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THE RELATIONSHIP OF SPASTICITY AND IMPAIRMENTS IN FORCE REGULATION AND NEUROMUSCULAR FATIGUE POST STROKE

by

Reivian Berrios Barillas, DPT

A Dissertation submitted to the Faculty of the Graduate School,
Marquette University,
in Partial Fulfillment of the Requirements for
the Degree of Doctor of Philosophy

Milwaukee, Wisconsin

December 2015

ABSTRACT
THE RELATIONSHIP OF SPASTICITY AND IMPAIRMENTS IN FORCE REGULATION AND NEUROMUSCULAR FATIGUE POST STROKE

Reivian Berrios Barillas, DPT

Marquette University, 2015

Hyperreflexia that causes muscle spasticity may contribute to limitations in force regulation and walking ability post stroke. Additionally, neuromuscular fatigue may reduce force regulation, which is important because fatigue can assist to strengthen muscles that control walking. Hyperreflexia may be caused by cortical disinhibition that allows Ia afferents to amplify excitatory synaptic inputs to motoneuron pools. Cortical disinhibition is presumably caused by stroke-related motor cortex damage. Although, other excitatory synaptic sources to motoneurons contribute to motor control, hyperreflexia may be one contributor that affects stroke survivors. However, hyperreflexia is reported infrequently to effect force regulation post stroke. The goal was to quantify stroke related hyperreflexia with (out) a fatiguing condition and relate the findings to clinical function.

To investigate how hyperreflexia affected force regulation in a non-fatiguing condition, stimulus frequency was examined in the soleus H-reflex response of stroke survivors and healthy controls. The H-reflex is an electrical analog of the stretch reflex and gives insight into the monosynaptic sensory pathway. After repetitive stimulation, stroke survivors had less H-reflex depression as compared to controls. Additionally, the slowest walking stroke survivors had less H-reflex depression. These results may indicate hyperreflexia contributes to rate depression and walking speed post stroke.

Further implications on how hyperreflexia affected force regulation were investigated with patellar tendon tap (TT) responses during a fatiguing knee extensor task in stroke survivors and healthy controls. Additionally, the contributions of voluntary muscle strength, neural drive and involuntary muscle property responses were probed. Central mechanisms may primarily affect force regulation after fatigue because stroke survivors had less muscle property and maximal voluntary contraction reductions, along with greater voluntary activation reduction as compared to controls. Likewise, stroke survivors had higher post TT responses and less TT change after fatigue, which may suggest hyperreflexia with paresis may contribute to decreased force regulation. Additionally, stroke survivors with fewer baseline central impairments had less clinical dysfunctions.

Hyperreflexia and impairments in the nervous system may decrease force regulation post stroke. Moreover, quantitative metrics of neuromuscular impairments may relate to clinical function measures, which may reveal central mechanisms need to be treated to improve force regulation.

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Reivian Berrios Barillas, DPT

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CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1. INTRODUCTION

Stroke survivors have motor deficits that cause impaired force regulation and walking dysfunction (Association, 2009). Impaired force regulation includes weakness, reductions in muscle length, velocity and/or activation (Milner, 2015). Discovering possible mechanisms for impaired force regulation post stroke could optimize treatment plans that aid in better mobility. A possible contributor to impaired force regulation is hyperreflexia, a spinal cord circuitry impairment. Amplified monosynaptic sensory inputs may be caused by cortical disinhibition, presumably from cortical damage post stroke (Lance, 1966). These amplified sensory inputs could increase stretch reflex gain and thus decrease force control. However, stroke literature infrequently reports spasticity as a contributing mechanism for force regulation impairment. To investigate spasticity on force regulation post stroke, laboratory neuromuscular measures of motor impairment were measured and correlated with clinical function metrics. In stroke literature, correlations between laboratory and clinical measures are reported infrequently. Additionally, how spasticity affected force regulation during a neuromuscular fatigue task was quantified. Neuromuscular fatigue can limit force and functional mobility endurance, but it is needed for muscle strengthening (Folland & Williams, 2007; Gabriel, Kamen, & Frost, 2006). After stroke, muscle fatigue may be impacted primarily by central contributions due to decreased neural drive (Horstman et al., 2008; Knorr, Ivanova, Doherty, Campbell, & Garland, 2011;

Riley & Bilodeau, 2002). Therefore, motor impairments of neuromuscular function with and without a fatiguing condition were investigated. The overall goal of the proposed studies was to quantify the relationship between stroke-related spasticity and (1) impairments in force regulation, (2) muscle fatigue and (3) measures of clinical function. Ultimately, these findings will assist in developing therapeutic interventions that improve force regulation and lead to better functional mobility in stroke survivors.

