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Fatigue and Mobility Post-Stroke

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ABSTRACT

Fatigue post-stroke is a disabling and persistent symptom affecting many stroke survivors. Despite its high prevalence, the pathophysiology underlying this phenomenon remains obscure. Thus, the aim of this thesis was to study the neuromuscular basis underlying fatigue post-stroke and its association with self-reported fatigue and with the performance of tasks incorporating balance and mobility components.

Community-dwelling stroke survivors who had mild to moderate deficits in functional balance and mobility participated in a series of investigations. Chapter 2 describes the initial validation of the Community Balance and Mobility (CB&M) scale for use in persons with chronic stroke. Chapter 3 reported the presence of self-reported fatigue, assessed with the Fatigue Assessment Scale and restricted functional balance and mobility, measured with the 6-minute walk test and with the CB&M. Based on the findings obtained from the twitch interpolation and transcranial magnetic stimulation techniques, stroke resulted in a shift of the origin of neuromuscular fatigue such that the participants with stroke were more susceptible to the development of central fatigue following a standardized fatigue task, whereas healthy subjects had more evidence of peripheral fatigue. Also, the results from Chapter 3 demonstrated that the susceptibility to central failure was positively associated with the increased self-reported fatigability and negatively with the 6-MWT and CB&M scores. In Chapter 4 changes in the intrinsic properties of the spinal motoneurons, manifested as prolongation of the afterhyperpolarization time-course estimated with the interval death rate transform method were demonstrated. Prolonged afterhyperpolarization may have contributed to the increased central fatigue observed on the paretic side of the participants with stroke.

In summary, the stroke-induced disturbances along the neuromuscular system together with the post-stroke deficits in functional balance and mobility may compromise the ability of the central nervous system to cope with the increased physiological demands during physical activities. This may lead to the increased perception of effort, which could influence the performance of activities of daily living and may partially underlie the general complaint of fatigue experienced by people with stroke. The findings reported in this thesis have advanced the understanding of a pathophysiological basis of fatigue post-stroke, which is essential for developing and guiding effective rehabilitation treatments.

KEYWORDS: stroke; neuromuscular fatigue; transcranial magnetic stimulation; interpolated twitch technique; voluntary activation; motor unit; mobility; balance

CO-AUTHORSHIP

This thesis contains materials from two published manuscripts (Chapter 2 and 3) and one manuscript in preparation to be submitted for peer review (Chapter 4). All of the experimental data presented in this dissertation were collected and interpreted by the author, Svetlana Knorr, under the mentorship of Dr. S. Jayne Garland and Dr. Tanya D. Ivanova. Svetlana Knorr was the first author and Dr. S. Jayne Garland was a co-author on all manuscripts.

Dr. S. Jayne Garland and Dr. Tanya D. Ivanova assisted in study design, data analysis, and manuscript preparation. Dr. Tanya D. Ivanova is a co-author on Chapter 3 and 4. Dr. Brenda Brouwer and Dr. Timothy J. Doherty were co-authors on Chapter 2 and 3, respectively, and assisted in manuscript preparation. Mr. James A. Campbell was a co-author for Chapter 3 and assisted with data collection.

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LIST OF ABBREVIATIONS

AHP	afterhyperpolarization
AMT	active motor threshold
BBS	Berg balance scale
BMI	body mass index
CB&M	community balance and mobility scale
CES-D	center for epidemiological studies – depression scale
CMSA	Chedoke McMaster stroke assessment
CNS	central nervous system
CP	common peroneal nerve
EMG	electromyography
EMGmax	maximal electromyography
ET	endurance time
FAS	fatigue assessment scale
FIM	functional independence measure
GABA	γ-aminobutyric acid
IDR	interval death rate
iEMG	integrated electromyography
ISI	interspike interval
MEP	motor evoked potential
MVC	maximal voluntary contraction
MU	motor unit
PASS	postural assessment scale for stroke
PNS	peripheral nerve stimulation
PT	peak torque
RPE	rate of perceived exertion
RMS	root mean square
sEMG	surface electromyography
SP	silent period
6-MWT	six-minute walk test
SOL	soleus
SRM	standardized response mean
TA	tibialis anterior
TMS	transcranial magnetic stimulation
TUG	timed ‘up and go’ test
VA	voluntary activation

CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

1.1 GENERAL INTRODUCTION

1.1.1 Stroke

Stroke, also referred to as a cerebrovascular accident, is defined as a sudden interruption or blockage of blood flow to all or part of the brain leading to the deprivation of oxygen and nutrients to the brain, subsequently causing the damage or death of the cells in the affected area and loss of brain function (Heart and Stroke Foundation, 2010). According to Statistics Canada, stroke affects more than 50,000 Canadians annually and is classified as one of the leading causes of persistent physical disability in adults. It is estimated that as many as 300,000 Canadians are living with post-stroke functional impairments, defined as the loss of normal function of part of the body (Stroke Statistics, 2010). The majority of community-dwelling stroke survivors live with physical deficits, including muscle weakness, poor motor control and balance instability, that significantly compromise their functional mobility and independence in performing activities of daily living, reintegration into the community, and quality of life (Clarke et al., 2002; Flansbjer et al., 2006; Mayo et al., 2002; Patterson et al., 2007). These physical deficits may also result in the increased fatigability often reported by stroke survivors (Colle et al., 2006; Michael et al., 2006).

1.1.2 Stroke-Induced Changes in the Neuromuscular System

The neuromuscular system is a complex system mediating force production and movement that incorporates different levels, from the higher-order central nervous system (CNS) structures to the muscle fibers. Stroke results in a cascade-like effect

initiated at the cortical level, but subsequently affects the spinal and muscle levels and manifests as physical impairments in force production and functional deficits in balance and mobility.

1.1.2a Cortical Level

Following a stroke, the affected cortex undergoes structural and functional changes that may lead to alterations in cortical excitability and/or inhibitory neuronal activity as well as altered brain activation patterns in the bilateral cortical and subcortical areas (Liepert et al., 2005; Luft et al., 2005; Traversa et al., 2000). Increased brain activation in the intact premotor and sensorimotor cortices ipsilateral and contralateral to the paretic side was observed during functional tasks performed with the paretic limb in individuals with chronic hemiparesis (Luft et al., 2004; Luft et al., 2005; Nelles et al., 1999). It appears that enhanced brain activation may reflect a compensatory mechanism with the intention of overcoming stroke-induced disturbances and lost function of some cortical networks in order to perform a task. Abnormal patterns of brain activation may be substantially taxing on the system since extra effort is required by the brain to execute a motor task and this may result in the increased perception of effort often reported by patients affected by stroke during the performance of a functional task (Solomon and Robin, 2005; Thickbroom et al., 2006).

For the last two decades, transcranial magnetic stimulation (TMS) has been utilized widely as a non-invasive electrophysiological technique to investigate responsiveness of the motor cortex and functional integrity of the descending motor pathway following a stroke (Liepert, 2006; Pennisi et al., 2002; Thickbroom et al., 2002). Based on the TMS-evoked parameters, such as cortical motor threshold and motor evoked potential, the

excitability of the motor cortex is decreased in the affected hemisphere of chronic stroke survivors (Byrnes et al., 2001; Liepert, 2006; Pennisi et al., 2002; Thickbroom et al., 2002; Wheaton et al., 2009). The duration of the cortical silent period, which is represented as a period of electromyographic (EMG) silence during sustained muscle contraction, is used as a marker of intracortical inhibition (Inghilleri et al., 1993; Wilson et al., 1993). Prolongation of the cortical silent period was observed in stroke survivors (Classen et al., 1997; Liepert, 2006). Thus, the alterations in the TMS-evoked parameters might be indicative of the disruptions between the intra- and inter-hemispheric excitatory and inhibitory circuits, loss of excitable tissue in the motor cortex, demyelination and/or loss of corticospinal conducting axons, leading to the suboptimal motor cortex output and disturbances in the recruitment of spinal motoneurons (Classen et al., 1997; Homberg et al., 1991; Pennisi et al., 2002).

Studies that have investigated the impact of changes along the corticospinal pathways on functional performance reported that the increased cortical motor threshold and reduced motor evoked potential amplitude obtained after stimulation of the affected hemisphere were associated with stroke-induced muscle strength deficits (Liepert, 2006; Pennisi et al., 2002; Thickbroom et al., 2002). Furthermore, the observed increase in the duration of the cortical silent period was correlated with motor control impairments including inability to initiate or hold a voluntary contraction as well as with the level of functional recovery (Classen et al., 1997). Thus, individuals with stroke who demonstrated close to normal TMS-parameters had better functional recovery in comparison to those people with more prominent post-stroke induced functional deficits.

1.1.2b Spinal and Muscle Levels

Mounting research evidence suggests that stroke leads to impairments at the segmental level of the spinal cord (Arasaki et al., 2006; Brown and Snow, 1990; Gemperline et al., 1995; McComas et al., 1973). Nerve conduction and needle EMG studies reported that a substantial proportion of motoneurons innervating the paretic limbs cease to function (Arasaki et al., 2006; Hara et al., 2000; Hara et al., 2004; Lukacs et al., 2008; McComas et al., 1973). This has been explained by partial trans-synaptic degeneration of motoneurons as a result of interruptions of corticospinal projections leading to the disturbances in axonal transport and deprivation of normal trophic inputs (Arasaki et al., 2006; Brown and Snow, 1990; McComas et al., 1973). The degeneration of motoneurons could subsequently alter the function and structural composition of their respective muscle fibers.

Motor units, which consist of a motoneuron and all the muscle fibers it innervates, are classified into several basic groups on the basis of the properties of the constituent muscle fibers. Slow contracting motor units consists of Type I muscle fibers, which produce little force but are resistant to fatigue. Fast contracting motor units produce greater forces and are composed of muscle fibers that are either resistant (Type IIa) or susceptible (Type IIb) to fatigue (Burke et al., 1973; Garnett et al., 1979). The majority of findings from studies that investigated stroke-induced reorganization in the muscle fiber composition, reported selective atrophy and loss of Type II muscle fibers as well as Type I muscle fiber hypertrophy and motor unit size enlargement due to collateral reinnervation (Dattola et al., 1993; Hara et al., 2004; Lukacs et al., 2008; McComas et al., 1973; Scelsi et al., 1984; Slager et al., 1985). This reorganization might have been caused by either primary

(e.g. motor unit denervation via trans-synaptic degeneration of motoneurons) or secondary (e.g. muscle disuse) consequences of the upper motoneuron lesion. In addition, no difference in the overall fiber type composition between the paretic and non-paretic side has been reported (Hachisuka et al., 1997; Sunnerhagen et al., 1999). A commonly-reported observation was that the degree of muscle reorganization was positively correlated with the severity of paresis. For example, participants who were able to ambulate without any assistive devices or with only minor post-stroke impairments had similar to control and non-paretic muscle fiber type composition (Hachisuka et al., 1997; Sunnerhagen et al., 1999), whereas an increase in the percentage of Type I muscle fibers in the tibialis anterior muscle was reported in participants with increased paresis (Scelsi et al., 1984). In summary, factors such as severity of hemiparesis and changes in the patterns of muscle activation and usage (e.g. involvement of a compensatory movement strategy or learned muscle disuse) could influence the pattern of alteration in the muscle fiber composition, subsequently affecting the overall force-generating capacity of a muscle.

Recruitment and discharge patterns of motor units are the fundamental neuromuscular mechanisms involved in the production of a voluntary force. Thus, as force demands increase, there is an increase in the firing rate of already active motor units as well as recruitment of additional motor units (Adam and De Luca, 2005). Accumulated evidence of a reduction in initial, mean and maximal discharge rates of active motor units and a failure to increase firing rates during increases in voluntary forces in paretic muscles have been observed during the chronic stage following a stroke (Frontera et al., 1997; Gemperline et al., 1995; Rosenfalck and Andreassen, 1980). Disruption in the synaptic

inputs to the motoneurons has been proposed to be plausible mechanisms explaining the stroke-induced abnormalities in motor unit recruitment and discharge patterns (Frontera et al., 1997; Gemperline et al., 1995). In addition, alterations in the motoneuron intrinsic properties would also play a critical role in the observed reduction in the discharge characteristics of motoneurons. For instance, the afterhyperolarization (AHP) is an intrinsic property of the motoneuron and its duration influences the discharge rate of the motoneurons and therefore, modulates the mechanical output of the muscle (Kernell, 1965; Kernell et al., 1999; Sawczuk et al., 1995). Animal and human studies report consistent evidence that aging is associated with lengthening of the AHP duration (Beaumont and Gardiner, 2003; Christie and Kamen, 2010; Piotrkiewicz et al., 2007); however, there is only one study that reported stroke-induced prolongation of the AHP time-course in the paretic biceps brachii muscle of participants following a stroke (Liang, 2010). Both, the process of aging and stroke, are associated with the reduction in the motoneuron discharge rates as well as with motor unit remodeling towards slower muscle fiber phenotype (Christie and Kamen, 2010; Frontera et al., 1997; Lukacs et al., 2008; Rice and Cunningham, 2002). A correlation between the motoneuron and muscle fibers characteristics has been established (Gossen et al., 2003; MacDonell et al., 2008; Zengel et al., 1985), and thus, a shift in the muscle type from fast to slow has been proposed to be as a potential mechanism underlying the observed prolongation in the AHP duration (Christie and Kamen, 2010; Liang et al., 2010; Piotrkiewicz et al., 2007). Also, the adaptability of the AHP parameters in response to changes in muscle activity level has been demonstrated in both animal models and humans (Christie and Kamen, 2010; Gardiner et al., 2005). Thus, lengthening of the AHP time-course in the paretic biceps

brachii muscle reported by Liang et al (2010) should be confirmed in the muscles of the lower extremity since the pattern of muscle utilization differs between the upper and lower extrimities, such that lower limb muscles are involved primarily in locomotion and postural tasks whereas upper limb muscles are utilized mainly in grasping and tasks involving dexterity.

In the presence of altered brain activation, suboptimal motor cortex output, impaired motor unit discharge pattern and structural rearrangement of motor units, a greater effort would need to be expended by individuals with stroke to perform any activities of daily living, especially those requiring long-lasting muscle contractions. Ultimately stroke survivors may experience increased sense of effort and fatigability (Gandevia, 1982). Furthermore, the collective consequences of these stroke-induced changes along the entire neuromuscular pathway result in deficits in motor control, which can manifest on a functional level as poor balance and limited mobility (Novak and Brouwer, 2009).

1.1.3 Assessment of Balance and Mobility Post-Stroke

Deficits in functional balance and mobility are common sequelae of stroke and are primary determinants of independent living in the community (Tyson et al., 2006). The aforementioned stroke-induced impairments in motor control and muscle weakness have been identified as the main factors negatively affecting functional balance and mobility (Flansbjer et al., 2006; Lamontagne et al., 2002; Patterson et al., 2007). Evaluative measures such as Berg Balance Scale (BBS) and Timed Up and Go (TUG) test are commonly used as tools to assess functional balance and mobility following stroke in clinical and community settings. The BBS consists of 14 tasks that are scored from 0 (unable to perform) to 4 (able to perform independently) and the difficulty of these tasks

increases from measuring static balance (e.g. standing or sitting unsupported) progressing to dynamic balance (e.g. step-touch or standing on one leg) (Berg et al., 1992). The TUG test measures the dynamic balance and functional mobility over a short-distance (Podsiadlo and Richardson, 1991). The time it takes for the participant sitting in a standard chair to stand up, walk forward 3 meters, and return to the seated position is measured, with a shorter time reflecting better dynamic balance and functional mobility. The utilization of these tools has been validated and proved to be sensitive to change in moderately- to severely-affected stroke survivors (Ng and Hui-Chan, 2005; Tyson and DeSouza, 2004). However, due to the reported ceiling effects, these tools have limited applicability for assessing functional balance and mobility in mildly-affected community-dwelling stroke survivors (Mao et al., 2002; Salbach et al., 2001). In order to monitor recovery over time and determine the effectiveness of rehabilitation interventions, it is critical to use an outcome measure that is appropriate to the person's level of abilities and sensitive enough to capture improvements in functional balance and mobility.

The Community Balance and Mobility (CB&M) scale was developed to assess balance and mobility in individuals with high ambulatory function but with persistent balance and mobility deficits following traumatic brain injury (Howe et al., 2006), but its utilization in population with stroke has not been validated yet. This scale consists of 13 tasks that challenge different aspects of balance and mobility (e.g. static versus dynamic balance, internal perturbations during performance of mobility tasks) and simulate the physical activities often encountered while living in the community (e.g. carrying groceries while walking and looking at the target). Thus, in comparison to the traditional measures of the balance and mobility (e.g. BBS and TUG), the score obtained on the

CB&M test is more reflective of functional deficits relevant to community ambulation. Also, the CB&M scores might be predictive of the performance on a long-distance mobility task, such as the six-minute walk test (6-MWT), which has been reported to deteriorate in chronic stroke survivors (van de Port et al., 2006).

The deficits post-stroke in functional balance and motor control of the lower limbs are known to contribute to the high-energy cost of mobility, in some cases estimated to be at least twice as that of age-matched controls (Gersten and Orr, 1971; Macko et al., 2001; Milot et al., 2006). This increased level of effort and energy expenditure during mobility tasks might contribute to the increased self-reported fatigability post-stroke, which was reported as one of the factors associated with poor mobility (Ingles et al., 1999; Michael et al., 2006; van de Port et al., 2006).

1.1.4 Fatigue Post-Stroke

Fatigue is described by patients with neurologic disorders including stroke survivors as an overwhelming sense of tiredness, feeling of exhaustion, and lack of physical and mental energy that interferes with activities of daily living (De Groot et al., 2003; Krupp and Pollina, 1996). Fatigue post-stroke has been studied primarily using self-report fatigue assessment scales, such as the Fatigue Assessment Scale. Based on the evidence, the self-reported experience of fatigue is a prominent disabling symptom affecting up to 72% of stroke survivors and is associated with profound deterioration of many aspects of everyday life and often interferes with the rehabilitation process (Glader et al., 2002; Michael et al., 2006; Morley et al., 2005). The etiology of fatigue in people with stroke remains obscure. It has been hypothesized that fatigue post-stroke results from a combination of psychosocial stress related to the adjustment to a new life situation as

well as neurologic alterations leading to the dysfunction in central and peripheral motor pathways (Sisson, 1998). Factors such as post-stroke depression, sleep disturbances, severity of neurologic impairments, age, co-morbidities, and lack of family support have been associated with the increased self-reported fatigability (Choi-Kwon et al., 2005; Glader et al., 2002; Ingles et al., 1999; Michael et al., 2006; Staub and Bogousslavsky, 2001; Tseng and Kluding, 2009). Although extensive research has been conducted to identify factors contributing to fatigue post-stroke, the neuromuscular basis of this phenomenon has received limited attention.

Neuromuscular fatigue is defined as any contraction-induced reduction in maximal force generating capacity (Bigland-Ritchie and Woods, 1984). It is a complex phenomenon with multiple processes and mechanisms involved at different levels, from the CNS structures to electrical and biochemical alterations within the muscle fibers (Enoka and Duchateau, 2008; Enoka and Stuart, 1992). Therefore, gradual reduction in force production may occur at any one or combinations of the various sites along the motor pathway from the CNS to the intramuscular contractile apparatus. Customarily, these sites are divided into either central or peripheral fatigue.

Central fatigue refers to a progressive contraction-induced reduction in the ability to activate a skeletal muscle voluntarily (Gandevia, 2001). The failure of voluntary muscle activation is explained by fatigue-induced alterations at supraspinal and/or spinal levels. For example, fatigue-induced suboptimal output from motor cortex, either due to inadequate input from the sites upstream of the motor cortex or decrease in motor cortex excitability, might result in suboptimal facilitation of alpha motoneurons and therefore suboptimal activation of muscle fibers (Gandevia et al., 1996; Sacco et al., 2000).

Furthermore, fatigue-related reduction in spinal excitability, resulting from increased inhibitory muscle afferent input or modifications in the intrinsic properties of motoneurons, could also contribute to the decline in voluntary neural drive to the active muscle (Gandevia, 1998; Garland, 1991; Sawczuk et al., 1995).

Peripheral fatigue refers to a loss of force due to a failure in the neuromuscular signal transmission and/or failure in the contractile apparatus of the muscle fibers (Kirkendall, 1990). Signal transmission failure occurs when impulses are not received by the muscle and this impairment can happen along the motor axons, at the level of neuromuscular junction, or along the surface of the muscle fibers (Bigland-Ritchie and Woods, 1984). Contractile failure occurs within the muscle fibers and is marked by fatigue-induced depression of the contractile properties tested independent of voluntary activation by using electrically evoked contractions (Kirkendall, 1990).

Different types of fatigue protocols have been used to induce neuromuscular fatigue in a variety of muscle groups in individuals with stroke (Hu et al., 2006; Riley and Bilodeau, 2002; Svantesson et al., 1999; Tang and Rymer, 1981; Toffola et al., 2001; Young and Mayer, 1982). Prior to the fatigue task, the maximal force-generating capacity and the ability of the CNS to activate muscles maximally were reported to be impaired more on the paretic side than on the non-paretic side, or when compared with healthy controls (Riley and Bilodeau, 2002; Svantesson et al., 1999). Furthermore, Riley and Bilodeau (2002) reported a progressive failure of voluntary activation on the paretic side in comparison to the non-paretic side during a sustained maximal fatiguing isometric contraction (n=2). This is an interesting finding, which should be investigated in a larger group, because it suggests that central fatigue develops to a greater extent in the paretic

than non-paretic limb.

During submaximal fatiguing tasks, the neural drive to the motor units of the paretic limb, reflected by the amplitude of the EMG signal, has been reported to be greater than that of the non-paretic limb and healthy controls, indicating that the muscles on the paretic side had to be recruited to a greater extent to achieve and maintain the same relative level of contraction intensity (Hu et al., 2006; Tang and Rymer, 1981). However, studies that used EMG power frequency analysis demonstrated significantly less shift in power frequencies after fatigue in the paretic limb relative to the non-paretic limb and healthy controls (Hu et al., 2006; Svantesson et al., 1999; Toffola et al., 2001). A reduction in power frequencies reflects, at least in part, a reduction in the conduction velocity of the electrical signal along the muscle fiber membrane, i.e. peripheral fatigue. Another example of peripheral fatigue, neuromuscular transmission failure, was also reported to be less evident in the paretic group during a sustained submaximal (20% MVC) fatigue task relative to the non-paretic and control groups (Hu et al., 2006). There was only one study, which bypassed central activation by stimulating the peripheral nerve, that demonstrated more pronounced fatigue in the paretic muscle in comparison to the non-paretic side and healthy volunteers (Young and Mayer, 1982). Also, those authors reported the emergence of "slow-twitch fatigable" motor units in the first dorsal interosseous muscle on the paretic side; motor units that produced larger forces with slower contraction times and demonstrated an increase in fatigability. The results of that study imply that the Type I alpha motoneurons collaterally reinnervated Type II muscle fibers leading to motor unit transformation as has been suggested by others (Dattola et al., 1993; Hara et al., 2004; Lukacs, 2005).

Based on the relatively few studies in the literature, it appears that increased central fatigue, evident by the impaired voluntary muscle activation, and less peripheral fatigue, evident by the decreased EMG spectral shift, were reported on the paretic side in comparison to the non-paretic and healthy controls. A potential shift in the muscle fiber composition in the paretic muscles, such as increased proportion of Type I muscle fibers (Hara et al., 2004; Lukacs et al., 2008; McComas et al., 1973), might partially explain less evident peripheral fatigue observed in the paretic muscles. Alternatively, impaired voluntary muscle activation leading to an inability to produce maximal muscle force on the paretic side would lower the intensity level for the submaximal contraction, which, in turn, might not be sufficient enough to induce muscle fatigue. Therefore, the absolute force differences between the paretic versus the non-paretic and/or control sides might be another plausible reason why fatigue on the paretic side was less evident. Also, failure in voluntary muscle activation observed during the fatiguing task on the paretic side might act as a protective shield against the development of peripheral fatigue. However, at this point it is not clear which site(s) proximal to the neuromuscular junction is involved in the reduction in voluntary activation. For instance, stroke-induced alterations in inhibitory and/or excitatory circuitry at the cortical level would contribute to the deficits in central activation. Furthermore, prolongation of the estimated AHP time-course would restrict the firing of the active motor units leading to a greater reliance on motor unit recruitment to produce any given absolute force as has been reported by others (Gemperline et al., 1995; Hu et al., 2006; Tang and Rymer, 1981), which could also result in central activation impairments. Susceptibility to central fatigue might be a contributing factor to the increased perception of tiredness during performance of

activities of daily living often reported by the stroke survivors, but this has not been investigated.

1.2 THESIS OUTLINE

The majority of stroke survivors report increased fatigability during the performance of daily activities necessary for independent living in the community. Psychosocial factors, such as depression and lack of social support, have been associated with increased self-reported fatigability. However, it is known that following a stroke significant alterations occur along the entire neuromuscular system, resulting in muscle weakness and deficits in motor control on the paretic side of the body, which subsequently affect functional balance and mobility, known to be important determinants of independent living in the community. Thus, the overall objective of this thesis was to elaborate on the neuromuscular basis of fatigue post-stroke and its association with self-reported fatigue and with functional mobility. This investigation was performed over three sets of experiments, the results of which are presented as separate thesis chapters.

