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests" (9).

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

INDICATIONS AND LIMITATIONS

The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality (*see* Table 1 for a list of these indications). The fact that investigators have used the 6MWT in these settings does not prove that the test is clinically useful (or the best test) for determining functional capacity or changes in functional capacity due to an intervention in patients with these diseases. Further studies are necessary to determine the utility of the 6MWT in various clinical situations.

Formal cardiopulmonary exercise testing provides a global assessment of the exercise response, an objective determination of functional capacity and impairment, determination of the appropriate intensity needed to perform prolonged exercise, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise. The 6MWT does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (1, 2). The information provided by a 6MWT should be considered complementary to cardiopulmonary exercise testing, not a replacement for it. Despite the difference between these two functional tests, some good correlations between them have been reported. For example, a significant correlation (r = 0.73) between 6MWD and peak oxygen uptake has been reported for patients with end-stage lung diseases (36, 37).

In some clinical situations, the 6MWT provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates better with formal measures of quality of life (38). Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea (39, 40). The reproducibility of the 6MWD (with a coefficient of variation of approximately 8%) appears to be better than the reproducibility of 1-second forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) (8, 41–43). Questionnaire indices of functional status have a larger short-term variability (22–33%) than does the 6MWD (37).

The shuttle-walking test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a 10-m course (44–47). The walking speed is increased every minute, and the test ends when the patient cannot reach the turnaround point within the required time. The exercise performed is similar to a symptom-limited, maximal, incremental treadmill test. An advantage of the shuttle walking test is that it has a better correlation with peak oxygen uptake than the 6MWD. Disadvantages include less validation, less widespread use, and more potential for cardiovascular problems.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocar-

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

Pretreatment and posttreatment comparisons
  Lung transplantation (9, 10)
  Lung resection (11)
  Lung volume reduction surgery (12, 13)
  Pulmonary rehabilitation (14, 15)
  COPD (16–18)
  Pulmonary hypertension
  Heart failure (19, 20)
Functional status (single measurement)
  COPD (21, 22)
  Cystic fibrosis (23, 24)
  Heart failure (25–27)
  Peripheral vascular disease (28, 29)
  Fibromyalgia (30)
  Older patients (31)
Predictor of morbidity and mortality
  Heart failure (32, 33)
  COPD (34, 35)
  Primary pulmonary hypertension (10, 36)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

dial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Rationale

Patients with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each patient determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons (31, 48–50) and thousands of patients with heart failure or cardiomyopathy (32, 51, 52) without serious adverse events. The contraindications listed previously here were used by study investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such patients performed a 6MWT; they are, therefore, listed as relative contraindications.

SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (1) chest pain, (2) intolerable dyspnea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

TECHNICAL ASPECTS OF THE 6MWT

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Rationale. A shorter corridor requires patients to take more time to reverse directions more often, reducing the 6MWD. Most studies have used a 30-m corridor, but some have used 20- or 50-m corridors (52–55). A recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft, but patients walked farther on continuous (oval) tracks (mean 92 ft farther) (54).

The use of a treadmill to determine the 6MWD might save space and allow constant monitoring during the exercise, but the use of a treadmill for 6-minute walk testing is not recommended. Patients are unable to pace themselves on a treadmill. In one study of patients with severe lung disease, the mean distance walked on the treadmill during 6 minutes (with the speed adjusted by the patients) was shorter by a mean of 14% when compared with the standard 6MWD using a 100-ft hallway (57). The range of differences was wide, with patients walking between 400–1,300 ft on the treadmill who walked 1,200 ft in the hallway. Treadmill test results, therefore, are not interchangeable with corridor tests.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the first portion of the worksheet (*see* the APPENDIX).

4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

   The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO_2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO_2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk. (57)

5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (*see* Table 2 for the Borg scale and instructions [58]).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

   Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now, or whenever you are ready."

TABLE 2. THE BORG SCALE

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

> After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."
>
> When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."
>
> When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."
>
> When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."
>
> When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."
>
> Do not use other words of encouragement (or body language to speed up).
>
> If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.
>
> When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."
>
> When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"

11. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.

12. Record the number of laps from the counter (or tick marks on the worksheet).

13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

14. Congratulate the patient on good effort and offer a drink of water.

QUALITY ASSURANCE

Sources of Variability

There are many sources of 6MWD variability (see Table 3). The sources of variability caused by the test procedure itself should be controlled as much as possible. This is done by following the standards found in this document and by using a quality-assurance program.

Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

Rationale. The 6MWD is only slightly higher for a second 6MWT performed a day later. The mean reported increase ranges from 0 to 17% (23, 27, 40, 41, 54, 59). A multicenter study of 470 highly motivated patients with severe COPD performed two 6MWTs 1 day apart, and on average, the 6MWD was only 66 ft (5.8%) higher on the second day (54).