In brief, Chapter 2 is a methodological study that was designed to establish the convergent validity of the CB&M as a measure to assess functional balance and mobility in persons post-stroke. It was hypothesized that because of the demanding tasks included in the CB&M, this measure would not be impacted by the presence of a ceiling effect and thus, would be a more sensitive measure to detect deficits in functional balance and mobility in comparison to the BBS and TUG tests.

The study reported in Chapter 3 investigated the effect of stroke on the mechanisms underlying neuromuscular fatigue. The primary objective was to evaluate the origins of fatigue post-stroke, focusing on the fatigue-induced changes in central excitability and

cortical inhibition in participants with stroke, which were compared to the age- and sex-matched controls. It was hypothesized that, following the fatigue task, peripheral fatigue would be more evident in the control group, whereas central fatigue would be present to a greater extent in the participants after stroke. The secondary objective of this study was to explore the associations between self-reported fatigue, neuromuscular fatigue, and functional mobility. The CB&M was utilized as a descriptive measure characterizing the deficits in functional balance and mobility in the participants with stroke. Also, the contribution of these functional deficits to long-distance mobility, measured with the 6-MWT, was investigated with anticipation that there would be a positive association between the CB&M and 6-MWT. Furthermore, greater central fatigue was hypothesized to be associated with higher levels of self-reported fatigue and with decreased performance on the functional balance and mobility tests.

In the study reported in Chapter 3, it was not feasible to determine if stroke resulted in changes in the spinal motoneurons, which also might contribute to central activation failure observed on the paretic side of the participants with stroke. For instance, stroke-induced changes in the intrinsic properties of motoneurons could result in slower motor unit firing rates, which would necessitate increased recruitment of motor units to produce a given force and potentially lead to an increased sense of effort. Thus, the purpose of the study reported in Chapter 4 was to examine changes in the duration of the estimated AHP time-course following stroke that may help to explain, in part, the underlying mechanism(s) of central fatigue. It was hypothesized that the duration of the post-spike AHP**,** which influences the capacity of the motoneuron to discharge action potentials, would be increased after stroke.

1.3 REFERENCES

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CHAPTER 2

VALIDITY OF THE COMMUNITY BALANCE AND MOBILITY SCALE IN COMMUNITY-DWELLING PERSONS AFTER STROKE[1]

2.1 INTRODUCTION

Balance deficits are among the most persistent impairments and common concerns of stroke survivors, as balance is fundamental to optimal mobility and performance of many activities of daily living (Tyson et al., 2006). Factors such as the severity of neurologic deficits, poor motor control and lower limb muscle weakness negatively affect the performance of tasks involving functional balance and mobility (Flansbjer et al., 2006; Lamontagne et al., 2002; Patterson et al., 2007). These stroke-induced deficits result in the increased level of effort and energy expenditure during activities involving balance and mobility (Gersten and Orr, 1971; Macko et al., 2001; Milot et al., 2006), which might also contribute to the increased post-stroke self-reported fatigability (Ingles et al., 1999; Michael et al., 2006; van de Port et al., 2006).

Several evaluation tools, including the Berg Balance Scale (BBS) (Berg et al., 1992), Postural Assessment Scale for Stroke (PASS) (Benaim et al., 1999), the balance subscale of the Fugl-Meyer test (Fugl-Meyer et al., 1975), and the Timed Up and Go (TUG) (Podsiadlo and Richardson, 1991) have been developed and frequently used to assess balance and mobility in patients with stroke. The psychometric properties of these scales are found to be good; however, ceiling effects can limit their utility when assessing patients with moderate to mild degrees of neurologic impairments (Mao et al., 2002; Salbach et al., 2001; Wang et al., 2005).

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Knorr S, Brouwer B, Garland SJ. Validity of the Community Balance and Mobility Scale in community-dwelling persons after stroke. Arch Phys Med Rehabil 2010; 91 (6):890-896.

Wang and colleagues examined the evaluative properties of the PASS (Wang et al., 2005). This scale consists of 12 items assessing the ability to maintain or change from a lying, sitting or standing posture with each item scored from 0 to 3. Notable ceiling effects were found as early as 3 months following stroke, limiting the ability of the PASS to discriminate between individual patients. While participants in the study had a wide spectrum of trunk control abilities (asymptomatic to bedridden) at intake, at 3 months post-stroke more than 75% of the participants achieved the highest scores for items on the PASS. The authors concluded that the sensitivity to change and the discriminative abilities of the PASS are limited to the first 3 months after stroke.

Similar findings were reported by Mao and colleagues who compared the psychometric properties of the balance subscale of the Fugl-Meyer test, BBS and PASS amongst participants with stroke of different severity (Mao et al., 2002). According to this study, all three balance measures demonstrated excellent interrater reliability and high internal consistency; however, all measures lacked the sensitivity to detect participants' improvement after 3 months post-stroke due to ceiling effects.

Salbach and colleagues evaluated the responsiveness of the TUG in stroke survivors at 8 and 38 days post-stroke (Salbach et al., 2001). In this study, the authors chose the value of 8.5 seconds as a point representing the maximum performance score for this test based on the normative values reported for a sample of healthy, elderly people (Bohannon, 2006). A greater number of participants achieved the cut-off score at the second evaluation (32%) compared to the first (8%), which might have contributed to the low responsiveness of the TUG.

To monitor recovery over time and determine the effectiveness of rehabilitative services, it is critical to choose an outcome measure that is suited to the patient's level of abilities and sensitive enough to capture improvements in balance and mobility following strokes of varied severity. Several commonly used scales lack sensitivity to change in those with moderate to mild impairments. The frequently reported ceiling effects negatively affect the ability of any clinical measure to detect change over time. Therefore, the practice of stroke rehabilitation is in need of an outcome measure of adequate sensitivity to assess balance and mobility in moderate to high functioning patients following stroke, who are in the process of returning to community living.

The CB&M incorporates the demanding tasks, commonly performed in the community (e.g. walking and looking at a target), to assess a wide range of mobility and balance abilities in ambulatory patients (Howe et al., 2006). The CB&M was initially designed for use with ambulatory patients following traumatic brain injury who are functioning at a high level yet have persistent balance problems. The properties of this scale showed high reliability and moderate to high validity in this patient group (Howe et al., 2006). Before considering the CB&M for use in stroke, it is necessary to examine whether the items are appropriate and the resolution of scoring adequate especially for those with moderately severe stroke. Floor effects, participants scoring the minimum possible score, would limit the utility of the CB&M in evaluating functional balance and mobility following stroke. To date this has not been examined.

The main objectives of the present study were: i) to examine the convergent validity of the CB&M against the BBS and TUG; ii) to determine the relative sensitivity of the CB&M to detect change in balance and mobility over a 5-month period compared to the

BBS and TUG; and iii) to evaluate floor and ceiling effects of the CB&M in participants in sub-acute and chronic phase after stroke (3 and 8 months post-stroke, respectively). Because the CB&M incorporates activities such as running, hopping, and stair climbing, the level of lower limb motor recovery and strength may be relevant. Thus, the secondary objective was to identify associations between the CB&M performance and lower limb motor recovery and strength.

We expected that convergent validity of the CB&M would be evident through a strong positive association with the BBS and a strong negative correlation with the TUG. We hypothesized that the CB&M would reveal the greatest sensitivity to change and the higher scores would reflect higher function and greater lower limb torque production.

2.2 METHODS

Participants were included in the study if the following criteria were met: i) first unilateral hemispheric stroke that required inpatient rehabilitation, ii) English speaking, and iii) scheduled for discharge to live in the community (private house or apartment) with or without paid health services. Those unable to follow simple verbal instructions or with serious co-morbidities (e.g. cancer, mobility limiting arthritis) were excluded. Ethics approval was obtained from the local institutional review board. All participants signed an informed consent prior to their participation.

2.2.1 Participants

Age, weight, height, sex, side of hemiparesis, type of stroke, time post-stroke, and the Functional Independence Measure (FIM) were collected to describe the sample studied. Body mass index (BMI) was calculated using the following equation: BMI (kg/m^2) =

weight (kg) ÷ (height (m))^2.

The FIM scores were used to describe the overall functional independence status of the study participants (Keith et al., 1987). This measure consists of 18 items, 13 of which relate to motor function (e.g. grooming, transfer, locomotion) and 5 items that measure social-cognitive abilities (e.g. comprehension, memory, social interaction, problem solving). Each item is scored using a 7-point ordinal scale (1 = complete assistance to perform activities of daily living and 7 = complete independence in performing basic activities of daily living). The possible total score ranges from the lowest to the highest level of independence (18-126, respectively). The reliability and validity of the FIM have been studied extensively (Daving et al., 2001; Dodds et al., 1993).

2.2.2 Assessment of Lower Limb Motor Control Impairments

Chedoke McMaster Stroke Assessment. The CMSA Impairment Inventory is a valid and reliable measure of the presence and severity of stroke-induced physical impairments (Gowland et al., 1993). The subscales for the leg and foot were used to evaluate the stages of motor recovery in the lower limb. The ability to perform standard movements was scored from 1 to 7 (1 = unable to perform and 7 = normal movement). High intra- and inter-rater reliability and moderate to high validity have been reported for the CMSA measure (Gowland et al., 1993).

2.2.3 Assessment of Functional Balance and Mobility

Berg Balance Scale. The BBS evaluates functional balance based on the performance of 14 tasks of varying difficulty including sitting and standing activities (Berg et al., 1992). Performance on each task is rated from 0 to 4 (0 = unable to perform

and 4 = able to perform independently). The maximum BBS score is 56, with higher scores representing better balance. Validity and reliability of the BBS have been established in patients with stroke (Berg et al., 1995; Mao et al., 2002; Tyson and DeSouza, 2004).

Timed Up & Go. The TUG is a functional mobility test that requires participants to stand up from an armchair, walk 3 meters, turn around, walk back to the chair and return to a seated position (Podsiadlo and Richardson, 1991). The time taken to complete the task is measured with a stopwatch and recorded in seconds, with shorter time representing better functional mobility. The TUG has been widely used as a valid and reliable measure to monitor changes in mobility skills in patients with stroke (Ng and Hui-Chan, 2005; Podsiadlo and Richardson, 1991; Salbach et al., 2001).

Community Balance and Mobility Scale. The CB&M evaluates balance and mobility status on 19 tasks including advanced functional balance and mobility activities (e.g. hopping on one leg, running) (Howe et al., 2006). Items are scored on a scale of 0 to 5 (0 = unable to perform and 5 = able to perform independently). One item is scored from 0 to 6, with an extra point given for carrying a basket while descending stairs. The CB&M was modified for participants with severe hemiparesis in the upper extremity by allowing them to perform carrying tasks one-handed. The maximum score is 96 points, with higher scores indicative of better balance and mobility. The validity and reliability of this outcome measure have been established for participants with traumatic brain injury (Howe et al., 2006), but not in patients with stroke.

2.2.4 Lower Limb Strength Assessment

A Biodex dynamometer (Biodex Medical System3, USA) was used to measure

isokinetic concentric joint torques of the flexors and extensors of the ankle, knee and hip in both the paretic and non-paretic limbs. Hip torques were tested in a 25º semi-reclined position, whereas both knee and ankle torques were tested in a near vertical seated position (85^{o} with 0º being horizontal, fully reclined). The ankle was tested at 30º/s and the knee and hip were both tested at 60º/s. These chosen velocities are consistent with most protocols used for study participants with stroke (Novak and Brouwer, 2009). For each joint tested, participants performed 2 sets of 3 maximal repetitions. Peak torques were measured for each of the 6 muscle groups tested on the paretic and non-paretic limbs and the peak torques were averaged across the 3 repetitions for each set. Because the center of mass of the ankle joint is relatively close to the axis of rotation and the gravity effect is limited and consistent across adults, only the torques generated at the hip and knee joints were normalized to body weight and corrected for gravity. Briefly, following the initial calibration, each limb segment was positioned parallel to the floor at the point of the maximal gravity effect and the weight of the limb was measured with the dynamometer. This limb weight correction was either added or subtracted from the measured torque, depending upon the direction of the limb movement (Taylor et al., 1991).

2.2.5 Testing Procedures

Data were acquired at two time points: a baseline assessment was scheduled within one month following discharge from inpatient rehabilitation and a follow-up assessment six months following discharge. The CMSA, FIM, and the lower limb strength assessment were performed at baseline; all other outcome measures were collected on both occasions.

2.2.6 Data Analysis and Statistics

Convergent Validity. Convergent validity was used to establish the degree to which the CB&M was associated with the BBS and TUG, both of the latter measures assess the same theoretical concepts (i.e. balance and mobility). Thus, to determine the convergent validity of the CB&M, the strength of the relationships among the CB&M, BBS and TUG was examined using the Spearman rank-order correlations. Correlation coefficients of 0.0-0.49 were interpreted as nonexistent or poor, those of 0.5-0.79 as moderate, and those 0.8 or higher as excellent.

Sensitivity to Change. The relative sensitivity to change was addressed using two approaches. First, the standardized response mean (SRM) was computed as the ratio of the mean change in scores divided by the standard deviation of the change scores (Liang et al., 1990). Cohen's criteria was used to evaluate the calculated effect size: 0.2 to 0.49 is considered small, 0.5 to 0.8 is moderate, and 0.8 or higher is large (Cohen, 1988). Second, the Wilcoxon signed-rank test was used to evaluate the difference in scores between the baseline and follow-up assessments for each scale.

Floor and Ceiling effects. The floor and ceiling effects were calculated as the percentage of the sample scoring the minimum or maximum possible scores, respectively. The BBS and CB&M have clear minimum (i.e. 0) and maximum scores (i.e. 56 and 96, respectively); however, the TUG is measured in seconds where lower values on the continuum reflect greater function. A measure of 8.1 seconds or less was selected as the maximum performance score based on the average TUG value reported for healthy people between 60 and 69 years old (Bohannon, 2006). Ceiling and floor effects $\geq$ 20% were considered significant (McHorney et al., 1994).

Strength in the Lower Limbs. The baseline differences in the torque-generating capacity of the flexors and extensors of the ankle, knee and hip joints bilaterally were evaluated with the dependent *t*-test statistics.

Associations of the CB&M, BBS, TUG to the CMSA and Strength in the Lower Limbs.

A series of Spearman rank-order correlations was carried out to determine the associations between the total score of the CB&M, BBS and TUG and the scores achieved on the leg and foot subscales of the CMSA at baseline. Given the interdependence between the hip, knee and ankle strength while performing mobility and balance tasks, the average peak torques for each joint on either the paretic or non-paretic limb were summed to get a measure of total strength for each side. These values were used to compute Spearman rank-order correlations between the performance of the CB&M, BBS and TUG test and strength on the paretic and non-paretic limbs assessed at baseline. All statistical analyses were carried out using SPSS 13.0 for Windows. The level of significance was set at $P<0.05$ and data are presented as mean ± SD unless otherwise stated.

2.3 RESULTS

2.3.1 Participants

Table 2.1 displays the demographic and clinical characteristics of the participants. Forty-four participants with a wide range of stroke-induced neurological impairments, aged 29 to 81 years were assessed approximately 3.3 months after the onset of stroke (baseline) and reassessed at follow-up (8.2 months post-stroke).

TABLE 2.1 Demographic and clinical characteristics of participants

Variable	All Participants (N=44)
Age (yrs)	62.6 ± 12.6
Body Mass Index (kg/m^2)	28.1 ± 5.5
Sex	
Women	20
Men	24
Side of Hemiparesis	
Right	16
Left	28
Type of Stroke	
Ischemic	41
Hemorrhagic	3
Time Post-Stroke (days)	
Baseline Assessment	98.6 ± 52.6
Follow-Up Assessment	246.8 ± 57.2
Stage of Motor Recovery at Baseline	
CMSA Leg score	6.0 (2-7)
CMSA Foot score	5.0 (2-7)
Functional Independence Measure	
Motor score	82.0 (20-91)
Cognitive score	33.0 (23-35)
Total score	114 (47-126)

Note: Values are mean ± SD, number, or median (range). Abbreviation: CMSA, Chedoke McMaster Stroke Assessment.

2.3.2 Convergent Validity

The scores of 44 participants were used to determine the association between the CB&M and BBS; however, 2 participants were unable to perform the TUG test at baseline and thus, convergent validities between the TUG and other scores were based on data from 42 participants. Significant associations between the CB&M and TUG (ρ = -0.75) and the BBS and TUG (ρ = -0.70) were evident ($P<0.001$) with excellent validity between the CB&M and BBS (ρ = 0.83, $P<0.001$).

2.3.3 Sensitivity to Change

Sensitivity to change of the CB&M and BBS was computed based on the scores of 44 participants that were assessed at the baseline and follow-up assessments, whereas 42 scores were used for the TUG test. The scores of all three balance/mobility scales changed significantly between the baseline and follow-up assessments (Table 2.2). However the SRM indicated a large effect size only for the CB&M and a small effect size for both the BBS and TUG measures (Table 2.2).

2.3.4 Floor and Ceiling Effects

The distribution of scores on the CB&M covered the scale's range; however, none of the participants achieved the maximum score possible (Figure 2.1A). Conversely, the scores on the BBS were clustered at the top end of the scale, with several participants reaching the maximum score of 56 resulting in ceiling effects of 34.1% and 47.7%, at baseline and follow-up, respectively (Figure 2.1B, Table 2.3). The TUG scores also exhibited a ceiling effect with 22.7% of participants able to complete the test at 8.1 seconds or less at baseline, increasing to 36.4% at follow-up (Figure 2.1C, Table 2.3).

TABLE 2.2 Sensitivity to change of the three balance and mobility measures

Variable	Baseline	Follow-Up	P	SRM
CB&M (/96)	42.7 ± 22.6	51.3 ± 24.6	<0.001	0.83
BBS (/56)	48.9 ± 12.4	50.4 ± 11.0	<0.01	0.42
TUG (s)	16.7 ± 17.1	13.7 ± 16.0	<0.01	0.34

Note: Values are mean ± SD. P values refer to the analyses between the baseline and follow-up assessments. Abbreviations: CB&M, Community Balance and Mobility Scale; BBS, Berg Balance Scale; TUG, Timed Up and Go test; SRM, Standardized Response Mean.

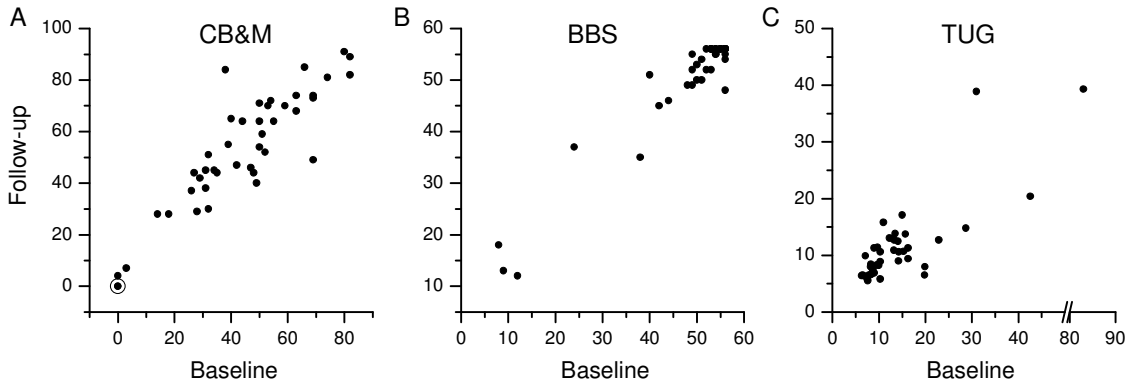

FIGURE 2.1 (**A**) Community Balance and Mobility Scale (CB&M), (**B**) Berg Balance Scale (BBS), and (**C**) Time Up and Go test (TUG) scores at baseline plotted against scores at follow-up assessment. Each point represents data from an individual participant. The circled point in the CB&M panel indicates multiple participants.

TABLE 2.3 Floor and ceiling effects of the CB&M, BBS, and TUG measures

Variable	Baseline (N = 44)		Follow-Up (N = 44)	
	Floor Effect	Ceiling Effect	Floor Effect	Ceiling Effect
CB&M	4 (9.1)	0 (0)	3 (6.8)	0 (0)
BBS	0 (0)	15 (34.1)*	0 (0)	21 (47.7)*
TUG	2 (4.5)	10 (22.7)*	0 (0)	16 (36.4)*

Note: Values are number (%) of participants that reached maximum or minimum possible scores. * denotes significant floor or ceiling effect (20% or greater) (McHorney et al., 1994). Abbreviations: CB&M, Community Balance and Mobility Scale; BBS, Berg Balance Scale; TUG, Timed Up and Go test; SRM, Standardized Mean Response.

None of the 3 measures demonstrated significant floor effects; however, 4 out of 44 participants scored zero on the CB&M at baseline and 3 participants at follow-up. On the TUG, 2 out of 44 participants were unable to perform the test at baseline, whereas all participants were able to complete the TUG at follow-up.

2.3.5 Associations of the CB&M, BBS, TUG to the CMSA and Lower Limb Strength

The CB&M, BBS and TUG measures were each moderately correlated with the CMSA leg/foot ($\rho = 0.50$ to 0.70, $P<0.01$). Significant strength deficits were observed in the flexors and extensors of the ankle, knee and hip joints of the paretic limb compared to the non-paretic limb (Figure 2.2A) and the strength of the paretic limb was associated with scores on the CB&M, BBS and TUG (Spearman's ρ ranged from 0.50 to 0.71, $P<0.001$). The strength of the non-paretic limb was significantly associated only with the CB&M and TUG scores (Spearman's $\rho = 0.46$ and -0.44, $P<0.01$, respectively); however the associations were considered poor. These findings are summarized in Table 2.4. The scores of the CB&M and the total of the average peak torque values on the paretic and non-paretic sides are depicted in Figure 2.2B.

2.4 DISCUSSION

In this study, the appropriateness and usefulness of the CB&M in evaluating functional balance and mobility in patients with a wide range of stroke-induced neurological impairments has been examined for the first time.

2.4.1 Convergent Validity

The convergent validity of the CB&M was excellent relative to the BBS and moderate against the TUG. The BBS and TUG results were negatively correlated as

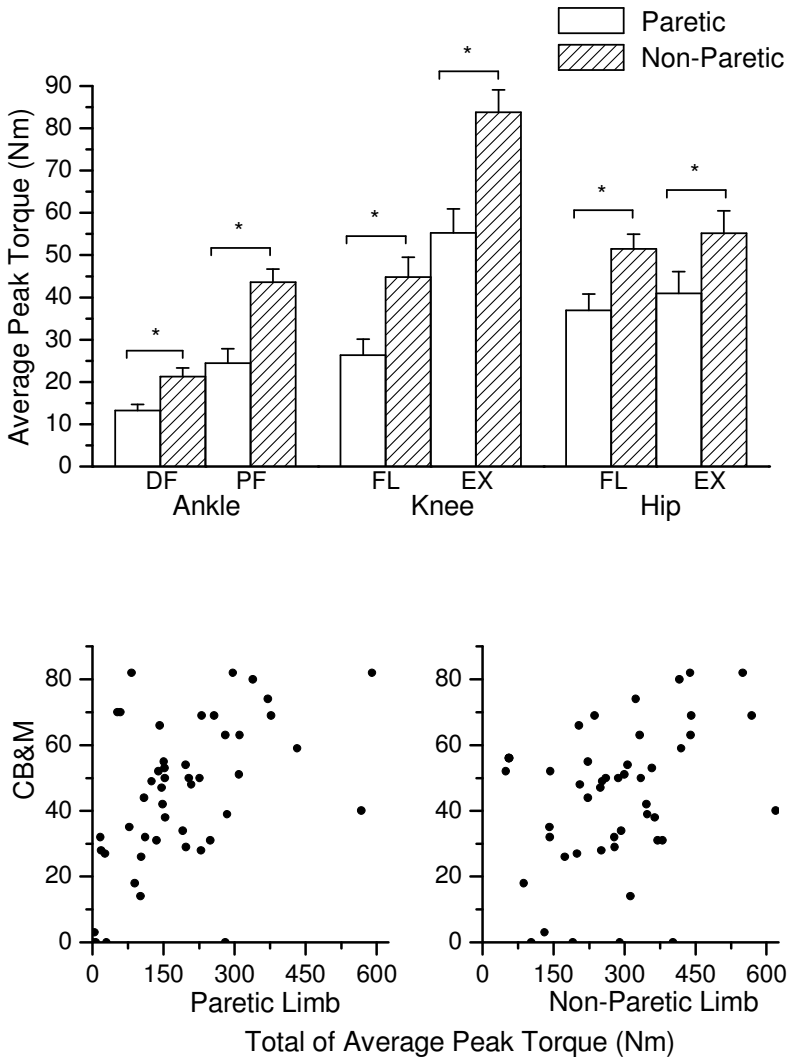

FIGURE 2.2 (**A**) Torque-generating capacity of dorsiflexor (DF), plantarflexor (PF), flexor (FL) and extensor (EX) muscles in the ankle, knee, and hip joint on the paretic and non-paretic side. Data are presented as mean ± SE. * denotes P<0.001. (**B**) CB&M scores at baseline plotted against the total of the average peak torque on the paretic limb (left panel) and the non-paretic limb (right panel). The total of the average peak torque was computed by summing the average peak torques for each joint on the paretic and non-paretic limbs.

TABLE 2.4 Correlations between the CB&M, BBS, TUG and CMSA and lower limb strength

Variables	CB&M (N = 44)	BBS (N = 44)	TUG (N = 42)
Stage of Motor Recovery			
CMSA Leg	0.63*	0.54*	-0.70*
CMSA Foot	0.61*	0.50*	-0.69*
Lower Limb Strength			
Paretic Limb	0.67*	0.50*	-0.71*
Non-Paretic Limb	0.46*	0.28	-0.44*

Note: Values are Spearman correlation coefficients. * denotes $P<0.05$. Abbreviations: CMSA, Chedoke McMaster Stroke Assessment; CB&M, Community Balance and Mobility Scale; BBS, Berg Balance Scale; TUG, Timed Up and Go test.

well, which was anticipated and in accordance with the findings of previous studies (Berg et al., 1992; Podsiadlo and Richardson, 1991). Overall, our findings provide evidence of strong convergent validity of the CB&M for measuring functional balance and mobility.

2.4.2 Floor and Ceiling Effects and Sensitivity to Change

The ability of a measure to detect change over time is of key importance in clinical practice to evaluate the effectiveness of a particular intervention or monitor the process of natural recovery following stroke. There is growing evidence suggesting that the evaluative ability of the presently available instruments designed to measure balance and mobility function (e.g. BBS, TUG) in patients with moderate to mild neurological impairments following stroke are hindered by ceiling effects (Mao et al., 2002; Salbach et al., 2001). The BBS measures static (e.g. standing or sitting unsupported) and dynamic (e.g. reaching forward or picking up objects) aspects of balance, whereas the TUG evaluates transfers and mobility. Despite the different focus of these two measures, they are moderately correlated ($\rho = -0.70$, $P<0.001$); likely because balance is a pre-requisite for the ability to walk unassisted. Thus, in combination, the BBS and TUG may be suitable for presenting an initial picture of patient's balance and mobility capacity, especially during the acute and shortly post-acute stages (up to 90 days from the stroke onset). Furthermore, during the acute and post-acute stroke period, the BBS and TUG demonstrated fair to good levels of sensitivity, especially in patients that were moderately to severely affected by stroke, but both measures were limited in detecting the patients' improvement after 90 days post-stroke (Mao et al., 2002; Salbach et al., 2001).

The results from this study support the findings of previous studies in terms of the limited sensitivity to change of both the BBS and TUG measures. Although statistical

significance was reached for all three measures, based on the computed SRM, the BBS and TUG scores demonstrated small effect sizes reflecting limited sensitivity to change compared to the CB&M. The ceiling effects associated with the BBS and TUG provide a plausible explanation for the contrasting results with the CB&M and furthermore make it impossible to correlate the changes over time between the scales.

Close examination of the results obtained from the CB&M demonstrated that those individuals approaching the maximal possible score on the BBS and the TUG times ≤8.1s, attained a wide range of scores (39-82) on the CB&M. The discrepancy among the results of the CB&M versus the BBS and TUG might be explained by the level of difficulty of items included in the CB&M measure. The items on the CB&M simulated the tasks that are frequently encountered while living in the community (e.g. running, carrying 3.4kg grocery bags in each hand whilst walking and looking at the target) that are more challenging than the items on the BBS and TUG and might be testing different aspects of balance and mobility capacity. The highest score that was achieved on the CB&M by the participants in our study was 82 out of a possible 96, suggesting that in comparison to the BBS and TUG, this scale provides enough challenge for moderate to high functioning individuals with stroke to evaluate the overall balance and mobility capacity required for successful and independent living in the community. Thus, the CB&M may be the more suitable measure for individuals with moderate to high function after stroke.

The CB&M also demonstrated a trend towards a floor effect. Although the floor effect did not reach statistical significance, it is noteworthy that individuals whose BBS scores were below 40 and/or had TUG times greater than 30s were unable to perform the

majority of the items on the CB&M. This observation suggests that the use of the CB&M may be more appropriate for ambulatory stroke survivors with moderate to mild post-stroke deficits, whereas the balance and mobility of individuals severely affected by stroke are more appropriately evaluated with the BBS and TUG measures. Further studies are required to determine the specific cut-off points on the BBS and TUG measures at which the CB&M may be introduced as the clinical measure of choice to evaluate balance and mobility in individuals with post-stroke neurologic and motor control impairments.

2.4.3 Associations of the CB&M, BBS, TUG to the CMSA and Lower Limb Strength

Bilateral muscle weakness with more prominent strength deficits on the contralateral side to the brain lesion is a common characteristic of adults with stroke that negatively impacts their functional abilities and recovery (Andrews and Bohannon, 2000; Harris et al., 2001; Newham and Hsiao, 2001). In agreement with other studies, the results of this study demonstrated a substantial reduction in the ability to generate isokinetic torque on the paretic side for the hip, knee and ankle muscles, in comparison to the non-paretic side. Numerous studies have shown that muscle strength in the lower extremities is an important variable contributing to balance and ambulatory function in healthy individuals as well as in adults with stroke (Eng et al., 2002; Patterson et al., 2007; Wolfson et al., 1995). Strength deficits in individual lower extremity muscle groups were reported to correlate with the severity of lower limb motor control impairments assessed by the CMSA, with functional balance measured with the BBS and mobility evaluated with the TUG and 6-minute walk test, respectively (Eng et al., 2002; Patterson et al., 2007). The present findings add to these by demonstrating significant associations between the

severity of stroke deficits, lower limb paretic muscle strength and the BBS and TUG. Additionally, as was expected, the scores obtained on the CB&M also revealed substantial associations with the residual motor impairments of the leg and foot and the torque-generating capacity in the lower limb on the paretic side. The greater associations among the TUG, CB&M and lower limb strength in comparison to the BBS can be explained by the more activity-dependent, challenging nature of these measures. Considering that participants were moderate to high functioning, it is unlikely that strength in the lower limb would be a principal limiting factor to standing and shifting weight as evaluated by the BBS. A noteworthy observation was that strength on the non-paretic limb (as well as the paretic limb) was significantly associated with the performance on the CB&M and TUG only. This further supports a notion that bilateral strength becomes a critical factor when the muscle moments required at the lower limb joints in order to perform activities such as level ground walking, stair negotiation or hopping exceed those associated with standing upright or raising from the chair (Nadeau et al., 2003; Sahlstrom et al., 1995).

2.4.4 Summary

The CB&M is a valid measure to evaluate functional balance and mobility in ambulatory patients with moderate to mild neurologic deficits secondary to stroke. It is easy to implement, requires minimal equipment and incorporates items that challenge functional balance and mobility beyond conventional measures of the BBS and TUG. Stroke-induced functional limitations and muscle weakness are associated with performance on the CB&M. This scale was superior to the BBS and TUG in detecting improvements in balance and mobility over a 5-month period in stroke survivors with

moderate to mild neurologic deficits, which is an important quality in evaluating the recovery process and physical therapy intervention.

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CHAPTER 3

THE ORIGINS OF NEUROMUSCULAR FATIGUE POST-STROKE AND ITS ASSOCIATION WITH SELF-REPORTED FATIGUE AND MOBILITY IN CHRONIC STROKE SURVIVORS[2]

3.1 INTRODUCTION

Fatigue experienced after a stroke is a disabling symptom affecting up to 72% of stroke survivors (Colle et al., 2006). Patients describe fatigue as an overwhelming sense of tiredness, feeling of exhaustion, lack of physical and mental energy (Michael et al., 2006). Self-report scales, such as the Fatigue Assessment Scale, are in common use to quantify the experience of fatigue. Although fatigue is a common symptom of post-stroke depression, evidence suggests that the experience of fatigue can exist independent of depression (Glader et al., 2002; Ingles et al., 1999; van der Werf et al., 2001).

The presence of fatigue often interferes with the rehabilitation process and impairs the patient's ability to regain function lost because of the stroke (Glader et al., 2002). In addition, van de Port and colleagues investigated the deterioration of mobility in chronic stroke survivors and observed that the presence of fatigue was one of the factors associated with poor mobility (van de Port et al., 2006). Muscle weakness and deficits in motor control of the lower limbs of the persons with stroke have been reported to result in the increased level of effort and energy expenditure during walking tasks (Gersten and Orr, 1971; Macko et al., 2001; Milot et al., 2006), which might contribute to the increased fatigability often reported by persons with stroke. Despite high prevalence and debilitating effects of the fatigue post-stroke, the neuromuscular basis of this

[2]A version of this chapter has been published and is used with permission.
Knorr S, Ivanova TD, Doherty TJ, Campbell JA, Garland SJ. The origins of neuromuscular fatigue post-stroke. Exp Brain Res 2011; 21 (2):303-315.

phenomenon remains poorly understood (Colle et al., 2006; Michael et al., 2006; Smith et al., 2008).

Neuromuscular fatigue is defined as any contraction-induced reduction in the ability to generate maximal muscle force (Bigland-Ritchie and Woods, 1984). Reduction of force production may occur at various sites along the motor pathway from the central nervous system (CNS) to the intramuscular contractile machinery. Suboptimal performance of the processes controlling the activation of the muscle at supraspinal and/or spinal levels contribute to central fatigue, defined as a progressive reduction in the voluntary ability to activate the muscle maximally (Gandevia et al., 1996). Peripheral fatigue is defined as a loss of force-generating capacity caused by processes occurring at or distal to the neuromuscular junction (Kirkendall, 1990).

Following a stroke, there are neurologic alterations affecting central and peripheral motor pathways, muscle weakness and loss of functional abilities (Liepert, 2006; Newham and Hsiao, 2001; Riley and Bilodeau, 2002; Thickbroom et al., 2002). Muscle weakness and impaired voluntary muscle activation have been reported bilaterally following a unilateral stroke (Newham and Hsiao, 2001; Riley and Bilodeau, 2002). Although the impairments are more pronounced on the paretic side, these findings emphasize the importance of using age- and sex-matched controls to evaluate changes on the non-paretic side.

To date, there are few studies that have investigated the influences of stroke on neuromuscular fatigue in persons with unilateral hemiparesis (Hu et al., 2006; Riley and Bilodeau, 2002; Svantesson et al., 1999; Tang and Rymer, 1981; Toffola et al., 2001). Different types of fatigue protocols have been used to induce neuromuscular fatigue.

According to the collective results from these studies, the muscles on the paretic side demonstrated less peripheral fatigability than muscles on the non-paretic side. The reduced fatigability on the paretic side of the participants with stroke was attributed to the lower absolute torque in the paretic versus the non-paretic and/or control sides and to the plausible muscle fiber rearrangement on the paretic side such as preferential atrophy of Type II muscle fibers and increased proportion of Type I fibers (Dattola et al., 1993; Hara et al., 2004; Lukacs et al., 2008). However, little attention has been paid to stroke-induced changes in central mechanisms contributing to the development of neuromuscular fatigue following the performance of a standardized fatigue task. This is an important aspect because susceptibility to central fatigue might be a contributing factor to a complaint of increased general fatigability during the activities of daily living frequently reported by stroke survivors.

The twitch interpolation technique (see methods) is a commonly used method to measure changes in the degree of voluntary activation. Transcranial magnetic stimulation (TMS) also provides insight into the excitability of the central motor pathway, hereafter referred to as central excitability, in healthy volunteers and persons post-stroke (Liepert, 2006; Taylor and Gandevia, 2001; Thickbroom et al., 2002). TMS evokes a short-latency excitatory response, termed motor evoked potential (MEP), which is recorded at the muscle level using surface electromyography (EMG). The MEP amplitude is used to assess the effects of fatigue on central excitability, which encompasses changes in the excitability of both cortical and spinal motoneurons and in corticospinal synaptic transmission (Kalmar and Cafarelli, 2004; Sogaard et al., 2006; Taylor et al., 1999). However, because the MEP is recorded peripherally, the fatigue-related changes in

neuromuscular signal transmission and/or propagation, estimated with the amplitude of the maximal compound muscle action potential (M wave) elicited with supramaximal electrical stimulation of the peripheral nerve, must be taken into consideration. The normalization of the MEP amplitude to the M wave amplitude has been a recommended method that allows attributing changes in the MEP amplitude to the processes upstream from the peripheral nerve (Kalmar and Cafarelli, 2004).

During a voluntary contraction, TMS also evokes an inhibitory response following a MEP, which is represented by a period of near silence in the surface EMG recordings and is termed the cortical silent period (SP). Research evidence indicates that although spinal mechanisms (e.g. refractoriness and recurrent inhibition of spinal motoneurons) contribute to the initial part of the cortical SP (~ 50 ms) following TMS, the late part (> 50 ms) is believed to be a cortical phenomenon mediated by γ-aminobutyric acid (GABA) inhibitory interneurons (Inghilleri et al., 1993; Taylor et al., 1999; Wilson et al., 1993; Ziemann, 2004).

The primary aim of the present study was to elaborate on the origins of neuromuscular fatigue post-stroke, specifically focusing on the fatigue-induced changes in voluntary activation, central excitability and cortical inhibition during and following a submaximal fatigue task in chronic stroke survivors. It was anticipated that in comparison to the control participants, baseline measures of the normalized MEP amplitude, voluntary activation and maximal torque-generating capacity would be lower in the participants with stroke, with a greater reduction on the paretic side. Furthermore, following the fatigue task, peripheral fatigue was hypothesized to be more evident in the control group, whereas manifestation of central fatigue would be present to a greater

extent in the participants after stroke. The secondary objective was to explore the associations between self-reported fatigue, fatigue-induced changes in voluntary activation, and functional mobility. Central fatigue was hypothesized to be associated with higher levels of self-reported fatigue and with decreased performance on the functional mobility test.

3.2 METHODS

3.2.1 Participants

The demographic and clinical characteristics of the participants after stroke are given in Table 3.1. Five male and 5 female community-dwelling stroke survivors with unilateral hemiparesis due to a first stroke (age: 58.6 ± 15.5 yrs; height: 170.0 ± 10.0 cm; weight: 74.0 ± 13.0 kg; time post-stroke: 15.9 ± 4.8 months) participated in this study. Ten age- and sex-matched controls with no history of neurological impairment were recruited to participate in the study (age: 56.2 ± 16.1 yrs; height: 174.0 ± 10.0 cm; weight: 71.4 ± 12.3 kg).

This was a sample of convenience with the following exclusion criteria for all participants: i) contraindications for TMS (e.g. epilepsy, heart pacemaker, metallic implants in the brain); ii) cardiac pathology restricting exertion; iii) acute or severe musculoskeletal conditions (e.g. acute ankle sprain, severe arthritis); iv) Chedoke McMaster Stroke Assessment (CMSA) Impairment Inventory score of less than 3 (see below), revealing an inability to hold a moderate level of torque steadily at a target line with muscles involved in ankle dorsiflexion; and v) inability to communicate, understand, comply with the study requirements and provide informed consent. This study was

TABLE 3.1 Characteristics of subjects with stroke

Subject	Sex	Age (years)	Time Post-Stroke (months)	Stroke Location	Side of Hemiparesis	CB&M Score (/96)	CMSA Score (/7)	
							Leg	Foot
1	F	48	15	Cerebellar	L	90	7	7
2	M	50	16	Basal Ganglia	R	84	7	7
3	F	79	13	Lacunar	L	64	5	3
4	M	78	24	Basal Ganglia	L	83	6	6
5	M	52	17	Basal Ganglia	R	77	5	5
6	F	29	8	Pons	R	83	6	6
7	F	73	17	Lacunar	L	48	6	3
8	M	58	23	Lacunar	L	73	5	5
9	M	54	12	Basal Ganglia	L	82	7	6
10	F	66	14	Basal Ganglia	L	33	5	3

Abbreviations: F, Female; M, Male; L, Left; R, Right; CB&M, Community Balance and Mobility scale; CMSA, Chedoke McMaster Stroke Assessment

approved by the Review Board for Health Sciences Research Involving Human Subjects at the University of Western Ontario, London, Canada and conformed to the standards established by the Declaration of Helsinki. All participants gave their informed written consent.

3.2.2 Motor Control, Balance and Mobility following Stroke

The subscales for the leg and foot of the CMSA were used to evaluate the stage of motor recovery of the paretic limb. The ability to perform standardized movements was scored from 1 to 7 (1 = unable to perform and 7 = normal movement) (Gowland et al., 1993).

The Community Balance and Mobility scale (CB&M) was used to assess post-stroke deficits in functional balance and mobility (Howe et al., 2006). This scale comprises 19 tasks scored from 0 to 5 (0 = unable to perform and 5 = able to perform independently) with an extra point given on one of the tasks. Thus the maximum score is 96 points, with higher scores indicative of better functional balance and mobility. The validity of the CB&M has been established in population with stroke (Knorr et al., 2010).

3.2.3 Self-Reported Fatigue

The Fatigue Assessment Scale (FAS) was used to establish the degree of self-reported fatigue in everyday activities (Michielsen et al., 2003). This scale consists of 10 items, which are rated from 1 to 5 (1 = never and 5= always). Scores range from 10 to 50, with higher scores indicating greater fatigue. Validity and reliability of the FAS have been established for people after stroke (Mead et al., 2007; Smith et al., 2008).

3.2.4 Depression

The undetected presence of depression might confound the interpretation of self-reported fatigue, and thus it should be assessed when studying the fatigue post-stroke phenomenon. Center for Epidemiological Studies – Depression Scale (CES-D) was used in this study to assess the presence of depression (Radloff, 1977). This self-report scale consists of 20 items, which are scored from 0 to 3 (0 = rarely or none of the time and 3 = most or all of the time), with a maximum score of 60. Total scores on the CES-D less than 16 were considered to be 'non-depressed' (Beekman et al., 1997). The CES-D has been established to be a valid and reliable measure for use with participants after stroke (Shinar et al., 1986).

3.2.5 Functional Long-Distance Mobility

The 6-MWT was used to measure long-distance functional mobility. All participants were instructed to walk as far as possible around a 73-m rectangular path during a 6-minute period, which included rest periods if needed. The 6-MWT has been demonstrated to be a valid and reliable measure in population with stroke (Eng et al., 2004; Flansbjer et al., 2005).

3.2.6 Apparatus

Each participant sat in an adjustable chair in upright position with his/her back against a rigid backrest (Figure 1A). Straps were fastened across the participant's waist and upper torso to minimize body movement while performing the isometric ankle dorsiflexion contractions. The participant's head was secured with an elastic tensor to the headrest to restrict any head movement throughout the entire experiment. The height of the chair was adjusted for each participant so the knee and ankle joints of the tested limb were at 90° flexion and 15° plantarflexion, respectively. A padded clamp placed superior

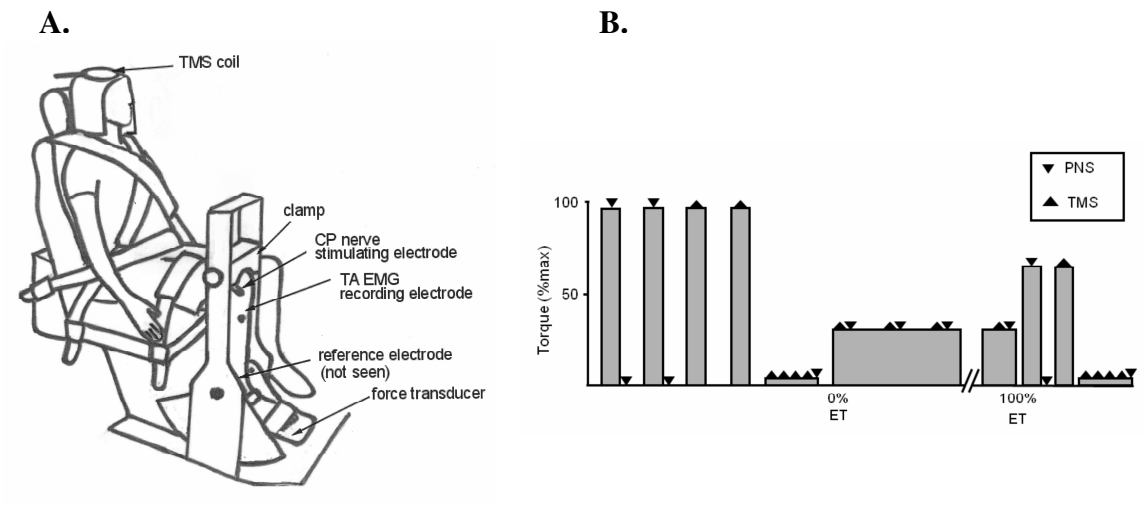

FIGURE 3.1 Schematic representation of experimental setup and procedures

A. Schematic of the experimental setup (see Methods). Note that the soleus EMG electrodes are hidden by the apparatus. **B.** Schematic of the experimental procedures. Pre-fatigue measures consisted of 4 maximal voluntary contractions (MVCs) of the ankle dorsiflexors with peripheral nerve stimulation (PNS, down pointing black triangles) being delivered in the first 2 MVCs and 2 s after the contractions and transcranial magnetic stimulation (TMS, up pointing black triangles) being applied during the next 2 MVCs. Following that, 4 TMS pulses and 1 PNS pulse were delivered during a brief isometric contraction sustained at 3% MVC. The fatigue task consisted of a submaximal (30% MVC) sustained isometric contraction held to the limit of endurance (100% of endurance time (ET)). A single TMS pulse followed by a single PNS pulse were applied every 60 s during the fatigue task. Post-fatigue measures consisted of 2 MVCs with PNS delivered during and 2 s after the first MVC and TMS interpolated during the second MVC. This was followed by 4 TMS pulses and 1 PNS pulse applied during the sustained 3% MVC contraction.

to the flexed knee joint and a rigid heel cup with non-compliant straps secured the heel and forefoot in a custom-made apparatus and prevented movement during the isometric contractions of the ankle dorsiflexors. A two-directional force transducer (Model: FR5-300-B000; 1.880mV/V; Tovey Engineering, Inc., AZ, USA) mounted below the foot-plate recorded the isometric torque of the right or left ankle dorsiflexors.

3.2.7 Surface Electromyography

Voluntary muscle activity and evoked responses were recorded from the tibialis anterior (TA) and soleus muscles with self-adhering surface EMG electrodes (Ag-AgCl, 8 mm diameter). The TA muscle was chosen because it is a primary dorsiflexor muscle of the ankle involved in locomotion and is easily accessible for the surface EMG recordings (Holmback et al., 2003). The soleus surface EMG was recorded to monitor the amplitude of any MEPs in the antagonist muscle evoked by transcranial magnetic stimulation delivered during the maximal voluntary contraction. The skin under each electrode was cleaned with 70% isopropyl alcohol prior to the placement of the electrodes. The active electrode was placed over the belly of the muscle, whereas the reference electrode was situated over the distal tendon of the muscle. Monopolar EMG recordings have been used to avoid the signal cancellation that is inherent in bipolar recordings (Kalmar and Cafarelli, 2004; Wilson et al., 1993). A strap electrode wrapped around the leg served as a ground.

3.2.8 Peripheral Nerve Electrical Stimulation

The common peroneal (CP) nerve of the tested limb was stimulated at rest as well as during the voluntary contractions using bipolar lead stimulating electrodes (anode

situated distally) positioned slightly inferior to the head of the fibula. A maximal twitch in the ankle dorsiflexors and a maximal M wave in the TA muscle were elicited at rest using a rectangular electrical pulse of 100 μs duration produced by a constant current stimulator (DS7AH, Digitimer, UK). The stimulation intensity was set at 20% higher than that required to evoke a maximal twitch and maximal M wave and remained constant during the experimental protocol. The peak-to-peak amplitude of the M wave was used to monitor the integrity of peripheral signal transmission in the TA muscle. Contractile properties of the ankle dorsiflexors were evaluated with the amplitude of the twitch peak torque (PT) evoked at rest.

3.2.9 Twitch Interpolation Technique

The twitch interpolation technique was employed to assess the extent of voluntary activation, which is reflective of voluntary neural drive (Allen et al., 1995). A supramaximal stimulus was applied to the CP nerve at the point of maximal voluntary torque, which was visually determined as the point of torque plateau despite strong verbal encouragement. A second supramaximal stimulus was delivered at rest ~ 2 s following the MVC. A standard equation (Voluntary activation (%) = (1 - superimposed twitch/resting twitch) x 100) was used to calculate the percent of voluntary activation. Thus, voluntary activation is considered maximal when there is no superimposed twitch evoked at the peak of the MVC in response to the supramaximal stimulation of the peripheral nerve.