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

Technician Training and Experience

Technicians who perform 6MWTs should be trained using the standard protocol and then supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

Rationale. One multicenter study of older people found that after correction for many other factors, two of the technicians had mean 6MWDs that were approximately 7% lower than the other two sites (31).

Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.

Rationale. Encouragement significantly increases the distance walked (42). Reproducibility for tests with and without encouragement is similar. Some studies have used encouragement every 30 seconds, every minute, or every 2 minutes. We have chosen every minute and standard phrases. Some studies (53) have instructed patients to walk as fast as possible. Although larger mean 6MWDs may be obtained thereby, we recommend that such phrases not be used, as they emphasize initial speed at the expense of earlier fatigue and possible excessive cardiac stress in some patients with heart disease.

TABLE 3. 6MWD SOURCES OF VARIABILITY

Factors reducing the 6MWD
  Shorter height
  Older age
  Higher body weight
  Female sex
  Impaired cognition
  A shorter corridor (more turns)
  Pulmonary disease (COPD, asthma, cystic fibrosis, interstitial lung disease)
  Cardiovascular disease (angina, MI, CHF, stroke, TIA, PVD, AAI)
  Musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.)
Factors increasing the 6MWD
  Taller height (longer legs)
  Male sex
  High motivation
  A patient who has previously performed the test
  Medication for a disabling disease taken just before the test
  Oxygen supplementation in patients with exercise-induced hypoxemia

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walking distance.

Supplemental Oxygen

If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in 6MWD. The type of oxygen delivery device should also be noted on the report: for instance, the patient carried liquid oxygen or pushed or pulled an oxygen tank, the delivery was pulsed or continuous, or a technician walked behind the patient with the oxygen source (not recommended). Measurements of pulse and SpO_2 should be made after waiting at least 10 minutes after any change in oxygen delivery.

Rationale. For patients with COPD or interstitial lung disease, oxygen supplementation increases the 6MWD (17, 59, 61, 63). Carrying a portable gas container (but not using it for supplemental oxygen) reduced the mean 6MWD by 14% in one study of patients with severe respiratory disability, but using the container to deliver supplemental oxygen during the exercise increased the mean 6MWD by 20–35% (59).

Medications

The type of medication, dose, and number of hours taken before the test should be noted.

Rationale. Significant improvement in the distance walked, or the dyspnea scale, after administration of bronchodilators has been demonstrated in patients with COPD (62, 63), as well as cardiovascular medications in patients with heart failure (19).

INTERPRETATION

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent (37). It is not known whether it is best for clinical purposes to express change in 6MWD as (*1*) an absolute value, (*2*) a percentage change, or (*3*) a change in the percentage of predicted value. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. In one study of 112 patients (half of them women) with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% confidence interval, 37–71 m) (64). This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant. In an observational study of 45 older patients with heart failure, the smallest difference in 6MWD that was associated with a noticeable difference in their global rating of worsening was a mean of 43 m (20). The 6MWD was more responsive to deterioration than to improvement in heart failure symptoms.

Reported Mean Changes in 6MWD After Interventions

Supplemental oxygen (4 L/min) during exercise in patients with COPD or interstitial lung disease increased mean 6MWD by approximately 95 m (36%) in one study (59). Patients taking an inhaled corticosteroid experienced a mean 33 m (8%) increase in 6MWD in an international COPD study (16). Patients with COPD in a study of the effects of exercise and diaphragmatic strength training experienced a mean increase in 6MWD of 50 m (20%) (65). Lung volume reduction surgery in patients with very severe COPD has been reported to increase 6MWD by a mean of 55 m (20%) (13).

Cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) in a recent study (66). In 25 older patients with heart failure, an angiotensin-converting enzyme inhibitor medication (50 mg captopril per day) improved 6MWD a mean of 64 m (39%) compared with a mean increase of only 8% in those receiving a placebo (19).

Interpreting Single Measurements of Functional Status

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. In one study, the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women (50). A mean 6MWD of 630 m was reported by another study of 51 healthy older adults (55). Differences in the population sampled, type and frequency of encouragement, corridor length, and number of practice tests may account for reported differences in mean 6MWD in healthy persons. Age, height, weight, and sex independently affect the 6MWD in healthy adults; therefore, these factors should be taken into consideration when interpreting the results of single measurements made to determine functional status. We encourage investigators to publish reference equations for healthy persons using the previously mentioned standardized procedures.

A low 6MWD is nonspecific and nondiagnostic. When the 6MWD is reduced, a thorough search for the cause of the impairment is warranted. The following tests may then be helpful: pulmonary function, cardiac function, ankle–arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

Conclusions

The 6MWT is a useful measure of functional capacity targeted at people with at least moderately severe impairment. The test has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease. These guidelines provide a standardized approach to performing the 6MWT. The committee hopes that these guidelines will encourage further research into the 6MWT and allow direct comparisons among different studies.

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