3.2.10 Transcranial Magnetic Stimulation

A single pulse of TMS was delivered with a Cadwell MES-10 magnetic stimulator (Kennewick, WA) connected to a 9-cm round coil centered over the vertex. Foam

earplugs were placed in the participant's ears to attenuate the discharge sound from the stimulator. The transcranial magnetic stimulator was set at 80% maximal output and the coil was moved over the vertex to locate the position eliciting the largest MEP in the TA muscle while the participant was holding a very low level of contraction (3% MVC). The coil then was secured to the headrest of the sitting chair and its position remained constant during the experiment. Following that, the active motor threshold (AMT), defined as the lowest stimulator output needed to elicit MEP responses visibly exceeding the level of background EMG (usually 200 μV to 500 μV peak-to-peak) in 5 of 10 consecutive stimulations during a 3% MVC of dorsiflexion, was determined for each participant. Then, the stimulator was set at the AMT + 20% maximal stimulator output and this stimulus intensity remained constant throughout the experimental protocol. The AMT was used in this study because resting motor thresholds in the TA of greater than 90% of maximal stimulator output were found in the pilot work and have been reported by others (Brouwer and Ashby, 1990; Kalmar and Cafarelli, 2006).

3.2.11 Experimental Protocol

The experimental protocol was identical for both the control and stroke groups. However, each control participant attended only one experimental session, whereas participants affected by stroke returned for a second experimental session, so fatigue could be assessed separately in the paretic and non-paretic limb. These repeated experiments were scheduled at least 7 days apart. Prior to the first experimental session, the testing order of the paretic and non-paretic limb was randomized. All participants in the control group performed the experimental procedures with their dominant leg, defined as the leg with which they would kick a football (Guette et al., 2005). Figure 1B depicts

the schematic representation of the measurements taken pre-fatigue, during fatigue, and post-fatigue.

Pre-Fatigue

Each experiment began with four brief MVCs (~ 3 s in duration) of the ankle dorsiflexors, separated by 120 s of rest to avoid fatigue. The MVC with the highest instantaneous peak torque that was within 10% of other maximal attempts was used to calculate the target torque for the fatigue task (30% MVC) and served as a baseline measure of the maximal voluntary torque-generating capacity. The CP nerve stimulation was delivered at the peak of the first two MVCs as well as ~2 s after the contractions to establish initial voluntary activation and to assess the amplitude of the M wave and twitch PT. TMS was delivered at the peak of the other two MVCs to compute the amplitude of the superimposed twitch torque and to measure the duration of the cortical SP, defined as the time interval from the delivery of the stimulus to the return of continuous voluntary EMG activity. The cortical SP duration was used as an indirect estimate of cortical inhibition. After the fourth MVC, 4 TMS pulses delivered at a rate of 0.25 Hz followed by a single peripheral stimulus were applied during a low torque isometric contraction (3% MVC). This number of TMS pulses was established during the pilot work based on the low variability of the MEP amplitude among pulses (coefficient of variation ranged between 2% and 14%). The average peak-to-peak amplitude of the 4 MEPs was computed and was normalized to the M wave amplitude evoked during the same intensity of isometric voluntary contraction in order to account for changes in peripheral signal transmission. The normalized MEP was used as an indirect estimate of central excitability.

During Fatigue

The fatigue protocol consisted of a sustained isometric voluntary contraction (30% MVC) held to the limit of endurance, defined as the point at which the participant was unable to maintain the submaximal contraction at the target torque for 3 consecutive seconds despite strong verbal encouragement. The torque produced by the participants and a line identifying the target torque level (30% MVC) were displayed for the participant on an oscilloscope. Each participant was asked to keep the torque steady on the line. A single TMS stimulus and a stimulus applied to the CP nerve were delivered every 60 s during the sustained fatiguing contraction. Following each stimulus the participant was reminded to regain the target torque level (30% MVC) as quickly as possible. The CP nerve stimulation was delivered as soon as the target torque level was stabilized at 30% MVC. To score the effort required to produce the target torque, the ratings of perceived exertion (RPE) using a modified Borg scale from 0 ('infinitely small') to 10 ('extremely large') were requested from the participants at 1-minute intervals prior to each TMS stimulus during the sustained fatiguing contraction (Borg, 1990).

Post-Fatigue

Immediately following the fatigue protocol, participants performed 2 MVCs with minimal rest period between the contractions to preserve the effect of fatigue. The CP nerve stimulation was delivered during and after the first MVC, whereas TMS was applied during the second MVC. This was followed by 4 TMS pulses and a single stimulus applied to the peripheral nerve during 3% MVC of ankle dorsiflexion.

3.2.12 Data Acquisition and Analysis

The torque signal was amplified using a bridge amplifier (Bridge 8; World Precision Instruments, Florida, USA) and sampled at 500 Hz. The EMG signals were amplified using an Isolated Patient Amplifier System (Model D360; Digitimer Limited, Hertfordshire, UK), band-pass filtered 10 – 1000 Hz and sampled at 2000 Hz. The torque and EMG signals were digitized using 16-bit data acquisition system (Power 1401 with Spike 2 v.6 software; Cambridge Electronic Design Ltd., Cambridge, UK) and were measured off-line using Spike 2 v.6 software (Cambridge Electronic Design Ltd., Cambridge, UK).

Surface EMG activity was full-wave rectified during maximal and submaximal voluntary contractions. Integrated EMG (iEMG) was measured for 0.5 s prior to either the TMS or peripheral nerve stimulus during MVCs and for 10 s prior to the TMS during the fatigue task. The single stimulation point closest to the time point of 0%, 50% and 100% of endurance time (ET) was chosen to measure the iEMG, cortical SP as well as the amplitudes of the MEP and M waves.

3.2.13 Statistical Analysis

The statistical analyses were carried out using SPSS 16.0 for Windows. A series of two-way repeated measures Analysis of Variance (ANOVA) with two factors (*Limb:* paretic and non-paretic) and (*Time:* Pre- and Post-Fatigue or 0%, 50%, 100% ET) was used as the primary statistical analysis of the neuromuscular fatigue data to assess differences between the paretic and non-paretic limbs of participants with stroke. Similarly a series of two-way mixed ANOVA with two factors (*Limb:* non-paretic and control) and (*Time:* Pre- and Post-Fatigue or 0%, 50%, 100% ET) was used as the secondary statistical approach to evaluate differences between the non-paretic and control

limbs. The Newman-Keuls test was used for post hoc comparisons. Dependent and independent Student's *t*-tests were conducted to compare the duration of the fatigue task between the paretic and non-paretic as well as between the non-paretic and control limbs, respectively. Also, an independent Student's t-test was used to compare the results on the 6-MWT between the stroke and control groups. Non-parametric Mann-Whitney U test was used to evaluate the scores reported on the FAS and CES-D between the stroke and control groups. Spearman rank-order correlation was carried out to determine the associations among the total score of the FAS, the 6-MWT, the CB&M and the change in voluntary activation observed in the stroke and control groups. It was also used to explore the correlations among the distance of the 6-MWT and the scores obtained by the participants with stroke on the CB&M and CMSA leg and foot subscales. Data in the text are presented as mean ± SD, unless otherwise stated. The level of significance was set at $P<0.05$.

3.3 RESULTS

In the present study, the participants with stroke exhibited moderate to mild motor impairments in the paretic limb (CMSA leg: 5.9 ± 0.9; CMSA foot: 5.1 ± 1.6). Also, the overall functional balance and mobility was compromised (CB&M: 71.7 ± 18.2) (Table 3.1). Although the location of the stroke was not part of the exclusion criteria, all participants with stroke experienced a subcortical lesion. The mean score on the CES-D scale was less than 16 and was not different between the participants after stroke and the age- and sex-matched controls (14.5 ± 3.7 and 14.8 ± 3.5; $P>0.05$, respectively). The FAS scores ranged from 11-28, with the participants after stroke reporting significantly

higher levels of fatigue in comparison to the control group (21.2 ± 3.9 and 13.9 ± 2.9; P<0.05, respectively).

3.3.1 Control vs. Non-paretic Limb

There were no significant differences between the non-paretic and control limbs on any of the pre-fatigue measures, including the AMT values (56.2 ± 3.8 % and 51.5 ± 8.0 %; P>0.05, respectively). Furthermore, the change from pre- to post-fatigue was similar between the non-paretic and control limbs, with the exception of a significantly greater increase in the cortical SP duration following the fatigue task performed with the control limb (Table 3.2). Taking these findings into consideration, the results and discussion sections will be focusing primarily on the observed differences between the paretic vs. non-paretic limbs.

3.3.2 Paretic vs. Non-paretic Limb

Pre-Fatigue

Prior to the fatigue task, the MVC peak torque and the amplitude of the normalized MEP were significantly reduced in the paretic limb in comparison to the non-paretic limb (Figure 3.2B and 3.3B). All other measured parameters were comparable between the paretic and non-paretic limbs, including the AMT values (57.0 ± 9.0 % and 56.2 ± 3.8 %; P>0.05, respectively).

During Fatigue

The mean submaximal (30% MVC) torque value for the fatigue task was significantly lower and the endurance time was significantly shorter on the paretic side in comparison to the non-paretic side (5.0 ± 2.0 Nm vs. 6.6 ± 2.3 Nm and 6.7 ± 3.4 min vs. 9.1 ± 4.0 min; P<0.05, respectively). At the beginning of the fatigue task (0% ET), the

TABLE 3.2 Central and peripheral changes following fatigue for the non-paretic and control Limbs

% Change	Non-Paretic	Control
MVC Peak Torque	- 36 ± 8 †	- 32 ± 12 †
Integrated EMGmax	- 22 ± 16 †	- 26 ± 17 †
Voluntary Activation	- 4 ± 6	- 5 ± 6
Cortical Silent Period	31 ± 32 †	80 ± 53 †*
MEP Amplitude % M wave	64 ± 55 †	58 ± 74 †
M wave Amplitude	- 15 ± 12 †	- 11 ± 10 †
Twitch PT	- 55 ± 25 †	- 43 ± 20 †

Abbreviations: MVC = Maximal Voluntary Contraction; EMGmax = Maximal Integrated Electromyography; TMS = Transcranial Magnetic Simulation; MEP = Motor Evoked Potential; PT = Peak Torque

% Change = (POST – PRE)/PRE*100

Positive values indicate post-fatigue measures were larger than pre-fatigue

Negative values indicate post-fatigue measures were smaller than pre-fatigue

* denotes significant difference from the non-paretic limb

† denotes significant difference between PRE- and POST-Fatigue

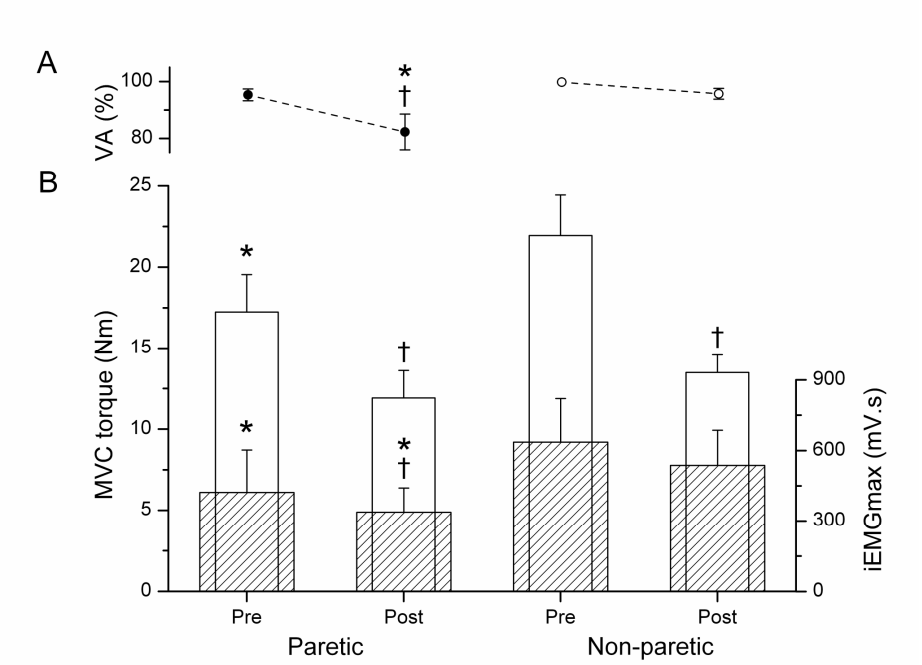

FIGURE 3.2 MVC torque, surface EMG and voluntary activation before and following fatigue

A. The mean values for the voluntary activation (VA) of the paretic (black circles) and non-paretic (open circles) limbs, pre- and post-fatigue. **B.** The maximal voluntary contraction (MVC) peak torque (left axis, open bars) and the integrated electromyography (iEMG) (right axis, diagonal hatched bars) for the paretic and non-paretic limbs, pre- and post-fatigue. The iEMG was calculated over 0.5 s prior to the interpolated stimulus.

† denotes significant difference from pre-fatigue, $P<0.05$. * denotes significant difference from the non-paretic limb, $P<0.05$. Data are expressed as mean ± SD

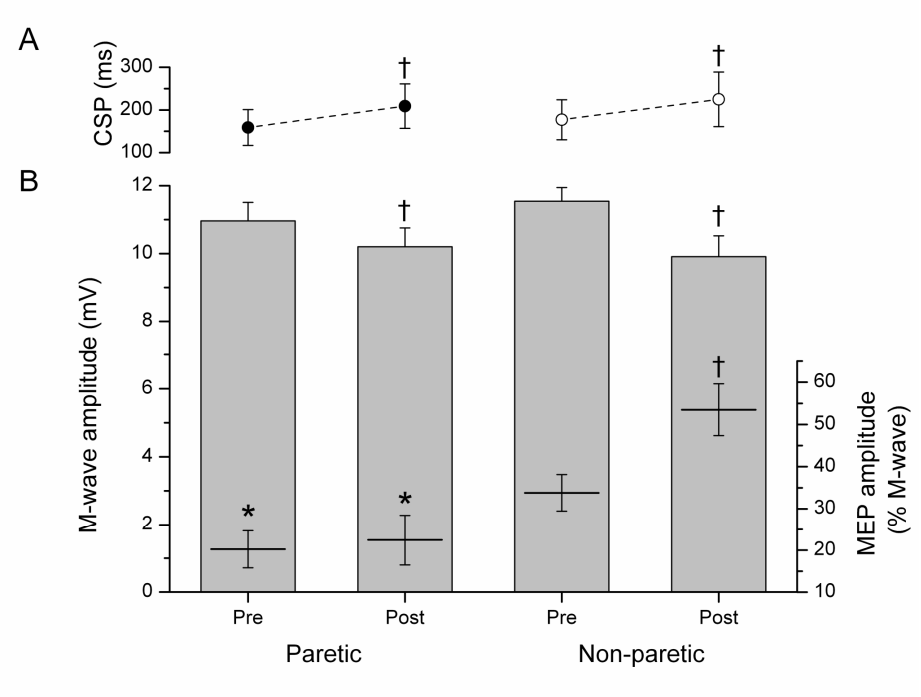

FIGURE 3.3 Duration of cortical silent period and amplitude of M wave and MEP before and following fatigue

A. The mean duration of the cortical silent period (SP) for the paretic (black circles) and non-paretic (open circles) limbs, pre- and post-fatigue. **B.** The mean amplitude of the maximal M wave (left axis, grey bars) and motor evoked potential (MEP) (right axis, horizontal lines) are shown for the paretic and non-paretic limbs before (Pre) and following fatigue (Post).

† denotes significant difference from pre-fatigue, $P<0.05$. * denotes significant difference from the non-paretic limb, $P<0.05$. Data are expressed as mean ± SD.

submaximal mean iEMG values, expressed as a percentage of the maximal iEMG (% iEMGmax), RPE scores and the cortical SP duration did not differ significantly between the limbs, whereas the amplitude of the normalized MEP was reduced on the paretic limb (Figure 3.4 and 3.5). During the fatigue task, the submaximal iEMG values increased significantly in both limbs, indicating an increase in the voluntary neural drive, with a greater increase being observed on the non-paretic side at 100% ET (Figure 3.4A). This was accompanied by a progressive increase in the RPE scores, reaching the maximum score of 10 out of 10 on both limbs at 100% ET. In comparison to the non-paretic side, the RPE scores reported at 50% ET were significantly higher on the paretic side of the participants after stroke (7.0 ± 1.6 and 5.9 ± 1.7, paretic and non-paretic limb; $P<0.05$, respectively) (Figure 3.4B).

Progressive lengthening of the cortical SP duration was evident throughout the fatigue task in both limbs. These findings are illustrated in Figure 3.5B and Figure 3.6. The prolongation of the cortical SP duration was accompanied by a gradual increase in the normalized MEP amplitude reaching statistical significance by the end of the fatigue task in the non-paretic limb only (Figure 3.5A). Contrary to that, the amplitude of the normalized MEP remained relatively constant on the paretic side of the participants after stroke and, at the end of the fatigue task, it was not significantly different from that measured at either 0% or 50% ET ($P>0.05$). These findings are depicted in Figure 3.5A and Figure 3.6.

Post-Fatigue

Immediately following the fatigue task, the MVC peak torque was reduced significantly to 71.31 ± 22.3% and 63.3 ± 8.0% of the pre-fatigue MVC for the paretic and non-paretic

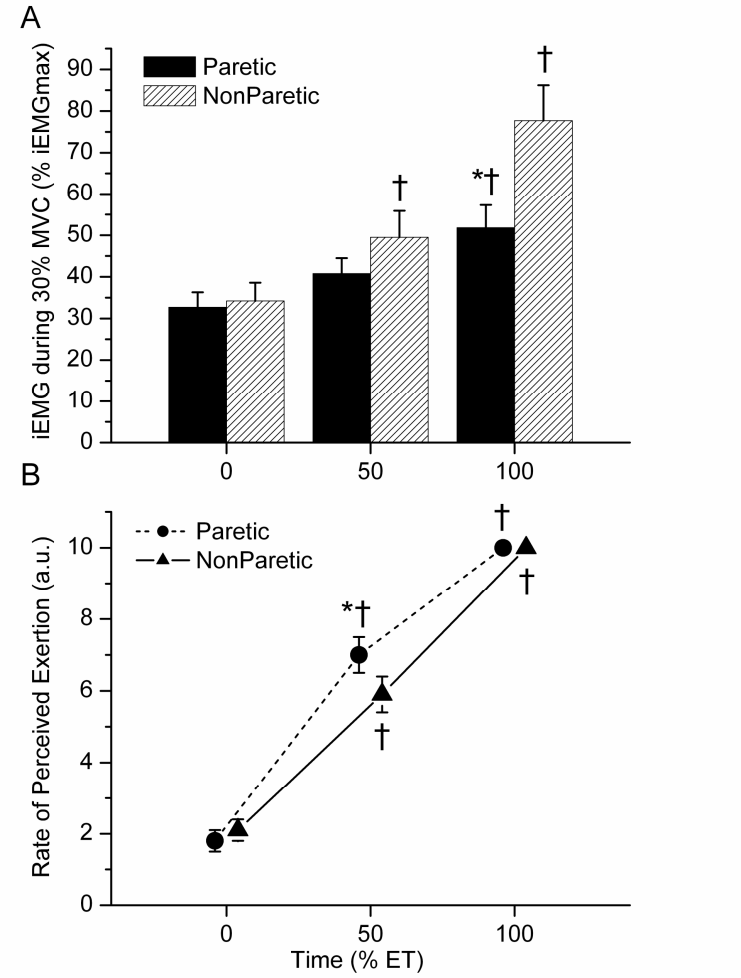

FIGURE 3.4 Changes in surface EMG and RPE during fatigue task

A. The mean values of the integrated electromyography (iEMG) measured over 10 s at 0%, 50% and 100% of endurance time (ET) of the fatigue task are shown in relative to the maximal iEMG values recorded during the pre-fatigue maximal voluntary contractions in the paretic (black bars) and non-paretic (diagonal hatched bars) limbs.

B. Ratings of perceived exertion (RPE) closest in time to 0%, 50% and 100% ET are depicted for the paretic (black circles, dashed line) and non-paretic (black triangles, solid line) limbs.

† denotes significant difference from 0% ET, $P<0.05$. * denotes significant difference from the non-paretic limb, $P<0.05$. Data are expressed as mean ± SE.

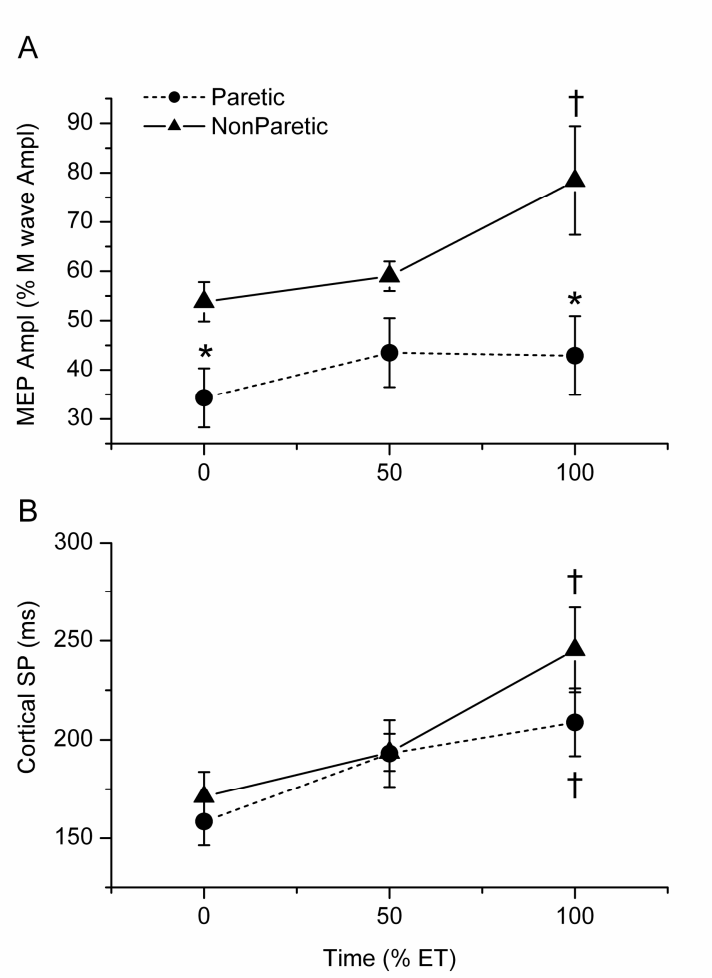

FIGURE 3.5 Changes in MEP amplitude and cortical silent period duration during fatigue task

The amplitude of the motor evoked potential (MEP) (**A**) and the duration of the cortical silent period (SP) (**B**) are shown for the duration of the fatigue task expressed as a percentage of the endurance time (ET) for the paretic (black circles, dashed line) and non-paretic (black triangles, solid line) limbs.

† denotes significant difference from 0% ET, $P<0.05$. * denotes significant difference from the non-paretic limb, $P<0.05$. Data are expressed as mean ± SE.

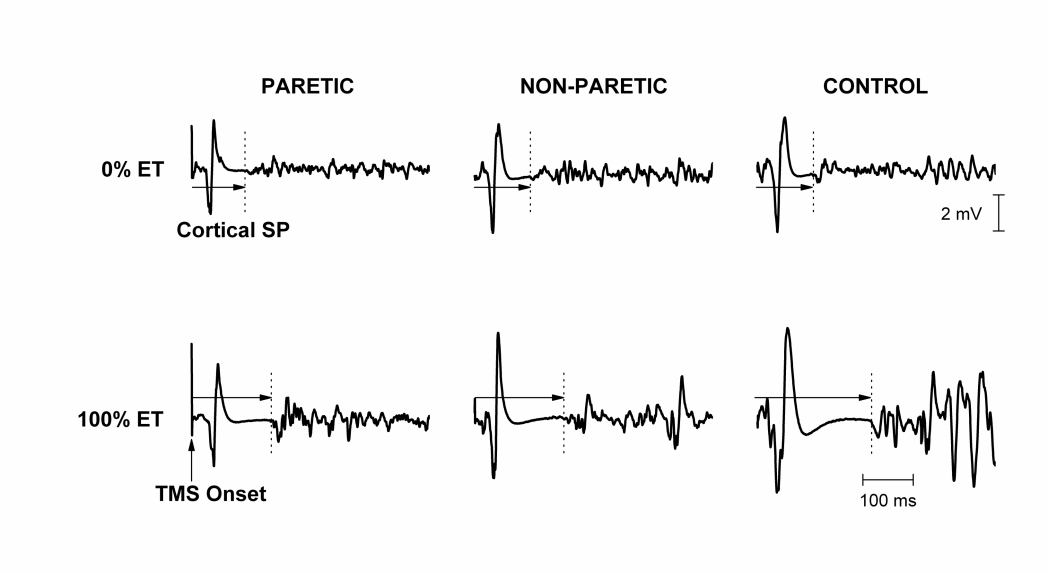

FIGURE 3.6 Representative recordings of EMG responses following transcranial magnetic stimulation during fatigue task

The representative recordings of the cortical silent period (SP) durations, measured from the onset of transcranial magnetic stimulation (TMS) to the point of the return of continuous voluntary electromyographic (EMG) activity, illustrate prolongation in the paretic (left), non-paretic (middle), and control (right) limbs from the beginning (0% of endurance time (ET); top row) to the end of the fatigue task (100% ET, bottom row). The peak-to-peak amplitudes of the motor evoked potential (MEP) increased significantly only in the non-paretic and control limbs during the fatigue task.

limbs, respectively (Figure 3.2B). The fatigue-induced changes in the cortical SP duration and the normalized MEP amplitude followed a similar pattern as during the fatigue protocol. That is, the cortical SP duration measured during the post-fatigue MVC increased in both limbs (Figure 3.3A), whereas the normalized MEP amplitude measured during 3% MVC following the fatigue task increased by 64% in the non-paretic limb, but on the paretic side the MEP amplitude did not change (P=0.65) and was significantly smaller than those measured in the non-paretic limb (Figure 3.3B).

Central fatigue, represented by a 13% reduction in voluntary activation, was observed to a greater extent in the paretic limb (Figure 3.2A). In addition, a significant increase in the amplitude of the superimposed twitch evoked by TMS at the peak of MVC following the fatigue task was also more evident in the paretic limb, which implies that cortical output was suboptimal at the point of stimulation despite maximal voluntary effort (Figure 3.7A). There was no change in the small MEPs evoked in the soleus muscle; therefore the superimposed twitch evoked by TMS was not contaminated by opposing force production in the ankle plantarflexor muscles. Peripheral fatigue, evident by the reduction in the amplitudes of the twitch PT and maximum M wave was observed in both limbs (Figure 3.3B and 3.7B).

3.3.3 Association of Fatigue with Function

The extent of central fatigue was correlated positively with the FAS scores ($n=20$; $\rho= 0.45$; $P<0.05$) and negatively with the distance covered by the participants during the 6-MWT and with the CB&M scores ($n=20$; $\rho= -0.47$ and $n=10$; $\rho= -0.58$; $P<0.05$, respectively) (Figure 3.8 and 3.9). In addition, the FAS scores were associated negatively with the 6-MWT ($n=20$; $\rho= -0.55$; $P<0.05$) (Figure 3.8C), but not with the

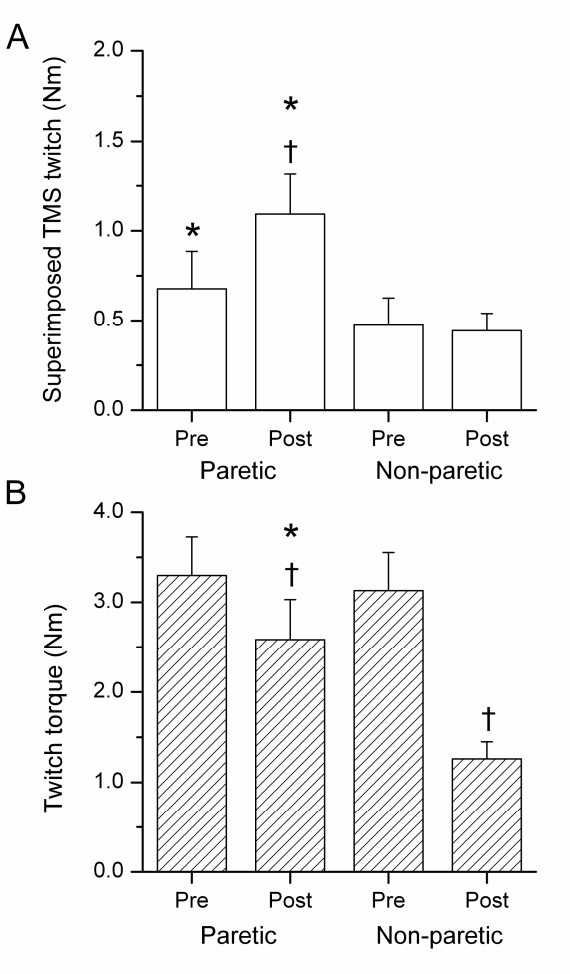

FIGURE 3.7 Twitch peak torque and amplitude of the superimposed twitch evoked by TMS before and following fatigue task

The amplitude of the superimposed twitch evoked by TMS (**A**, open bars) and the mean peak torque of the maximal twitch (**B**, diagonal hatched bars) are shown for the paretic and non-paretic limbs before (Pre) and following fatigue (Post).

† denotes significant difference from pre-fatigue, $P<0.05$. * denotes significant difference from the non-paretic limb, $P<0.05$. Data are expressed as mean ± SD.

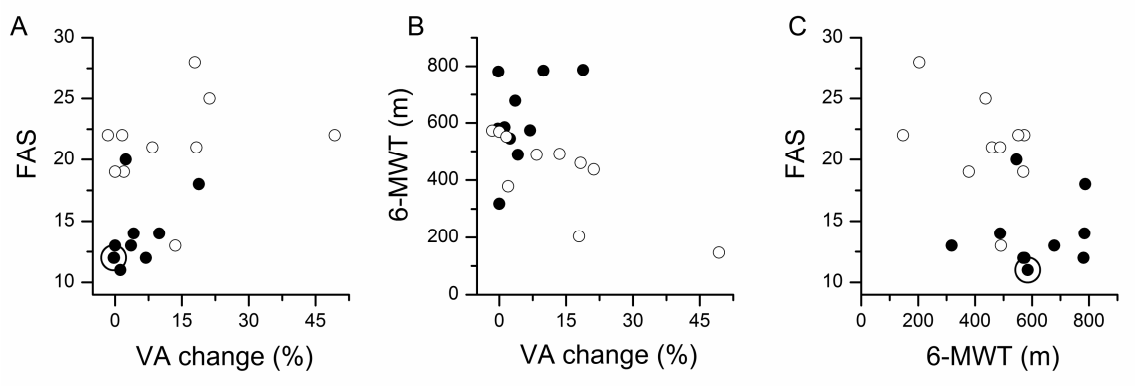

FIGURE 3.8 Associations among the VA change, FAS and 6-MWT scores

Change in Voluntary Activation (VA change) on the paretic limb from pre- to post-fatigue is plotted against the scores obtained on the Fatigue Assessment Scale (FAS) (**A**) and six-minute walk test (6-MWT) (**B**). Scores obtained on the 6-MWT are plotted against the FAS scores in panel **C**. Open circles (○) indicate participants in the stroke group and filled circles (●) indicate control subjects. Each point represents data from an individual participant. The circled points indicate multiple participants.

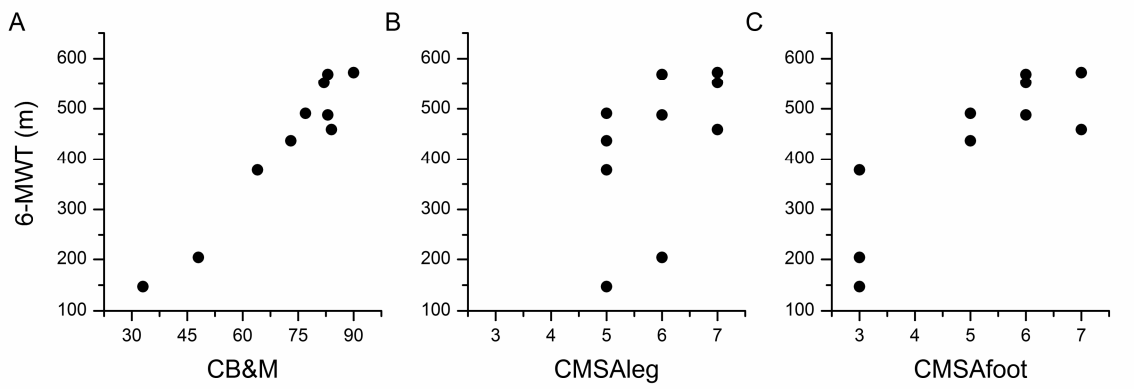

FIGURE 3.9 Associations among the scores obtained on the CB&M, CMSA leg and foot subscales vs. 6-MWT

Community Balance and Mobility (CB&M) (**A**), Chedoke McMaster Stroke Assessment (CMSA) leg (**B**) and foot (**C**) scores plotted against the six-minute walk test (6-MWT) scores obtained by the participants with stroke. Each point represents data from an individual participant.

CB&M or with the CMSA leg and foot scores obtained from the participants with stroke (n=10; ρ =-0.27; -0.19; -0.14; P>0.05, respectively). However, significant positive associations were established between the 6-MWT and the scores on the CB&M (n=10; ρ= 0.83; P<0.05) as well as with the scores on the CMSA leg and foot subscales obtained on the paretic limb of the participants with stroke (n=10; ρ= 0.57 and 0.78; P<0.05, respectively) (Figure 3.9).

3.4 DISCUSSION

The main objective of the present study was to investigate the origins of neuromuscular fatigue in persons with stroke, with a special focus on centrally-mediated factors. The main finding was the difference in the origins of neuromuscular fatigue, with central fatigue being more evident on the paretic side of the participants after stroke in comparison to their non-paretic side. The findings of comparable periods of the cortical SP duration between the paretic and non-paretic limbs, yet significantly reduced MEP amplitudes on the paretic side indicate that a subcortical stroke had differential effects on central excitability and cortical inhibition, which might have contributed to the genesis of central fatigue. Significant associations among the fatigue-induced changes in voluntary activation, self-reported fatigue and performance on the 6-MWT suggest that central fatigue may lead to an enhanced perception of effort, which could influence the performance on the functional mobility task and may partially underlie the more general complaint of fatigue, which was experienced to a greater extent by people with stroke.

3.4.1 Pre-Fatigue

Prior to the fatigue task, central excitability, represented by the MEP amplitude, was reduced in the chronic stroke survivors with a subcortical lesion, which has been

previously reported by others (Byrnes et al., 2001; Pennisi et al., 2002; Thickbroom et al., 2002). Thickbroom and colleagues (2002) also observed a positive association between the MEP amplitude and strength in the paretic upper limb muscles. Although the underlying mechanisms responsible for the MEP amplitude reduction following a subcortical lesion are not known, it has been suggested that interruptions in the afferent inputs to the cortex (e.g. thalamo-cortical and/or striato-cortical inputs) could alter the balance between excitatory and inhibitory inputs to the cortex and subsequently decrease the excitability of the corticomotor neurons (Byrnes et al., 2001; Classen et al., 1997). The MEP amplitude may also be modulated at the segmental level; however, it has been reported that spinal motoneuron excitability increased following a stroke (Udby and Nielsen, 2009) and thus, would be less likely to contribute to the observed pre-fatigue reduction in the MEP amplitude.

3.4.2 During Fatigue

During the sustained submaximal contraction, the maintenance of the target force is achieved by the incremental recruitment of new motor units and/or by increasing the firing rates of already recruited motor units, which is reflected in a progressive enlargement in the surface EMG activity (Adam and De Luca, 2005; Bigland-Ritchie et al., 1986). In addition, it has been reported previously that an increase in the surface EMG recording, which is indicative of an increased voluntary neural drive, was associated with an increase in the RPE scores (Sogaard et al., 2006). In the present study, at 50% ET there was a significantly greater perception of effort during the fatigue task on the paretic side even though the surface EMG had not increased significantly at that time. This suggests that an increased sense of effort, which has been reported previously in

pure motor strokes (Gandevia, 1982), might be influenced by activity in neural centers upstream of the motor cortex that are contributing to the centrally-generated motor command (Carson et al., 2002; Gandevia and McCloskey, 1977; Jones, 1995). This might have led to an increased rate of perceived exertion and potentially influenced the limit of endurance, which was reached significantly sooner on the paretic side.

The amplitude of the MEP and the duration of the cortical SP measured during the submaximal sustained fatiguing contraction have been reported to increase progressively in studies using healthy participants (Sacco et al., 1997; Sogaard et al., 2006; Taylor et al., 1996). The findings from the present study demonstrated that a submaximal fatiguing contraction resulted in a similar pattern of change in the TMS-evoked parameters in the non-paretic limb, indicating that the development of fatigue enhanced the excitability of the cortical and/or spinal motoneuronal systems and occurred in conjunction with an increase in cortical inhibition. Contrary to that, there was only a marginal increase in the normalized MEP amplitude with a significant prolongation of the cortical SP duration during the fatigue task on the paretic side. Although the duration of the cortical SP was progressively increasing throughout the fatigue task, it had a small influence on the ability to maintain the target submaximal torque because the cortical SP duration was shorter than that of the muscle twitch torque.

In a series of experiments, single- and paired-pulse TMS techniques were used to investigate the fatigue-induced changes in central excitability and cortical inhibition in healthy participants (Benwell et al., 2006; Benwell et al., 2007). The duration of the short- and long-interval cortical inhibition evoked by the paired-pulse TMS is suggested to be mediated by the $GABA_A$ and $GABA_B$-ergic intracortical inhibitory interneurons,

respectively (Werhahn et al., 1999). According to Benwell and colleagues (2006; 2007), the fatigue-induced prolongation of the cortical SP duration, which is believed to be mediated by the $GABA_B$-ergic intracortical inhibitory interneuron networks located upstream of the primary motor cortex, might result in suboptimal voluntary drive from the premotor centers to the primary motor cortex. Furthermore, they suggested that an increase in the MEP amplitude, along with attenuation in the short- and long-interval cortical inhibition within the primary motor cortex, compensates for the increase in intracortical inhibition upstream of the primary motor cortex. Thus, in the present experiment, an inability to modulate central excitability and/or intracortical inhibition within the primary motor cortex might provide a plausible explanation for the lack of an increase in the MEP amplitude in the presence of an increased duration of the cortical SP observed on the paretic side of the participants with stroke. This might subsequently lead to suboptimal neural drive from the primary motor cortex, evident by an increment in torque evoked by TMS during the MVC, which will be discussed below.

3.4.3 Post-Fatigue

The fatigue task produced a substantial reduction in the maximal torque-generating capacity in both limbs, indicating the presence of neuromuscular fatigue. The marginal change in the degree of voluntary muscle activation accompanied by a significant reduction in peripheral signal transmission and failure in the contractile machinery suggest that neuromuscular fatigue was primarily peripheral in origin in the non-paretic limb. Different findings were observed in the paretic limb where peripheral fatigue was accompanied by a considerable reduction in voluntary activation. Indeed, even if the 3 participants with notable hemiparesis (stage 3 on the CMSA foot subscale) were

removed, the same results of central fatigue following the fatigue task were obtained on the paretic side signifying that voluntary activation failure occurs even in the absence of marked motor control deficiencies.

Peripheral fatigue may have been more evident on the non-paretic side because the larger force production could result in higher levels of local intramuscular pressure, increased blood flow occlusion and larger accumulation of metabolic by-products on the non-paretic side than the paretic side (Crenshaw et al., 1997; Enoka and Stuart, 1992; Sjogaard et al., 1986). It is also possible that changes in the muscle fiber composition in the paretic muscles (increase in Type I and loss of Type II muscle fibers), which have been reported by others (Dattola et al., 1993; Lukacs et al., 2008; Scelsi et al., 1984; Slager et al., 1985), might result in less peripheral fatigue in the paretic muscles. Finally, central fatigue, which was observed to a greater extent on the paretic side, might have protected against the development of peripheral fatigue by causing an earlier cessation of the fatigue task on the paretic side.

The presence of central fatigue on the paretic side is in accordance with the pilot findings (n=2) from the study conducted by Riley and Bilodeau (2002), in which supramaximal electrical stimulation was delivered to the biceps brachii muscle every 10 s during a 60 s sustained MVC of the elbow flexors. They reported that the ability to maintain maximal muscle voluntary activation decreased progressively throughout the contraction only on the paretic side compared to the non-paretic side. However, the increment in force following motor point stimulation provides no evidence as to which site(s) proximal to the neuromuscular junction is involved in the reduction in voluntary activation. Therefore, the findings from the present study extend those of Riley and

Bilodeau (2002) by showing an increase in the superimposed twitch amplitude evoked by TMS during the post-fatigue MVC. An increment in torque evoked by TMS during the MVC suggests that the neural drive from the motor cortex was suboptimal to activate and/or drive the motor units maximally despite maximal voluntary effort (Gandevia et al., 1996; Sogaard et al., 2006). Although spinal sources of central fatigue cannot be excluded (Garland, 1991; Garland and McComas, 1990), the fact that torque increments were present following cortical stimulation suggests that motoneurons could be activated with additional descending drive. Thus, suboptimal output from the motor cortex might have contributed, at least in part, to the failure in voluntary activation observed on the paretic side. Unlike the interpolated twitch technique, the contribution of failure of cortical drive to the overall decrease in voluntary activation is problematic to quantify because the amplitude of the superimposed twitch evoked by TMS cannot be expressed as a fraction of the twitch evoked by the same stimulus in the relaxed muscle as the excitability of the cortical and spinal motoneurons differs significantly between the active and resting states (Di Lazzaro et al., 1998; Gandevia, 2001; Taylor and Gandevia, 2008; Ugawa et al., 1995).

3.4.4 Association of Fatigue with Function

In the present investigation, the participants post-stroke with mild to moderate motor deficits experienced appreciably greater fatigue in their everyday activities and had decreased performance on the long-distance functional mobility task compared to the age- and sex-matched controls, despite the fact that both groups were not affected by depression. This finding contributes to the pool of evidence suggesting that self-reported fatigue can be present independent of post-stroke depression. Stroke-induced deficits in

motor control and balance are known to negatively influence functional mobility due to a biomechanical inefficiency of walking and an increased level of effort and energy expenditure (Milot et al., 2006; Patterson et al., 2007; Pohl et al., 2002). This was confirmed in the present study by a strong relationship between the 6-MWT and the CB&M and CMSA foot scores. Furthermore, central fatigue was correlated negatively with the performance on the functional mobility and balance tasks and positively with self-reported fatigue. Thus, participants with more central fatigue experienced more self-reported fatigue, walked a shorter distance on the 6-MWT and had decreased performance on the CB&M test than participants with less central fatigue. Although these associations do not imply a causal relationship, they suggest that an inability of the central motor pathways to cope with the increased physiological demand during physical activities may lead to an increased sense of effort and possibly contribute to the general complaint of self-reported perception of fatigue during activities of daily living, especially in people with stroke. Contrary to previous studies (Michael et al., 2006; Tseng and Kluding, 2009), significant correlations were not observed between self-reported fatigue and stroke-induced deficits in the lower limb motor control, balance and mobility. This might be due to the differences in the participants, in that the subjects in the current study had greater functional abilities than those participants in the studies cited above. However, these findings reinforce the notion that self-reported fatigue is a multidimensional phenomenon and factors other than the severity of motor deficits may contribute to it.

3.4.5 Summary

The results from this study demonstrated that stroke resulted in a shift of the origin of neuromuscular fatigue induced by a sustained submaximal (30% MVC) fatiguing contraction. Performance of the same fatiguing task resulted primarily in suboptimal performance of the contractile apparatus in the non-paretic lower limb muscles, whereas fatigue of central origin was observed to a greater extent on the paretic side of the participants with a subcortical lesion. The inability to modulate central excitation in the face of increased cortical inhibition likely contributed to the genesis of central fatigue, which might partially influence the performance on the functional balance and mobility tasks and explain self-reported fatigue often experienced by persons with stroke.

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CHAPTER 4

MOTONEURON AFTERHYPERPOLARIZATION TIME-COURSE FOLLOWING STROKE

4.1 INTRODUCTION

The results from Chapter 3 supporting the presence of central fatigue and the higher levels of perceived exertion in the paretic limb than in the non-paretic and control limbs may result, in part, from changes in the spinal motoneurons after stroke. A reduction in the mean motor unit firing rates and a reduced ability to modulate the motor unit discharge rate with increasing torque demands during voluntary contractions have been observed in the paretic muscles during the chronic stage following stroke (Frontera et al., 1997; Rosenfalck and Andreassen, 1980; Gemperline et al., 1995; Jakobsson et al., 1992). The net effect of these stroke-induced disturbances in the rate coding of motor units would necessitate the recruitment of more motor units to produce a given force, which has been demonstrated as an abnormally high level of surface electromyographic (EMG) activity recorded in the paretic muscles for a given muscle force (Tang and Rymer, 1981; Gemperline et al., 1995). An increased reliance on motor unit recruitment to maintain force production might contribute to a greater magnitude of central muscle activation failure observed in the study reported in Chapter 3.

In addition to the partial loss of excitation from the descending motor pathways to the segmental motoneurons and interneurons, changes in the intrinsic properties of the motoneurons might be another potential mechanism responsible for the stroke-induced alterations in the motoneuron discharge behavior (Gemperline et al., 1995). The post-spike afterhyperpolarization (AHP) is one of the intrinsic properties of the motoneuron, the duration of which influences the capacity of the motoneuron to discharge action

potentials (Kernell, 1965; Sawczuk et al., 1995). Evidence from animal and human models is accumulating to support the premise that motoneurons respond to the alterations in neuromuscular activity by changing their properties (Beaumont and Gardiner, 2002; Munson et al., 1997; Christie and Kamen, 2010). However, there is a paucity of literature on the effects of stroke on the properties of the motoneurons in humans. There is only one study that has investigated stroke-induced changes in the AHP duration in human participants (Liang et al., 2010). In that study, the estimated duration of the AHP was prolonged in the motoneurons of the paretic biceps brachii muscle of the participants with stroke. The generalizability of findings in the motoneurons controlling the paretic upper limb muscles to the ones controlling the paretic lower limb muscles is equivocal since the patterns of muscle utilization differ between the upper and lower limb muscles (i.e. biceps brachii is involved primarily in phasic activities (e.g. lifting), whereas tibialis anterior is recruited during prolonged activities (e.g. locomotion)). Also, there is evidence from the literature in aging suggesting that reduction in motor unit firing rates seen with aging is more pronounced in the upper than lower extremities muscles (Dalton et al., 2009; Dalton et al., 2010). Thus, the purpose of this study was to determine if the time-course of the motoneuron AHP in the lower limb muscle was prolonged after stroke.

4.2 METHODS

4.2.1 Participants

Ten participants with stroke-related deficits volunteered to participate in this study after providing informed written consent. This was a sample of convenience, recruited

from a stroke support walking group, with the following exclusion criteria: i) inability to hold an isometric dorsiflexion torque steadily; ii) intolerance to needle insertion (e.g. previous fainting episodes); and iii) inability to communicate, understand, comply with the study requirements and provide informed consent. The Chedoke McMaster Stroke Assessment (CMSA) Impairment Inventory was used to evaluate the stage of motor recovery of the paretic limb. The ability to perform standardized movements was scored from 1 to 7 (1 = unable to perform and 7 = normal movement) (Gowland et al., 1993). The study conformed to the standards established by the Declaration of Helsinki and was approved by the local university ethics committee.

4.2.2 Apparatus and Signal Acquisition

Each participant sat in an adjustable chair so the knee and ankle joints of the tested limb were at 90° flexion and 15° plantarflexion, respectively. Straps were fastened across the waist and upper torso to minimize body movement while performing isometric voluntary contractions with the ankle muscles. A padded clamp placed superior to the flexed knee joint and a rigid heel cup secured the heel and forefoot in the custom-made apparatus and non-compliant straps prevented movement during isometric contractions of the ankle muscles. A two-directional force transducer (Model: FR5-300-B000; 1.880mV/V; Tovey Engineering, Inc., AZ, USA) mounted below the foot-plate recorded the isometric torque of the ankle dorsi- and plantar-flexors. The torque signal was amplified using a bridge amplifier (Bridge 8; World Precision Instruments, Florida, USA) and sampled at 500 Hz.

Voluntary muscle activity was recorded from the tibialis anterior (TA) and soleus (SOL) muscles with self-adhering bipolar surface EMG electrodes (Ag-AgCl, 8 mm

diameter; 2.5 cm center-to-center distance) placed over each muscle belly. The skin under each electrode was cleaned with 70% isopropyl alcohol prior to the placement of the electrodes. A strap electrode wrapped around the ankle served as a ground. The surface EMG signals were band-pass filtered between 10 Hz and 1,000 Hz and sampled at 2,500 Hz.

Intramuscular motor unit action potentials from the TA muscle were recorded using an insulated Teflon-coated stainless steel fine wire electrode. The electrode consisted of three 50μm diameter wires (California Fine Wire Company, CA, USA) that were bonded together and passed through a 25-gauge hypodermic needle for intramuscular insertion. A small hook was made at the terminal end of the fine wire electrode that held the electrode in place after the needle was removed. The exposed tips of two out of 3 wires formed a bipolar electrode that recorded extracellular motor unit action potentials from the TA muscle. The third wire allowed the freedom to configure the bipolar electrode differently, should the first configuration yield an undesirable signal. The signal was band-passed filtered (10-10,000 Hz), differentially amplified (CMMR > 90 dB at 60 Hz; input impedance 10 MΩ; Colbourne Electronics, PA, USA) and sampled at 25,000 Hz.

4.2.3 Experimental Protocol

Participants were asked to gradually increase the ankle dorsiflexor torque until a single TA motor unit could be identified with a dual window discriminator (BAK Electronics, Inc. MD, USA). The discriminator triggered on each motor unit action potential and a 1-s running average of motor unit discharge frequency was displayed on a computer monitor in front of the participant. Audio feedback of each motor unit discharge was provided with a speaker. Participants were asked to systematically vary

the discharge rate of the single motor unit between its minimal discharge rate and 10 Hz, according to a predetermined protocol (MacDonell et al., 2007). Briefly, initially participants sustained a 7-8 Hz discharge rate for 2-3 min, which was followed by a longer period (3-5 min) of discharge at the lowest tonic discharge rate for that motor unit. After that, the motor unit discharge rate was gradually increased to the higher frequencies (8-10 Hz) for 1 min. Participants gradually decreased the discharge rate again until the lowest stable motor unit discharge rate (5-6 Hz) was reached and this was maintained for the final 2 min of the protocol. Participants were instructed to transition between each of the discharge rate frequencies as slowly and smoothly as possible. Only smooth transitions were included in the data analysis. Short rest periods (~ 5-30 sec) were given when the participant found it difficult to control the discharge rate of the motor unit or when the recruitment of additional motor units interfered with the recordings. Following the rest period, the participant resumed the protocol at the discharge rate at which the protocol was ceased. Once enough data were recorded from each motor unit, the participant was asked to perform 2 maximal voluntary contractions (MVC) with the ankle dorsiflexors followed by 2 MVCs with the ankle plantarflexors. A one-minute rest period was provided between MVCs. This protocol was performed on the paretic and non-paretic sides on separate days.

4.2.4 Data Analysis

The torque and EMG signals were monitored on-line and stored off-line for processing using 16-bit data acquisition system (Power 1401 with Spike 2 v.6 software; Cambridge Electronic Design Ltd., Cambridge, UK) and Spike 2 v.6 software (Cambridge Electronic Design Ltd., Cambridge, UK).

A template-matching algorithm in the Spike 2 software package was used to classify the motor unit waveform from the intramuscular recordings based on the motor unit amplitude and shape characteristics. This was followed by careful manual inspection of the motor unit action potential train to ensure accuracy of the automatic motor unit classification. Any sections of data where motor unit action potentials could not be classified with 100% certainty were excluded from subsequent analysis.

With presently available techniques, it is not possible to make intracellular motor unit recordings in human muscle and since a bipolar EMG recording results in considerable cancellation of the signal as well as distortion of the action potential shape, the duration of the motoneuron AHP cannot be deduced from the extracellular motor unit EMG recordings. Thus, the estimation of the time-course of the motoneuron AHP was performed using the Interval Death Rate (IDR) transform based on the motor unit discharge interspike interval (ISI) histogram (Matthews, 1996). The validity and reliability of the IDR method have been established (Powers and Binder, 2000; MacDonell et al., 2007; Gossen et al., 2003). The IDR utilizes the ISIs of the tonically-discharging motor unit action potentials, also referred to as spikes, and represents the probability of the spike occurrence as a function of time since the last spike (for the details underlying the methodology refer to Matthews, 1996). Briefly, a 1-s running mean of the motor unit discharge rate (i.e. 500 ms prior and 500 ms following the ISI being sorted) was calculated and used to sort or "slice" each instantaneous ISI between 50 ms and 300 ms from the spike train into a distinct discharge frequency sub-population (Figure 4.1A and B). This way the ISIs were grouped together in sub-populations, based on the mean discharge rates. Each sub-population then was used to construct a histogram

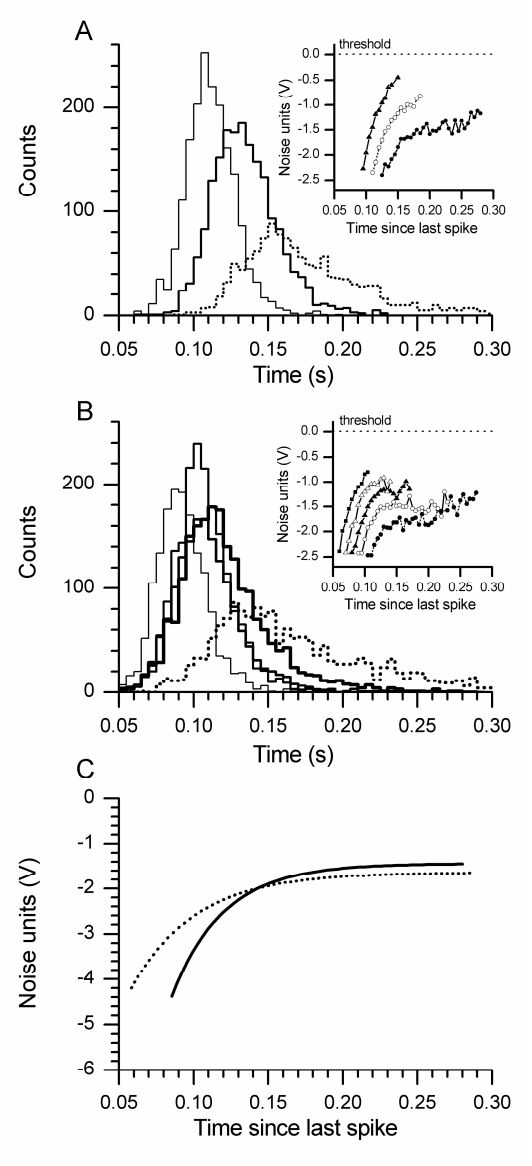

FIGURE 4.1 Representative AHP trajectories along with the ISI histograms are illustreated for the paretic and non-paretic sides

Panel **A** and **B** are representative examples of the interspike interval (ISI) sub-population histograms for the non-paretic (**A**) and paretic (**B**) sides with the inserts indicating the fast, intermediate and slow ISI sections of the histograms. The motoneuron AHP trajectories (**C**) on the paretic (dashed line) and non-paretic (solid line) were derived using the IDR analysis.

with 5 ms bin width that represented the distribution of ISIs about a given mean discharge rate. Each of these histograms was converted into a death rate plot and a transform was applied, which converted these plots into a trajectory that represented a segment of the final portion of the motoneuronal AHP. These trajectory segments were overlapped to form a compound trajectory that was fitted with a simple first order exponential curve, the time constant of which served as an index of the AHP time course (Figure 4.1 C).

Root mean square (RMS) of the surface EMG activity in the ankle dorsi- and plantarflexor muscles was measured for 0.5 s at the peak of each MVC. The activation of the TA muscle during the experimental protocol was evaluated by calculating the RMS of the surface EMG for the time periods when the indentified single motor unit was tonically discharging. Torque variability was assessed during the same time periods by applying a high pass filter with a –3dB low-frequency cut-off 0.75 Hz and calculating the standard deviation of the resultant signal.

4.2.5 Statistical Analysis

The statistical analysis was carried out using SPSS 16.0 for Windows. Paired Student's *t*-tests were used to compare the differences in the peak torque of the MVCs and maximal surface EMG recordings, whereas independent samples Student's *t*-tests were conducted to assess the difference in the ISI duration, AHP time course, torque variability and submaximal surface EMG recordings assessed during the motor unit discharge protocol between the paretic and non-paretic sides. Data in the text are presented as mean ± SD, unless otherwise stated. The level of significance was set at $P<0.05$.

TABLE 4.1 Demographic and clinical characteristics of participants

	Participants (N=10)
Age (yrs)	55.4 ± 6.6
Body Mass Index (kg/m^2)	26.6 ± 3.8
Sex	
Women	2
Men	8
Side of Hemiparesis	
Right	4
Left	6
Time Post-Stroke (months)	58.0 ± 42.1
Stage of Motor Recovery (out of 7)	
CMSA Leg score	5 (3-7)
CMSA Foot score	5 (2-7)

Note: Values are mean ± SD, number, or median (range).

Abbreviation: CMSA, Chedoke McMaster Stroke Assessment.

4.3 RESULTS

The demographic and clinical characteristics of the participants are presented in Table 4.1. Participants displayed mild to severe functional deficits on the paretic side, as measured by the CMSA leg and foot subscales. Four out of 10 participants had difficulties ambulating without an assistive device (e.g. cane or ankle brace). The maximal dorsiflexion torques were comparable between the paretic and non-paretic sides, whereas the MVC torques produced with the plantarflexors on the paretic side were significantly less than those produced on the non-paretic side (Table 4.2). The surface EMG activity in the TA and SOL muscles on the paretic side during the dorsi- and plantarflexor MVCs, respectively, was significantly less than on the non-paretic side (Table 4.2).

Seventeen TA motor units on the paretic side and 18 TA motor units on the non-paretic side were collected in 32 experiments from 10 participants with stroke. A sample of representative recordings collected on the paretic and non-paretic sides during the motor unit discharge protocol is shown in Figure 4.2. Participants maintained an average dorsiflexor torque of 8.2 ± 5.5% MVC (range: 1.0-18.4% MVC) on the paretic and 6.2 ± 3.0% MVC (range: 1.3-11.6% MVC) on the non-paretic side, which were not significantly different (P=0.18). Participants were able to maintain steady force production as demonstrated by a low torque variability of 0.08 Nm and 0.03 Nm for the paretic and non-paretic limb, respectively. During the motor unit discharge protocol the surface EMG TA activity expressed as a percentage of the maximal EMG (% EMGmax) was significantly greater on the paretic compared to the non-paretic side (20.4 ± 10.7 % vs. 8.3 ± 5.0 %, respectively, $P<0.05$).

TABLE 4.2 MVC peak torque, surface EMG, AHP time constant and ISI duration on the paretic and non-paretic sides

	Paretic	Non-Paretic
MVC Peak Torque (Nm)		
Dorsiflexion	18.6 ± 8.0	22.7 ± 7.6
Plantarflexion	31.6 ± 17.8*	44.7 ± 8.3
Surface EMGmax (mV)		
TA during Dorsiflexion	82.2 ± 22.9*	137.1 ± 46.5
SOL during Plantarflexion	53.0 ± 36.7*	109.6 ± 74.2
Afterhyperpolarization Time-Constant (ms)	40.0 ± 8.3*	35.1 ± 5.1
Interspike Interval Duration (ms)	145.2 ± 20.5*	131.3 ± 9.6

Abbreviations: MVC = Maximal Voluntary Contraction; EMGmax = Maximal Electromyography; TA = Tibialis Anterior; SOL = Soleus

* denotes significant difference from the non-paretic limb ($P<0.05$)

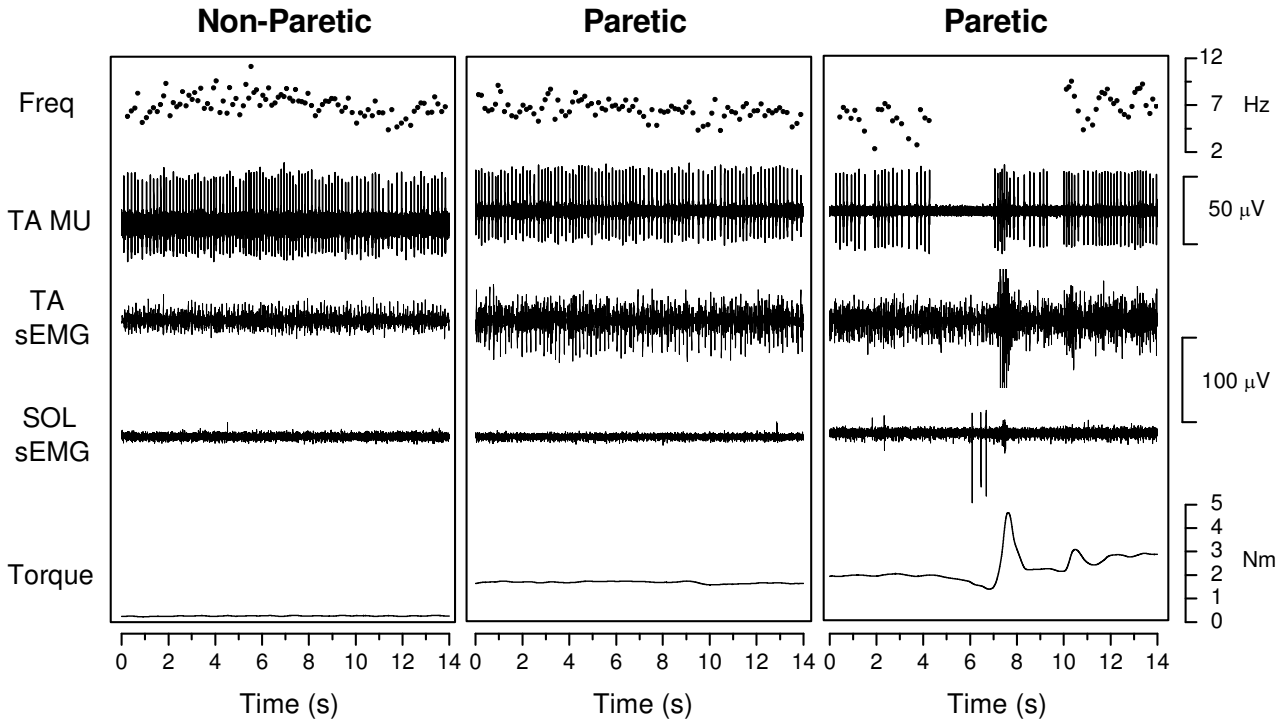

FIGURE 4.2 A sample of representative recordings collected on the non-paretic (left panel) and paretic (middle and right panel) sides from a single participant during the motor unit discharge protocol. The traces from top to bottom represent the instantaneous firing rate frequency (Freq); the intramuscular recording of motor unit action potential from the tibialis anterior (TA MU); surface electromyographic (sEMG) recording from the tibialis anterior (TA) and soleus (SOL); and torque of the ankle dorsiflexors. The right panel points out the difficulty of maintaining the steady firing rates of a MU on the paretic side of the participants with stroke.

For the estimation of the AHP time constants, each AHP compound trajectory involved transforming a minimum of three sliced histograms per motor unit. Representative AHP trajectories along with the ISI histograms are presented for the paretic and non-paretic sides in Figure 4.1. On average 5,411 ± 1,645 and 6,421 ± 1,601 ISIs were used on the paretic and non-paretic side, respectively, per analysis with a minimum of 1000 ISIs per histogram. The mean duration of the ISIs was significantly different between the sides (145.2 ± 20.5 ms and 131.3 ± 9.6 ms on the paretic and non-paretic side, respectively). The mean time constant of compound AHP trajectories was 40.0 ± 8.3 ms (range: 26.0 – 63.9 ms) on the paretic and 35.1 ± 5.1 ms (range: 26.8 – 49.0 ms) on the non-paretic side, which were statistically different (Table 4.2).

4.4 DISCUSSION

The main objective of the present study was to investigate the estimated time-course of the motoneuron AHP in the TA muscle following stroke. The AHP time-course was estimated using the IDR analysis based on the motor unit discharge ISI histogram (Matthews, 1996). According to the findings, the AHP time-course was significantly prolonged on the paretic side in comparison to the non-paretic side of the participants with stroke. This suggests that in addition to the post-stroke changes at the cortical level, leading to suboptimal output from the motor cortex, alterations at the spinal level, such as prolongation of the estimated AHP time-course, are also present after stroke, which may contribute to the heightened central activation failure reported in Chapter 3.

The consequences of cortical lesions are often evident in changes in motoneuron output such as reduction in the firing rates and abnormalities in the recruitment and

modulation of motoneuron discharge patterns (Frontera et al., 1997; Rosenfalck and Andreassen, 1980; Gemperline et al., 1995). The observed increase in the time-course of the AHP might contribute to commonly-reported reduction in the motor unit discharge rate in the paretic muscles of stroke survivors. These cumulative disturbances in the recruitment and discharge characteristics of motoneurons may contribute to a reduced voluntary muscle activation and decreased force-generation ability, often observed on the paretic side of stroke survivors (Newham and Hsiao, 2001; Riley and Bilodeau, 2002). The suboptimal functioning of the neuromuscular system may lead to the increased effort during voluntary activities leading to fatigue.

In the present study, the maximal dorsiflexion torque-generating capacity was comparable between the paretic and non-paretic sides of the participants with stroke; however, the maximal surface EMG signal recorded from the TA muscle was significantly reduced on the paretic side. Preferential atrophy and degeneration of Type II muscle fibers as well as reinnervation of muscle fibers by collateral sprouting from the remaining Type I motoneurons have been suggested by different authors as potential explanations (Dattola et al., 1993; Lukacs et al., 2008; Slager et al., 1985; Scelsi et al., 1984). This post-stroke muscle fiber rearrangement would result in a substantial reduction in the force output of each individual muscle fiber, which would make the TA a less powerful and slower conducting muscle (Milner-Brown and Stein, 1975). Also, taking into consideration that the overall dorsiflexion torque was comparable between the two sides of participants with stroke yet the maximal surface TA EMG signal was depressed suggests that the contribution of the TA muscle to the net isometric maximal torque of the ankle dorsiflexion was lower on the paretic side. This further points to a

compensatory strategy involving a greater contribution of the dorsiflexion synergist muscles (e.g. peroneus tertius, extensor hallucis and digitorum longus muscles) being used on the paretic side.

In the present study, we investigated post-stroke changes in the AHP time-course, which is an important intrinsic property of the motoneuron because it controls the discharge frequency and therefore modulates the mechanical output of the muscle (Kernell, 1965). The mean AHP time-course estimated on the non-paretic side in this investigation is consistent with the values reported in other investigations conducted in humans without any neurological deficits (MacDonell et al., 2008; MacDonell et al., 2007; Christie and Kamen, 2010). Thus, this result suggests that the intrinsic properties of the motoneurons on the non-paretic side remained unchanged following stroke. In contrast, the AHP time-course was significantly prolonged on the paretic side in comparison to the non-paretic side during the chronic stage post-stroke. This is in accordance with the finding reported recently by Liang and colleagues (2010), who also observed lengthening in the AHP duration in the biceps brachii muscle. In that study, the method proposed by Person and Kudina (1972) was used to estimate the duration of the AHP. In brief, this method is based on the observation that as the mean of the ISI increases, the variability of the ISI remains constant until a particular mean ISI duration and thereafter the variability increases substantially. The point at which the variability of the ISI increases markedly is taken as an indicator of the AHP duration. Although Powers and Binder (2000) established a correlation between the direct measurement of the AHP duration in cats' motoneurons and the estimated AHP duration based on the transition point, these authors also reported that the estimated AHP duration was shorter

and suggested that the method developed by Matthews (1996) was more accurate for estimating the AHP time-course.

Based on the observed prolongation of the AHP reported in the present investigation and by Liang and colleagues (2010), it is possible that the slowing of motor unit firing rates after stroke may, in part, be the result of a lengthened motoneuron AHP. The underlying physiological mechanism involved in the prolongation of the AHP time-course following stroke awaits further investigation, but stroke-induced motor unit remodeling towards a greater prevalence of Type I muscle fibers (Dattola et al., 1993; Hara et al., 2004; Lukacs, 2005; Lukacs et al., 2008), might lead to long-term alterations in intrinsic motoneuron properties as has been reported in animal work (Beaumont and Gardiner, 2002; Cormery et al., 2000).

There is an established positive association between the motoneurons' AHP time-course and the contractile properties of their innervated muscle fibers (Gossen et al., 2003; MacDonell et al., 2008; Zengel et al., 1985), therefore, it is reasonable to postulate that prolongation of the AHP time-course on the paretic side is suggestive of slowing in the contractile properties of the motor units following stroke, which has previously been reported by others (McComas et al., 1973; Frontera et al., 1997; Young and Mayer, 1982). Although future studies should investigate whether changes in the time-course of the AHP also result in changes in the contractile properties of the motor units following a stroke, hypothetically speaking, the slowing in the contractile properties of the motor units together with the reduced firing and modulation rates of motor units would result in increased motor unit recruitment in order to generate any given muscle force on the paretic side of the participants with stroke. In the present investigation significantly

increased surface EMG activity in the TA muscle during the motor unit discharge protocol was noted on the paretic side, while submaximal torque level was similar between the paretic and non-paretic sides and there was no apparent co-contraction of soleus muscle. Indeed, similar observations were reported by others (Gemperline et al., 1995; Tang and Rymer, 1981), who also reported an abnormally high level of surface EMG activity for a given muscle force. An increase in motor unit recruitment in the face of a reduction in firing rate may lead to increased perception of effort and self-reported fatigability reported in Chapter 3.

4.4.1 Summary

The lengthening of the AHP time-course in the TA muscle on the paretic side of stroke survivors is indicative of stroke-induced plasticity in the intrinsic properties of motoneurons. Although the specific underlying changes leading to the AHP prolongation as well as their functional significance remain to be elucidated in future studies, the changes noted support the notion that both spinal and cortical changes may be contributing to the neuromuscular fatigue noted in people after stroke.

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CHAPTER 5

GENERAL DISCUSSION AND CONCLUSION

5.1 GENERAL DISCUSSION

The overall objective of this thesis was to elaborate on the neuromuscular basis of fatigue post-stroke and its association with self-reported fatigue and functional mobility. The main findings of this thesis were that 1) the Community Balance and Mobility (CB&M) scale is a valid measure in chronic stroke survivors with mild to moderate deficits in functional balance and mobility; 2) stroke results in a shift of the origin of neuromuscular fatigue, making chronic stroke survivors more vulnerable to central fatigue; 3) stroke-induced prolongation of the estimated afterhyperpolarization (AHP) duration of the spinal motoneurons was observed on the paretic side of the participants with stroke; 4) the susceptibility to central fatigue was associated with higher levels of self-reported fatigability and decreased performance on the functional balance and mobility tasks. Alterations along the neuromuscular system in stroke survivors and post-stroke impairments in functional balance and mobility may have resulted in an increased level of effort required to perform regular activities of daily living, which might explain the self-reported perception of fatigue often reported by the participants with stroke.

Due to medical advances, the number of stroke survivors is increasing and many are reintegrating back to living in the community (Stroke Statistics, 2010). Therefore, the population of interest in this thesis was community-dwelling ambulatory stroke survivors who had mild to moderate neurological and functional deficits. The motor control deficits in the lower limb of the participants in this investigation were assessed with the

Chedoke McMaster Stroke Assessment leg and foot subscales (Gowland et al., 1993), whereas impairments in functional balance and mobility were evaluated using the CB&M scale (Howe et al., 2006). The validity of the CB&M in stroke population was established in the study reported in Chapter 2. The CB&M evaluates the performance of tasks that are commonly encountered during activities of daily living, including such challenging tasks as negotiating stairs or holding a laundry basket while going down the stairs. Thus, the score obtained on the CB&M is more comprehensive and representative of an individual's functional status in the community. The apparent ceiling effects of the Berg Balance Scale (BBS) and Timed-Up and Go (TUG) test made the CB&M scale superior in detecting improvements in balance and mobility over a 5-month period, which is an important quality in evaluating the recovery process and the effectiveness of physical therapy interventions. However, the observed trend towards the floor effect indicates that the CB&M scale is more suitable for individuals with higher functional capacity.

A subset of participants from the study reported in Chapter 2 volunteered in the study reported in Chapter 3. Despite good functional recovery following a stroke, these participants complained of the increased fatigability during performance of daily activities, which was assessed with the Fatigue Assessment Scale (Michielsen et al., 2003). Fatigue is a common complaint in persons with stroke, which interferes with the rehabilitation process and is associated with reduced participation in ambulatory activities of daily living and decreased quality of life (Glader et al., 2002; Michael et al., 2006). Depression, sleep disturbances, anxiety, chronic pain, age, co-morbidities, medications, degree of neurologic deficits and overall physical deconditioning following stroke are

some of the factors that have been associated with self-reported fatigue post-stroke (Glader et al., 2002; Ingles et al., 1999; Michael et al., 2006; Staub and Bogousslavsky, 2001; Tseng and Kluding, 2009). In addition to the aforementioned factors, the results from this thesis demonstrated that central fatigue is another factor contributing to fatigue post-stroke (Chapter 3). Central fatigue was elucidated with the use of the twitch interpolation and transcranial magnetic stimulation techniques to monitor changes in voluntary activation and in motor cortex output, respectively, before and after the standardized fatigue task. Based on the evidence reported in Chapter 3, a standardized fatigue task resulted in a failure of the central nervous system to activate muscles in the paretic limb (central fatigue), whereas the same fatiguing task resulted in a greater muscle fatigue (peripheral fatigue) in the non-paretic and control muscles. The significant increment in torque on the paretic side following the TMS pulse during the post-fatigue maximal voluntary contractions suggested that extra output was available from the motor cortex but it was not accessible with volitional maximal effort performed with the paretic side. This suggests that, in the affected hemisphere, the excitatory neural inputs from 'upstream' of the motor cortex were inadequate to overcome the fatigue-induced cortical inhibition, leading to suboptimal activation of corticomotor neurons and thus, may have played an important role in the genesis of central fatigue post-stroke. In addition to the inability to modulate cortical excitability in response to the increased cortical inhibition, any stroke-induced changes at the spinal level would contribute to the observed central activation failure.

The evidence that patterns of motoneuron firing rates and rate modulation are disturbed following a stroke has been accumulating for some time. For instance, it has

been reported that motoneuron discharge rates are abnormally low in the paretic muscles and increase in the contraction force is not always associated with increase in the motoneuron discharge rate (Frontera et al., 1997; Gemperline et al., 1995; Rosenfalck and Andreassen, 1980; Young and Mayer, 1982). These disturbances in motoneuron discharge characteristics have been suggested to be due to alterations in synaptic inputs to the motoneuron pool (Gemperline et al., 1995), but changes in the intrinsic properties of the motoneuron would also contribute to the abnormalities in the behavior of the spinal motoneurons. Thus, the aim of the study reported in Chapter 4 was to investigate the influence of stroke on the estimated time-course of the AHP, which is an intrinsic property of the motoneuron that is known to influence the motoneuron discharge rates (Kernell, 1965). The Interval Death Rate transform method was used to estimate the AHP time course (Matthews, 1996). According to these results, the estimated AHP time-course was significantly prolonged on the paretic side of the participants with stroke, which might partly explain the slowing in the motoneuron discharge rates and increased motoneuron recruitment that has been observed on the paretic side of stroke survivors (Gemperline et al., 1995; Tang and Rymer, 1981). Hypothetically, stroke-induced disturbances in the balance between the discharge and recruitment characteristics might lead to changes in the effort needed to drive a motoneuron pool, which, in turn, may contribute to the genesis of central fatigue noted on the paretic side of participants with stroke in the study reported in Chapter 3.

Susceptibility to central muscle activation failure following a standardized fatigue task was positively related with the self-reported fatigue and both of these measures were negatively associated with the performance of the 6-MWT. Although these correlations

do not imply a causal relationship, a possible connecting factor among these measures might be an enhanced perception of effort, which has been reported previously in people with motor strokes (Gandevia, 1982). It is believed that perception of effort is partly based upon afferent feedback from the periphery and on the magnitude of the centrally-generated motor command, which might be influenced by the activity in neural centers upstream of the motor cortex (Carson et al., 2002; Gandevia and McCloskey, 1977; Jones, 1995). This is supported by the findings obtained from healthy persons where fatigue-induced failure in central activation was associated with the increased rate of perceived exertion (Sogaard et al., 2006). The data in Chapter 3 reveal an increased perception of effort at 50% ET in the participants with stroke as well as an earlier termination of the fatigue task. Also, the participants with stroke in these experiments experienced impairments in motor control of the lower limbs and deficits in functional balance and mobility, which were strongly associated with the decreased performance on the 6-MWT. These stroke-induced disturbances along the neuromuscular system are known to contribute to the increased level of effort and energy expenditure during walking tasks as has been reported by others (Gersten and Orr, 1971; Macko et al., 2001; Milot et al., 2006) and might also result in the increased perception of fatigability often reported by persons with stroke.

The findings of this thesis are unique in several respects. First, the analytical techniques employed in this thesis (i.e. TMS, IDR analysis) were utilized in people with stroke under experimental procedures in which they have not been used previously. Second, this work is the first to demonstrate that stroke results in a shift of the origin of the neuromuscular fatigue predisposing people with stroke to increased central fatigue,

which is another factor contributing to the fatigue post-stroke. Finally, the findings reported in this thesis advance the understanding of a pathophysiological basis of fatigue post-stroke, which is essential for developing and guiding effective rehabilitation treatments.

5.2 LIMITATIONS AND FUTURE STUDIES

There are several limitations to this thesis. The community-dwelling participants with mild to moderate post-stroke neurological deficits who volunteered for the experiments performed in this thesis may have been at a higher functional level and have had fewer co-morbidities than the general chronic stroke population. Thus, this sample of convenience might not be representative of the entire spectrum of community-dwelling stroke survivors. However, the experiments required a level of motor control that allowed them to hold a moderate level of torque steadily at a target line or ability to control motor unit firing rates, as examples, so the generalizability of the findings are limited to participants post-stoke with similar characteristics to those described in this thesis.

According to the findings reported in Chapter 2, the CB&M is a valid measure to evaluate functional balance and mobility in ambulatory patients with mild to moderate neurological deficits secondary to stroke. However, the baseline assessment was conducted at 3 months from the onset of stroke, thus substantial recovery in balance and mobility could have occurred during the initial 90 days. Therefore, the usefulness of the CB&M for patients earlier post-stroke needs to be examined in the future studies. In addition, further studies are required to determine the specific cut points on the BBS and

TUG measures at which the CB&M would be a preferred clinical measure to evaluate functional balance and mobility after stroke.

Task-specificity (e.g. the intensity, duration and type of contraction) as well as fiber type composition of an active muscle play a critical role in the development of fatigue (Enoka and Stuart, 1992). The neuromuscular fatigue task in this thesis consisted of a sustained isometric voluntary contraction (30% MVC); sustained contractions for several minutes are not representative of the type of muscle contractions performed during typical activities of daily living. Intermittent fatiguing contractions were not used because during the pilot work it was observed that the participants with stroke required extra time to stabilize the torque at the target level, especially on the paretic side, which would make it impossible to standardize the fatigue protocol. Since one of the main objectives of this thesis was to examine stroke-induced changes in neuromuscular mechanisms underlying fatigue, it was critical to collect data in a standardized manner.

The TA muscle was chosen in this thesis because it is a primary dorsiflexor muscle of the ankle, which is involved in postural and locomotor activities, and is easily accessible for surface and intramuscular EMG recordings. Although the surface EMG and motor unit signals collected during dorsiflexion were from the TA muscle, similar findings could be expected for other lower limb muscles (e.g. soleus) that are also involved in postural and locomotor activities. However, this should be confirmed in the future studies.

The main limitation of the IDR analysis for estimation of the AHP time-course is its requirement for large numbers of motor unit action potentials. This requirement makes the IDR analysis easiest to apply during low force contractions (<30% MVC) to avoid

fatigue. Thus, the highest threshold motor units of the TA muscle were not sampled. The generalizability of the AHP prolongation to motor units other than low threshold ones is limited. However, considering that the majority of everyday activities are performed at low forces, this should be a relatively minor concern.

In healthy persons, the gradual failure in central activation, measured during MVCs that were incorporated into the fatigue protocol, was associated with the progressive increase in the rate of perceived exertion (Sogaard et al., 2006). Although this relationship has not been studied in the present investigation due to challenges in designing an experimental protocol that would allow to collect data in a standardized manner, it is possible that the stroke-related disturbances along the motor pathway leading to increased central activation failure might also result in enhanced perception of effort. Taking into consideration that self-reported fatigue is based on the individual perception of fatigability during the performance of daily activities, it is important to investigate the potential associations among central activation failure, rate of perceived exertion and self-reported fatigue in persons with stroke.

The findings reported in Chapter 3 and 4 shed some light on the underlying pathophysiology of fatigue post-stroke, which is essential for developing and guiding effective rehabilitation treatments. Numerous neurological changes (i.e. abnormal brain activation patterns, impaired central neural drive, disturbances in motor unit discharge rate and recruitment characteristics) are observed following stroke. These stroke-induced neuromuscular impairments can lead to muscle weakness and increased energy demand (Gersten and Orr, 1971; Milot et al., 2006) that can limit performance of activities of daily living and can result in an increased sense of effort and fatigability. Therefore, any

rehabilitation interventions that facilitate cortical neuroplasticity and restore central drive and spinal excitability, as well as increase muscle strength and endurance might be potential strategies to reducing fatigue post-stroke. These are important avenues for future research in the field of fatigue post-stroke.

5.3 CONCLUSION

Chronic stroke survivors with mild to moderate neurological and functional balance and mobility impairments reported increased fatigability during the activities of daily living. Also, central fatigue, evident by central activation failure, was observed to a greater extent on the paretic side of the participants with stroke and might be a result of stroke-induced alterations in the cortical (i.e. reduced MEP amplitude) and spinal (i.e. prolongation of the AHP time-course) sites. This increased susceptibility to central fatigue might lead to an increased perception of effort that could influence negatively the performance of balance and mobility tasks and could contribute to the general complaint of fatigue experienced by people with stroke.

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APPENDIX A

ETHICS APPROVAL

STUDY 1

Office of Research Ethics

The University of Western Ontario
Room 00045 Dental Sciences Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
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Western

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. S.J. Garland

Review Number: 12585 **Revision Number:**

Protocol Title: Client-centered 'tune-ups': do they enhance physical capacity, mobility function and community reintegration in stroke survivors?

Department and Institution: Physical Therapy, University of Western Ontario

Sponsor: HEART AND STROKE FOUNDATION

Ethics Approval Date: September 22, 2006 **Expiry Date:** August 31, 2009

Documents Reviewed and Approved: UWO Protocol, Experimental Letter of information/consent, Control Letter of information/consent and Debriefing letter

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted full board approval to the above named research study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

This approval shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;

b) all adverse and unexpected experiences or events that are both serious and unexpected;

c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. John W. McDonald

Deputy Chair: Susan Hoddinott

Ethics Officer to Contact for Further Information		
☑ Janice Sutherland (jsutherl@uwo.ca)	☐ Jennifer McEwen (jmcewen4@uwo.ca)	☐ Denise Grafton (dgrafton@uwo.ca)

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Office of Research Ethics

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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. S.J. Garland
Review Number: 15970 **Review Level:** Full Board
Review Date: February 24, 2009
Protocol Title: The origins of fatigue post-stroke
Department and Institution: Physical Therapy, University of Western Ontario
Sponsor:
Ethics Approval Date: April 3, 2009 **Expiry Date:** June 30, 2010
Documents Reviewed and Approved: UWO Protocol and Letter of Information and Consent Form - Stroke Patient dated 03/23/2009 and Letter of Information and Consent Form - Healthy Individuals dated 3/23/2009
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert

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The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue,
Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF FULL BOARD APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION / DEPARTMENT:	UBC CREB NUMBER:
Jayne Garland	UBC/Medicine, Faculty of	H09-00999

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Svetlana Knorr
Tania Ivanova

SPONSORING AGENCIES:
- Natural Sciences and Engineering Research Council of Canada (NSERC) - "Plasticity of Human Motoneurone Properties"

PROJECT TITLE:
Plasticity of Human Motor Neuron Properties

THE CURRENT UBC CREB APPROVAL FOR THIS STUDY EXPIRES: November 10, 2010

The full UBC Clinical Research Ethics Board has reviewed the above described research project, including associated documentation noted below, and finds the research project acceptable on ethical grounds for research involving human subjects and hereby grants approval.

REB FULL BOARD MEETING REVIEW DATE:
November 10, 2009

DOCUMENTS INCLUDED IN THIS APPROVAL:

Document Name	Version	Date	DATE DOCUMENTS APPROVED:
Protocol:			
Research Protocol	N/A	December 16, 2009	
NSERC grant	N/A	October 19, 2005	
Consent Forms:			
Motoneuron AHP UBC consent form	N/A	December 10, 2009	
Questionnaire, Questionnaire Cover Letter, Tests:			
Chedoke McMaster Stroke Assessment	N/A	January 1, 1994	**December 17, 2009**
Other Documents:			
Western consent form	N/A	January 5, 2005	
Western ethics certificate	N/A	January 5, 2005	
Western ethics	N/A	November 3, 2004	
Western ethics certificate revised	N/A	November 12, 2008	

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.

2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices. *3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.*
The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.
Approval of the Clinical Research Ethics Board by one of: Dr. Peter Loewen, Chair Dr. James McCormack, Associate Chair

APPENDIX B

RIGHTS AND REPRINT PERMISSIONS

STUDY 1

ELSEVIER ORDER DETAILS

Aug 25, 2011

Order Number	500625886
Order Date	Aug 25, 2011
Licensed content publisher	Elsevier
Licensed content publication	Archives of Physical Medicine and Rehabilitation
Licensed content title	Validity of the Community Balance and Mobility Scale in Community-Dwelling Persons After Stroke
Licensed content author	Svetlana Knorr,Brenda Brouwer,S. Jayne Garland
Licensed content date	June 2010
Licensed content volume number	91
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End Page	896
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Expected completion date	Nov 2011
Estimated size (number of pages)	150
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STUDY 2

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APPENDIX C

COMMUNITY BALANCE AND MOBILITY SCALE

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

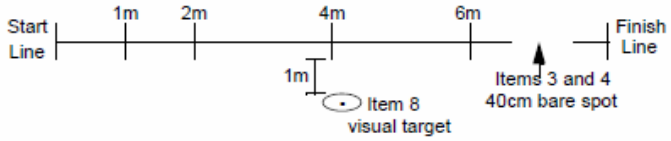
Patient ID Number ☐☐ ☐☐☐☐ (Investigator, Patient #)

Patient Initials ☐☐ (F L)

Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Community Balance & Mobility Scale (Page 1)

Test Set Up:



1. Unilateral Stance

Instructions to patient: Stand on your right/left leg and hold for as long as you can up to 45 seconds. Look straight ahead.
Instructions to therapist: Begin timing as soon as the patient's foot leaves the ground. Do not allow for the patient to brace the elevated leg against the supporting leg. Stop timing if stance foot moves from starting position or opposite foot touches ground.

Right limb	**Left** limb
☐0 45 seconds, steady and coordinated	☐0 45 seconds, steady and coordinated
☐1 ≥ 20 seconds	☐1 ≥ 20 seconds
☐2 10 to 20 seconds	☐2 10 to 20 seconds
☐3 4.5 to 9.99 seconds	☐3 4.5 to 9.99 seconds
☐4 2 to 4.49 seconds	☐4 2 to 4.49 seconds
☐5 Unable to sustain	☐5 Unable to sustain

2. Tandem Walking

Instructions to patient: Walk forward on the line, heel touching toes. Keep your feet pointing straight ahead. Look ahead down the track, not at your feet. I will tell you when to stop.
Instructions to therapist: Position the patient with one foot positioned on the 8m track. If able, allow the patient to take a maximum of 7 steps for which the heel is on the line and the heel-toe distance is ≤ 8 cm (3 inches).

☐0 Unable to complete 1 step on the line independently, i.e. requires assistance, upper extremity support, or takes a protective step

☐1 Able to complete 1 step independently, acceptable to toe out

☐2 Able to complete 2 to 3 consecutive steps on the line, acceptable to toe out

☐3 Able to complete > 3 consecutive steps, acceptable to toe out

} heel-to-toe distance < 3 inches

☐4 Able to complete > 3 consecutive steps, in good alignment (heel-toe contact, feet straight on the line, no toeing out), but demonstrates excessive use of equilibrium reactions

☐5 Able to complete 7 consecutive steps, in good alignment (heel-toe contact, feet straight on the line, no toeing out), and in a steady & coordinated manner. Excessive use of equilibrium reactions or looking at feet is **not** acceptable.

Version: September 23, 2008

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

Patient ID Number ☐☐ ☐☐☐☐ Patient Initials ☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Investigator Patient # F L DD MM YYYY

Community Balance & Mobility Scale (Page 2)

3. 180 degree Tandem Pivot

Starting position: Tandem stance on bare spot in track - aligned heel to toe, no toeing out, arms at sides, head in neutral position and eyes forward. Patient allowed to choose either foot in front and may use assistance or upper extremity support to achieve, but not sustain, tandem stance.

Instructions to patient: Lifting your heels just a little, pivot all the way around to face the opposite direction without without stopping and maintain your balance in this position.

Instructions to therapist: When right foot is in front in tandem position, patient to turn towards left. When left foot is in front in tandem position, patient to turn towards right. Therapist may assist patient to assume starting position. Test is over when patient puts heels down or steps out of position.

☐$_0$ Unable to sustain tandem stance independently i.e. requires assistance or upper extremity support

☐$_1$ Sustains tandem stance but unable to unweight heels and/or initiate pivot

☐$_2$ Initiates pivot but unable to complete 180 degree turn

☐$_3$ Completes 180 degree turn but discontinues pivot (e.g. pauses on toes)

☐$_4$ Completes 180 degree turn in a continuous motion but unable sustain reversed position (**Not acceptable:** heel -toe distance > 8 cm (3 inches))

☐$_5$ Completes 180 degree turn in a continuous motion and sustains reversed position (acceptable to have feet slightly angled out in reversed position). **Not acceptable:** heel-toe distance > 8cm (3 inches); excessive use of equilibrium reactions.

4. Lateral Foot Scooting

Starting position: Patient to stand on the line beside the bare spot in the track in unilateral stance on right/left foot, arms at sides. Foot is perpendicular to the track.

Instructions to patient: Stand on your right/left leg and move sideways by alternately pivoting on your heel and toe. Keep pivoting straight across until you touch the line and maintain your balance in this position.

Instructions to therapist: The patient moves laterally along the length of the bare spot (40 cm). For the grading, one lateral pivot is defined as either pivoting on heel, moving toes laterally OR pivoting on toes, moving heel laterally.

Right limb	**Left** limb
☐$_0$ Unable to sustain unilateral stance independently	☐$_0$ Unable to sustain unilateral stance independently
☐$_1$ Able to perform 1 lateral pivot in any fashion	☐$_1$ Able to perform 1 lateral pivot in any fashion
☐$_2$ Able to perform 2 lateral pivots in any fashion	☐$_2$ Able to perform 2 lateral pivots in any fashion
☐$_3$ Able to perform ≥ 3 pivots but < 40 cm	☐$_3$ Able to perform ≥ 3 pivots but < 40 cm
☐$_4$ Able to complete 40 cm in any fashion acceptable to be unable to control final position	☐$_4$ Able to complete 40 cm in any fashion acceptable to be unable to control final position
☐$_5$ Able to complete 40 cm continuous, rhythmical motion demonstrating a controlled stop briefly maintaining unilateral stance. **Not acceptable** to pause while pivoting to regain balance, veer from a straight line, excessive use of equilibrium reactions, or excessive trunk rotation while pivoting	☐$_5$ Able to complete 40 cm continuous, rhythmical motion demonstrating a controlled stop briefly maintaining unilateral stance. **Not acceptable** to pause while pivoting to regain balance, veer from a straight line, excessive use of equilibrium reactions, or excessive trunk rotation while pivoting

Version: September 23, 2008

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

Patient ID Number ☐☐ ☐☐☐☐ (Investigator / Patient #) Patient Initials ☐☐ (F L) Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Community Balance & Mobility Scale (Page 3)

5. Hopping Forward

Starting position: Unilateral stance on right/left with entire foot on the track. Heel placed on inside edge of starting line.

Instructions to patient: Stand on your right/left foot. Hop twice straight along this line to pass the 1 m mark with your heel. Maintain your balance on your right/left leg at the finish.

Instructions to therapist: It is recommended that the therapist assess safety prior to commencing task by having the patient hop in one spot. Patient is successful in completing 1 m when the heel of the foot is touching or beyond the 1 m line.

Right limb	**Left** limb
☐$_0$ Unable	☐$_0$ Unable
☐$_1$ 1 to 2 hops, uncontrolled	☐$_1$ 1 to 2 hops, uncontrolled
☐$_2$ 2 hops, controlled but unable to complete 1 meter	☐$_2$ 2 hops, controlled but unable to complete 1 meter
☐$_3$ 1 meter in 2 hops but unable to sustain landing	☐$_3$ 1 meter in 2 hops but unable to sustain landing
☐$_4$ 1 meter in 2 hops but difficulty controlling landing (hops or pivots)	☐$_4$ 1 meter in 2 hops but difficulty controlling landing (hops or pivots)
☐$_5$ 1 meter in 2 hops, coordinated with stable landing	☐$_5$ 1 meter in 2 hops, coordinated with stable landing

6. Crouch and Walk

Starting position: Bean bag is placed to right or left side of 2m mark on the track according to which hand the patient will use to pick it up.

Instructions to patient: Walk forward and, without stopping, bend to pick up the bean bag and then continue walking down the line.

Instructions to therapist: This task is performed using only half of the track. Start timing when the patient's foot leaves the ground. Stop timing when both feet cross the 4m line.

☐$_0$ Unable to crouch (descend) to pick up bean bag independently

☐$_1$ Able to descend but unable to maintain crouch to pick up bean bag or rise to stand independently

☐$_2$ Descends and rises but hesitates, unable to maintain forward momentum

☐$_3$ Crouches and walks in continuous motion, time $\leq$ 8 seconds and demonstrates protective step at any time

☐$_4$ Crouches and walks in continuous motion, time $\leq$ 8 seconds and/or uses excessive equilibrium reaction to maintain balance. **Not acceptable** to veer off course

☐$_5$ Crouches and walks in continuous and rhythmical motion, time $\leq$ 4 seconds. **Not acceptable** to veer off course or to use excessive equilibrium reactions.

Version: September 23, 2008

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

Patient ID Number ☐☐ ☐☐☐☐ (Investigator / Patient #) Patient Initials ☐☐ (F L) Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Community Balance & Mobility Scale (Page 4)

7. Lateral Dodging

Starting position: Starting at the 2m mark with feet perpendicular to the track. The toes of both feet should cover the track.

Instructions to patient: Move sideways along the line by repeatedly crossing one foot in front of and over the other. Place part of your foot on the line with every step. Reverse direction whenever I call "Change!" Do this as fast as you can, yet at a speed that you feel safe.

Instructions to therapist: Patient moves laterally back and forth along the line, between the 2 m and 4 m marks by repetatively crossing one foot over and in front of the other. It is acceptable for the patient to look at the line to monitor foot placement. Begin timing as soon as the patient's foot leaves the ground. To cue the patient to change direction, call out "change!" when one foot passess the 2 and 4 m marks. The patient should believe direction changes are **random**. One cross-over = crossing one leg over to land beside the other and returning the back leg to an uncrossed position. One cycle = the patient completes cross-overs for a 2 m distance and return. The test requires that the patient perform 2 of these cycles (a total of 8 m).

☐$_0$ Unable to perform 1 cross-over in both directions without loss of balance or use of support

☐$_1$ 1 cross-over in both directions without use of support, but unable to contact the line with part of the foot

☐$_2$ 1 or more cycles to and from the 2m mark, but unable to contact line with every step

☐$_3$ 2 cycles in any fashion (to the 2m line and back twice) and one part of the foot contacts line during every step

☐$_4$ 2 cycles in any fashion as descirbed in the response above (3) in 12 to 15 seconds

☐$_5$ 2 cycles in <12 seconds in a continuous, rhythmical fashion with coordinated direction changes immediately after verbal cue

8. Walking & Looking

Instructions to patient: Walk at your usual pace to the end of the line. I will tell you when to look at the circle. Keep looking at the circle while you walk past it. I will then tell you when to look straight ahead again. Try not to veer off course while you walk.

Instructions to therapist: Start timing when the patient's foot leaves the ground. Stop timing when both feet cross the 8m finish line. At the 2m mark, ask the patient to "Look at the circle". Cue the patient to "Keep looking at the circle' as they look back over their shoulder until they reach the 6m mark. At the 6m mark, ask the patient to "Look straight ahead and continue walking until the end of the line". Stand beside the target so that you can assess the patient's ability to maintain fixation. It may be necessary to have another person present to walk along side the patient to ensure safety. It is acceptable to continue to remind the patient of where they should be looking at each segment. To score in the opposite direction, repeat the task starting from the opposite end of the line.

Target to the **right**

☐$_0$ Unable to walk and look e.g. stops

☐$_1$ Performs but loses visual fixation at or before 4 m mark

☐$_2$ Performs but loses visual fixation after 4 m mark

☐$_3$ Performs and maintains visual fixation between 2 to 6 m mark but protective step

☐$_4$ Performs and maintains visual fixation between 2 to 6 m mark but veers

☐$_5$ Performs, straight path, steady and coordinated $\leq$ 7 seconds

Target to the **left**

☐$_0$ Unable to walk and look e.g. stops

☐$_1$ Performs but loses visual fixation at or before 4 m mark

☐$_2$ Performs but loses visual fixation after 4 m mark

☐$_3$ Performs and maintains visual fixation between 2 to 6 m mark but protective step

☐$_4$ Performs and maintains visual fixation between 2 to 6 m mark but veers

☐$_5$ Performs, straight path, steady and coordinated $\leq$ 7 seconds

Version: September 23, 2008

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

Patient ID Number ☐☐ ☐☐☐☐ (Investigator / Patient #)

Patient Initials ☐☐ (F L)

Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Community Balance & Mobility Scale (Page 5)

9. Running with Controlled Stop

Instructions to patient: Run as fast as you can to the end of the track. Stop abruptly with both feet on the finish line and hold this position.

Instructions to therapist: Begin timing when initial foot leaves ground. Stop timing when both feet reach the finish line It does not matter whether the feet land consecutively or simultaneously on the finish line.

☐ 0 Unable to run (with both feet off ground for a brief instant), demonstrates fast walking or leaping from foot to foot

☐ 1 Runs in any fashion, time > 5 seconds

☐ 2 Runs in any fashion, time > 3 seconds, but ≤ 5 seconds, unable to control stop (uses protective step or excessive equilibrium reactions

☐ 3 Runs, time > 3 seconds, but ≤ 5 seconds, with controlled stop, both feet on line. **Not acceptable** to use excessive equilibrium reactions

☐ 4 Runs in any fashion, time ≤ 3 seconds, unable to control stop with both feet on the line (uses protective step(s) or excessive equilibrium reactions

☐ 5 Runs in a coordinated, rhythmical manner and performs a controlled stop with both feet on the line, ≤ 3 seconds **Not acceptable** to use excessive equilibrium reactions.

10. Forward to Backward Walking

Instructions to patient: Walk forward to the halfway mark, turn around and continue to walk backward until I say, "Stop". Try not to veer off course. Walk as quickly as you can, yet at a speed that you feel safe.

Instructions to therapist: Start timing when the patient's foot leaves the ground. Stop timing when both feet cross the 8m finish line. The patient is to turn at the 4m mark. It is acceptable for the patient to turn in any direction. Count the number of steps required to turn 180 degrees. **Note:** The first step in the turn is angled away from the forward trajectory. The last step in the turn completes the 180 degree turn and is oriented towards the starting line, initiating backwards walking. It is also acceptable to pivot on one foot rather than stepping around.

☐ 0 Unable to complete task (requires assistance or upper extremity support)

☐ 1 Performs but must stop to regain balance at any time during the task

☐ 2 Performs with reduced speed, time > 11 seconds and/or requires 4 or more steps to turn

☐ 3 Performs in ≤ 11 seconds and/or veers from straight path during backwards walking

☐ 4 Able to complete task in a continuous motion, ≤ 9 seconds and/or uses protective step(s) during or just after turn

☐ 5 Able to complete task in a continuous motion with brisk speed, ≤ 7 seconds, maintains straight path throughout

Version: September 23, 2008

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

Patient ID Number ☐☐ ☐☐☐☐ Patient Initials ☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Investigator Patient # F L DD MM YYYY

Community Balance & Mobility Scale (Page 6)

11. Walk, Look & Carry

Starting Position: Start patient at the end of the track carrying a plastic grocery bag in each hand by the handle, with a 7.5 pound (3.4 kg) weight inside each bag.
Instructions to patient: Walk at your usual pace to the end of the line carrying the grocery bags. I will tell you when to look at the circle. Keep looking at it while you walk past it. I will then tell you when to look straight ahead again. Try not to veer off course while you walk.
Instructions to therapist: Start timing when the patient's foot leaves the ground. Stop timing when both feet cross the 8m finish line. At the 2m mark, ask the patient to "Look at the circle". Cue the patient to "Keep looking at the circle' as they look back over their shoulder until they reach the 6m mark. At the 6m mark, ask the patient to "Look straight ahead and continue walking until the end of the line". Stand beside the target so that you can assess the patient's ability to maintain fixation. It may be necessary to have another person present to walk along side the patient to ensure safety. It is acceptable to continue to remind the patient of where they should be looking at each segment. To score in the opposite direction, repeat the task starting from the opposite end of the line.
Note: Patient to only carry one grocery bag if unable to perform bilaterally due to motor control problems of the upper extremity. Indicate that the patient was only able to carry one bag.

Target to the **right**

☐0 Unable to walk and look e.g. has to stop to look, or requires assistance or upper extremity support at any point during the test

☐1 Able to continuously walk and initiate looking, but loses visual fixation on circle at or before 4m mark

☐2 Able to continuously walk and look, but loses visual fixation on circle after 4 m mark i.e. while looking back over the shoulder

☐3 Able to continuously walk and fixate upon the circle between the 2m and 6m mark, but demonstrates a protective step. Acceptable for patient to demonstrate inconsistent or reduced speed.

☐4 Able to continuously walk and fixate upon the circle between the 2m and 6m mark but veers off course. Acceptable for patient to demonstrate inconsistent or reduced speed.

☐5 Able to continuously walk and fixate upone circle between 2m and 6m mark, maintains a straight path, in a steady & coordinated manner, ≤ 7 seconds **Not acceptable** to walk at an inconsistent or reduced speed or to be looking down at feet.

Target to the **left**

☐0 Unable to walk and look e.g. has to stop to look, or requires assistance or upper extremity support at any point during the test

☐1 Able to continuously walk and initiate looking, but loses visual fixation on circle at or before 4m mark

☐2 Able to continuously walk and look, but loses visual fixation on circle after 4 m mark i.e. while looking back over the shoulder

☐3 Able to continuously walk and fixate upon the circle between the 2m and 6m mark, but demonstrates a protective step. Acceptable for patient to demonstrate inconsistent or reduced speed.

☐4 Able to continuously walk and fixate upon the circle between the 2m and 6m mark but veers off course. Acceptable for patient to demonstrate inconsistent or reduced speed.

☐5 Able to continuously walk and fixate upone circle between 2m and 6m mark, maintains a straight path, in a steady & coordinated manner, ≤ 7 seconds **Not acceptable** to walk at an inconsistent or reduced speed or to be looking down at feet.

Version: September 23, 2008

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

Patient ID Number ☐☐ ☐☐☐☐ Patient Initials ☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Investigator Patient # F L DD MM YYYY

Community Balance & Mobility Scale (Page 7)

12. Descending Stairs

Starting Position: Quiet standing at top of staircase (minimum 8 steps). Depending on patient's skill on the stairs, may begin by descending from the first or third step at the bottom of the flight.
Instructions to patients: Walk down the stairs. Try not to use the railing.
Instructions to therapist: Depending on patient's skill on the stairs, may use a cane as in level 1 or level 2.

*Bonus: If the patient achieves a score of 4 or 5, and if deemed safe by the rating therapist, the patient is asked to repeat the task and descend stairs while carrying a weighted basket (laundry basket with 2 pound weight in it). It is acceptable for the patient to intermittently look at the steps.
Add one bonus point to the score of 4 or 5 if the patient can descend the stairs safely while carrying the basket without the need for continuous monitoring of their foot placement. If the patient is unable to hold the basket with one or both arms, they are not eligible for the bonus point.
Instructions to patient: Hold this basket, keeping it in front of you at waist level. Walk down the stairs and try not to look at your feet. You may look at the steps once in a while for safety.

☐$_0$ Unable to step down 1 step, or requires railing or assistance

☐$_1$ Able to step down 1 step with/without cane } no railing

☐$_2$ Able to step down 3 steps with/without cane, any pattern } no railing

☐$_3$ 3 steps reciprocal or full flight in step-to pattern } no cane, no railing

☐$_4$ Full flight reciprocal, awkward, uncoordinated* } no cane, no railing

☐$_5$ Full flight reciprocal, rhythmical and coordinated* } no cane, no railing

☐$_{+1}$ *BONUS for carrying basket

Version: September 23, 2008

Heart & Stroke Trial

☐ Baseline ☐ 6 mo ☐ 12 mo

Patient ID Number ☐☐ ☐☐☐☐ (Investigator / Patient #) Patient Initials ☐☐ (F L) Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Community Balance & Mobility Scale (Page 8)

13. Step Ups X 1 Step

Starting Position: In front of step at bottom of stairs

Instructions to patient: i) Step up and down on this step as quickly as you can until I say "Stop". The pattern is right-left up and right-left down. Try not to look at your feet. ii) Step up and down on this step as quickly as you can until I say "Stop". The pattern is left-right up and left-right down. Try not to look at your feet.

Instructions to therapist: Start timing when the patient's foot leaves the ground. Stop timing after the completion of 5 cycles. A cycle is one complete step up and one complete step down.

Right

☐ 0 Unable to step up, requires assistance or railing

☐ 1 Steps up, requires assistance or railing to descend

☐ 2 Steps up and down (1 cycle)

☐ 3 Completes 5 cycles, acceptable to demonstrate incoordination or inconsistent speed/rhythm

☐ 4 Completes 5 cycles in > 6 seconds but < 10 seconds, acceptable to demonstrate incoordination or inconsistent speed/rhythm

☐ 5 Completes 5 cycles in ≤ 6 seconds, rhythmical and coordinated manner

} unacceptable to look at feet

Left

☐ 0 Unable to step up, requires assistance or railing

☐ 1 Steps up, requires assistance or railing to descend

☐ 2 Steps up and down (1 cycle)

☐ 3 Completes 5 cycles

☐ 4 Completes 5 cycles in > 6 seconds but < 10 seconds

☐ 5 Completes 5 cycles in ≤ 6 seconds, rhythmical

} unacceptable to look at feet

Version: September 23, 2008

APPENDIX D

BERG BALANCE SCALE

Heart & Stroke Trial

☐ Consent ☐ Baseline ☐ 3 mo ☐ 6 mo ☐ 6+2 mo ☐ 9 mo ☐ 12 mo ☐ 12 +2 mo ☐ 15 mo

Patient ID Number ☐☐ ☐☐☐☐ Patient Initials ☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Investigator Patient # F L DD MM YYYY

Berg Balance Scale (Page 1)

1. Sitting to Standing

Instruction: Please stand up. Try not to use your hands for support
Grading: Please mark the lowest category which applies

- ☐ 4 Able to stand, no hands and stabilize independently
- ☐ 3 Able to stand independently using hands
- ☐ 2 Able to stand using hands after several tries
- ☐ 1 Needs minimal assist stand or stabilize
- ☐ 0 Needs moderate or maximal assist to stand

2. Standing Unsupported

Instruction: Stand for two minutes without holding.
Grading: Please mark the lowest category which applies.

- ☐ 4 Able to stand safely 2 minutes
- ☐ 3 Able to stand 2 minutes with supervision
- ☐ 2 Able to stand 30 seconds unsupported
- ☐ 1 Needs several tries to stand 30 seconds unsupported
- ☐ 0 Unable to stand 30 seconds unassisted

*If subject is able to stand 2 minutes safely, score full makes for sitting unsupported

3. Sitting Unsupported Feet on Floor

Instruction: Sit with arms folded for two minutes.
Grading: Please mark the lowest category which applies

- ☐ 4 Able to sit safely and securely 2 minutes
- ☐ 3 Able to sit 2 minutes under supervision
- ☐ 2 Able to sit 30 seconds
- ☐ 1 Able to sit 10 seconds
- ☐ 0 Unable to sit without support 20 seconds

Version: September 23, 2008

Heart & Stroke Trial

☐ Consent ☐ Baseline ☐ 3 mo ☐ 6 mo ☐ 6+2 mo ☐ 9 mo ☐ 12 mo ☐ 12 +2 mo ☐ 15 mo

Patient ID Number ☐☐ ☐☐☐☐ (Investigator / Patient #)

Patient Initials ☐☐ (F L)

Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Berg Balance Scale (Page 2)

4. Standing to Sitting

Instruction: Please sit down
Grading: Please mark the lowest category which applies

- ☐ 4 Sits safely with minimal use of hands
- ☐ 3 Controls descent by using hands
- ☐ 2 Uses back of legs against chair to control descent
- ☐ 1 Sits independently but has uncontrolled descent
- ☐ 0 Needs assistance to sit

5. Transfers

Instruction: Please move from chair to bed and back again. One way toward a seat with armrests and one way toward a seat without armrests.

Grading: Please mark the lowest category which applies.

- ☐ 4 Able to transfer safely with minor use of hands
- ☐ 3 Able to transfer safely definite need of hands
- ☐ 2 Able to transfer with verbal cueing and/or supervision
- ☐ 1 Needs one person to assist
- ☐ 0 Needs two people to assist or supervise to be safe

6. Standing Unsupported with Eyes Closed

Instruction: Close your eyes and stand still for 10 seconds
Grading: Please mark the lowest category which applies

- ☐ 4 Able to stand 10 seconds safely
- ☐ 3 Able to stand 10 seconds with supervision
- ☐ 2 Able to stand 3 seconds
- ☐ 1 Unable to keep eyes closed 3 seconds but stays steady
- ☐ 0 Needs help to keep from falling

Version: September 23, 2008

Heart & Stroke Trial

☐ Consent ☐ Baseline ☐ 3 mo ☐ 6 mo ☐ 6+2 mo ☐ 9 mo ☐ 12 mo ☐ 12 +2 mo ☐ 15 mo

Patient ID Number ☐☐ ☐☐☐☐ Patient Initials ☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Investigator Patient # F L DD MM YYYY

Berg Balance Scale (Page 3)

7. Standing Unsupported with Feet Together

Instruction: Place your feet together and stand without holding
Grading: Please mark the lowest category which applies

- ☐ 4 Able to place feet together independently and stand 1 minute safely
- ☐ 3 Able to place feet together independently and stand for 1 minute with supervision
- ☐ 2 Able to place feet together independently but unable to hold for 30 seconds
- ☐ 1 Needs help to attain position but able to stand 15 seconds feet together
- ☐ 0 Needs help to attain position and unable to hold for 15 seconds

8. Reaching Forward with Outstretched Arm

Instruction: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at end of fingertips when arms are at 90 degrees, fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position)

Grading: Please mark the lowest category which applies.

- ☐ 4 Can reach forward confidently >10 inches
- ☐ 3 Can reach forward >5 inches safely
- ☐ 2 Can reach forward >2 inches safely
- ☐ 1 Reaches forward but needs supervision
- ☐ 0 Needs help to keep from falling

9. Pick up Object from the Floor

Instruction: Pick up the shoe/slipper which is placed in front of your feet
Grading: Please mark the lowest category which applies

- ☐ 4 Able to pick up slipper safely and easily
- ☐ 3 Able to pick up slipper but needs supervision
- ☐ 2 Unable to pick up but reaches 1-2 inches from slipper and keeps balance independently
- ☐ 1 Unable to pick up and needs supervision while trying
- ☐ 0 Unable to try, needs assistance to keep from falling

Version: September 23, 2008

Heart & Stroke Trial

☐ Consent ☐ Baseline ☐ 3 mo ☐ 6 mo ☐ 6+2 mo ☐ 9 mo ☐ 12 mo ☐ 12 +2 mo ☐ 15 mo

Patient ID Number ☐☐ ☐☐☐☐ (Investigator / Patient #)

Patient Initials ☐☐ (F L)

Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Berg Balance Scale (Page 4)

10. Turning to Look Behind Over Left and Right Shoulder

Instruction: Turn to look behind you over toward left shoulder. Repeat to the right.
Grading: Please mark the lowest category which applies

- ☐ 4 Looks behind from both sides and weight shifts well
- ☐ 3 Looks behind one side only; other side shows less weight shift
- ☐ 2 Turns sideways only but maintains balance
- ☐ 1 Needs supervision when turning
- ☐ 0 Needs assist to keep from falling

11. Turn 360 Degrees

Instruction: Turn completely around in a full circle, and pause. Then turn a full circle in the other direction.

Grading: Please mark the lowest category which applies.

- ☐ 4 Able to turn 360 safely in < 4 seconds each side
- ☐ 3 Able to turn 360 safely one side only < 4 seconds
- ☐ 2 Able to turn 360 safely but slowly
- ☐ 1 Needs close supervision or verbal cueing
- ☐ 0 Needs assistance while turning

Dynamic Weight Shifting While Standing Unsupported

12. Count Number of Times Step Touch Measured Stool

Instruction: Place each foot alternately on the stool. Continue until each foot has touched the stool for four times.
Grading: Please mark the lowest category which applies

- ☐ 4 Able to stand independently and safely and complete 8 steps in 20 seconds
- ☐ 3 Able to stand independently and complete 8 steps in >20 seconds
- ☐ 2 Able to complete 4 steps without aid with supervision
- ☐ 1 Able to complete >2 steps, needs minimal assistance
- ☐ 0 Needs assistance to keep from falling/unable to try

Version: September 23, 2008

Heart & Stroke Trial

☐ Consent ☐ Baseline ☐ 3 mo ☐ 6 mo ☐ 6+2 mo ☐ 9 mo ☐ 12 mo ☐ 12 +2 mo ☐ 15 mo

Patient ID Number ☐☐ ☐☐☐☐ (Investigator / Patient #) Patient Initials ☐☐ (F L) Date ☐☐ ☐☐ ☐☐☐☐ (DD MM YYYY)

Berg Balance Scale (Page 5)

13. Standing Unsupported One Foot in Front

Instruction: (Demonstrate to subject). Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your foot is ahead of the toes of the other foot.

Grading: Please mark the lowest category which applies

- ☐ 4 Able to place foot tandem independently and hold 30 seconds
- ☐ 3 Able to place foot ahead of other independently and hold 30 seconds
- ☐ 2 Able to place take small step independently and hold for 30 seconds
- ☐ 1 Needs help to step but can hold for 15 seconds
- ☐ 0 Loses balance while stepping or standing

14. Standing on One Leg

Instruction: Stand on one leg as long as you can without holding.

Grading: Please mark the lowest category which applies.

- ☐ 4 Able to lift leg independently and hold > 10 seconds
- ☐ 3 Able to lift leg independently and hold 5-10 seconds
- ☐ 2 Able to lift leg independently and hold ≥ 3 seconds
- ☐ 1 Tries to lift leg; unable to hold 3 seconds but remains standing independently
- ☐ 0 Unable to try or needs assist to prevent fall

APPENDIX E

CHEDOKE MCMASTER STROKE ASSESSMENT
Leg and Foot Subscales

Participant ID code: _____ **Date:** _____

Chedoke-McMaster Stroke Assessment

(Affected Limb Only)

Affected Limb: ☐ Right ☐ Left

Leg	Foot
1 ☐ Not yet stage 2	1 ☐ Not yet stage 2
2 ☐ Resistance to passive hip or knee flexion ☐ Facilitated hip flexion ☐ Facilitated extension	2 ☐ Resistance to passive dorsiflexion ☐ Facilitated dorsiflexion or toe extension ☐ Facilitated Plantar flexion
3 ☐ Aduction to neutral ☐ Hip flexion to 90° ☐ Full extension	3 ☐ Plantarflexion > than 1/2 range ☐ Some dorsiflexion ☐ Extension of toes
4 ☐ Hip flexion to 90° then extension synergy ☐ Bridging hips with equal weight bearing ☐ Knee flexion beyond 100°	4 ☐ Some eversion ☐ Full inversion ☐ Dorsiflexion, then plantarflexion
5 ☐ Extension synergy, then flexion synergy ☐ Raise thigh off bed ☐ Hip extension with knee flexion	5 ☐ Toe extension with ankle plantarflexion ☐ Ankle plantarflexion, then dorsiflexion ☐ Full eversion
6 ☐ Lift foot off floor 5 times in 5 seconds ☐ Full range internal rotation ☐ Trace a pattern: Forward, side, back, return	6 ☐ Tap the foot 5 times in 5 seconds ☐ Foot circumduction ☐ Full eversion
7 ☐ Rapid high stepping 10 times in 5 seconds ☐ Trace a pattern quickly: Forward, side, back. Reverse pattern. ☐ Hop on weak leg	7 ☐ Heel touching forward, then toe touching behind, 5 times in 10 seconds. ☐ Circumduction, quickly, reverse ☐ Up on toes then back on heels 5 times
Stage:	**Stage:**

APPENDIX F

FATIGUE ASSESSMENT SCALE

Participant ID code: _____ **Date:** _____

FATIGUE ASSESSMENT SCALE

The following 10 statements refer to how you usually feel. Please read each statement carefully, then circle **one** out of five answer categories, varying from Never to Always. **1** = Never; **2** = Sometimes; **3** = Regularly; **4** = Often; and **5** = Always.

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	1	2	3	4	5
2. I get tired very quickly	1	2	3	4	5
3. I don't do much during the day	1	2	3	4	5
4. I have enough energy for everyday life	1	2	3	4	5
5. Physically, I feel exhausted	1	2	3	4	5
6. I have problems to start things	1	2	3	4	5
7. I have problems to think clearly	1	2	3	4	5
8. I feel no desire to do anything	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, I can concentrate quite well	1	2	3	4	5

APPENDIX E

CENTER FOR EPIDEMIOLOGICAL STUDIES SCALE
Depression Scale

Participant ID code: _____ Date: _____

Centre for Epidemiological Studies Scale (CES-D) (Page 1)

Instructions: Below is a list of ways you might have felt or behaved. Please indicate how often you felt this way during the past week.

	Rarely or none of the time (<1 day)	Some or little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me	☐0	☐1	☐2	☐3
2. I did not feel like eating; my appetite was poor	☐0	☐1	☐2	☐3
3. I felt that I could not shake off the blues even with help from my family or friends	☐0	☐1	☐2	☐3
4. I felt that I was just as good as other people	☐0	☐1	☐2	☐3
5. I had trouble keeping my mind on what I was doing	☐0	☐1	☐2	☐3
6. I felt depressed	☐0	☐1	☐2	☐3
7. I felt that everything I did was an effort	☐0	☐1	☐2	☐3
8. I felt hopeful about the future	☐0	☐1	☐2	☐3
9. I thought my life had been a failure	☐0	☐1	☐2	☐3
10. I felt fearful	☐0	☐1	☐2	☐3
11. My sleep was restless	☐0	☐1	☐2	☐3

Participant ID code: _____ Date: _____

Centre for Epidemiological Studies Scale (CES-D) (Page 2)

	Rarely or none of the time (<1 day)	Some or little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
12. I was happy	☐0	☐1	☐2	☐3
13. I talked less than usual	☐0	☐1	☐2	☐3
14. I felt lonely	☐0	☐1	☐2	☐3
15. People were unfriendly	☐0	☐1	☐2	☐3
16. I enjoyed life	☐0	☐1	☐2	☐3
17. I had crying spells	☐0	☐1	☐2	☐3
18. I felt sad	☐0	☐1	☐2	☐3
19. I felt that people dislike me	☐0	☐1	☐2	☐3
20. I could not get "going"	☐0	☐1	☐2	☐3

CURRICULUM VITAE

SVETLANA KNORR

ACADEMIC BACKGROUND

University of Western Ontario, London, ON 2010 – present
- Master of Physical Therapy

University of Western Ontario, London, ON 2007 – present
- Ph.D. Candidate, Graduate Program in Health and Rehabilitation Sciences (Physical Therapy)

Thesis Title: Fatigue and mobility post-stroke

York University, Toronto, ON 2006
- M.Sc., School of Kinesiology and Health Science

Thesis Title: Time course of central fatigue transferability in the lower limb

York University, Toronto, ON 2003
- B.Sc. (Honours), School of Kinesiology and Health Science with specialization in Fitness Assessment and Exercise Counseling

ACADEMIC ACCOMPLISHMENTS

➢ SCHOLARLY REFEREED PUBLICATIONS

ARTICLES PUBLISHED OR ACCEPTED IN REFEREED JOURNALS
- **Knorr S,** Ivanova TI, Doherty TJ, Campbell JA and Garland SJ. *The origins of neuromuscular fatigue post-stroke*. (Exp Brain Res. 2011 In Press).
- **Knorr S,** Brouwer B, and Garland SJ. *Validity of the Community Balance and Mobility Scale in Community-Dwelling Individuals after Stroke.* Arch Phys Med Rehabil. 91(6): 890-896, 2010.
- Garland SJ, Gray VL, and **Knorr S**. *Muscle Activation Patterns and Postural Control Following Stroke.* Motor Control 13(4): 387-411, 2009.

ABSTRACTS
- **Knorr S,** Brouwer B, and Garland SJ. *Validity of the Community Balance and Mobility Scale in Community-Dwelling Individuals after Stroke.*
- **Knorr S,** Ivanova TI, Doherty TJ, and Garland SJ. *The Origins of Fatigue Post-stroke*. Appl. Physiol. Nutr. Metab. 34 (Suppl. 1): S50, 2009.
- **Knorr S** and Cafarelli E. *Time course of central fatigue transferability in the lower limb.* Med. Sci. Sports Exerc. 39 (5): S 331, 2007.

➢ CONFERENCE PRESENTATIONS

- **Canadian Society of Exercise Physiology Conference** *(Vancouver, CA)*

"The origins of fatigue post-stroke" *(Poster Presentation)* Nov, 2009

- **Ontario Exercise Neuroscience Conference** *(London, CA)*

"The origins of fatigue post-stroke" *(Oral Presentation)* June, 2009

- **Aging, Rehabilitation & Geriatric Care Symposium** (*London, CA*) Feb., 2008

"Physiological and functional recovery of balance and mobility after stroke" *(Poster Presentation)*

- **American College of Sports Medicine Conference** (*New Orleans, USA*)

"Time course of central fatigue transferability" (*Poster Presentation*) May, 2007

- **Ontario Exercise Neuroscience Conference** (*St –Catherine's, CA*)

"How central is central fatigue?" (*Oral Presentation*) June, 2006

ACADEMIC ACHIEVEMENT SCHOLARSHIPS & AWARDS

- **OGS Scholarship**
  University of Western Ontario 2011
- **OGS Scholarship**
  University of Western Ontario 2010
- **OGSST Scholarship**
  University of Western Ontario 2009
- **Western Graduate Research Scholarship**
  University of Western Ontario 2007-2011
- **University of Western Ontario Tuition Scholarship**
  University of Western Ontario 2007
- **York University Faculty of Graduate Studies Research Scholarship**
  York University 2004
- **York University Graduate Entrance Scholarship** (Master's level)
  York University 2004
- **York University Continuing Student Scholarship**
  York University 2002
- **School of Kinesiology and Health Science Honour Roll Award**
  York University 2003

ACADEMIC WORK EXPERIENCE

➢ *RESEARCH ASSISTANSHIPS*

Project title: "Community Reintegration in Stroke Survivors" 2007 - 2010
Supervisor: Dr. Garland
(*University of Western Ontario & University of British Columbia*)
Project title: "How central is central fatigue?" Summer, 2005
Supervisor: Dr. Cafarelli *(York University)*

- ***TEACHING ASSISTANSHIPS***

Department of Physical Therapy, *University of Western Ontario*

- *Professional Practice* Fall, 2008
- *Critical Appraisal & Evidence-Based Practice* Winter, 2008/09
- *Professional Consolidation* Summer, 2007/08/09

School of Kinesiology and Health Science, *York University*

- *Human Anatomy* Summer, 2005/06
- *Fitness Assessment and Exercise Counseling* Winter, 2005
- *Human and Exercise Physiology* Fall/Winter, 2004/05