1.2. STROKE PATHOGENESIS ALTERS MOTOR CONTROL REGULATION

Stroke is a leading source of adult disability caused by brain cell blood loss created by a transient or permanent ischemic condition, or pathological processes that impair one or more brain blood vessels (Association, 2009). As a result, damaged neurons and glial cells of the motor cortex can limit motor regulation and produce long-lasting impairments and dysfunctions (Association, 2009; Jorgensen et al., 1995).

1.2.1. Stroke-related Clinical Impairments and Dysfunctions Effect Motor Control

Motor cortex damage post stroke can cause multiple motor control abnormalities. Typical motor effects of a stroke survivor are flaccid or spastic limbs, organ or limb paralysis, decreased sensation, fatigue, muscle atrophy and altered muscle activation (Fredericks & Saladin, 1996). Non-paretic muscles can demonstrate weakness as well (Gerrits et al., 2009). Spasticity is defined as a velocity dependent motor impairment that amplifies stretch reflex responses (Lance, 1980). Spasticity may be caused by cortical disinhibition of the Ia afferent, which permits unregulated Ia EPSPs to increase motor unit output, (Lance, 1966). As a result, these motor impairments can hinder movement after a stroke.

Clinical tests can reveal several motor impairments and mobility dysfunctions post stroke. For instance, stroke survivors have extremity impairments in limb sensation, reflexes, range of motion, synergistic patterns and coordination when assessed with the Fugl Myer test (Gladstone, Danells, &

Black, 2002). Likewise, clinicians report balance deficits post stroke with chair transfers and single leg stance challenges, when using the Berg Balance Scale (Berg, Wood-Dauphinee, Williams, & Maki, 1992). These impairments could limit maneuvering around objects or changing directions safely when ambulating post stroke (Fritz, Pittman, Robinson, Orton, & Rivers, 2007), which the Dynamic Gait Index test can reveal (Jonsdottir & Cattaneo, 2007). Furthermore, stroke survivors walk slower (tested with the Ten Meter Walk Test) (Mudge & Stott, 2009). Therefore, as a result of these deficits, 30% of chronic ischemic stroke survivors are unable to ambulate without an assistive device (Aha, 2009). However, these clinical tests alone do not reveal the physiological mechanisms for the impairments and dysfunctions post stroke.

1.2.2. Motor Control Assessed by Clinical Metrics and Neuromuscular Function Post Stroke

A significant relationship between clinical and quantitative laboratory metrics of motor control may provide a better understanding of the mechanisms contributing to post stroke deficits. For example, laboratory measures of hip flexor dynamic maximal voluntary contractions (MVC) magnitudes may be related to self-selected walking speed post stroke (Kuhnen et al., 2015), which may suggest weakness predict walking speed. Likewise, stroke survivors with greater torque fluctuations of the hip flexors had reduced walking speeds and impaired balance (Hyngstrom, Kuhnen, Kirking, & Hunter, 2014). In other words, unsteadiness of the paretic hip flexors may predict balance. However, the exact

cause of force regulation post stroke that leads to clinical impairments is not well understood.

Central mechanisms not fully explored in laboratory testing may cause these persistent neuromuscular changes (Bhagchandani & Schindler-Ivens, 2012; Roche et al., 2012). For example, spasticity may arise from a presynaptic mechanism of limited reciprocal inhibition inputs post stroke (Bhagchandani & Schindler-Ivens, 2012; Roche et al., 2012), which may decrease force control. Unfortunately, laboratory measures of hyperreflexia are reported infrequently to correlate with clinical function. Using clinical and laboratory metrics together may provide a better understanding of force regulation alterations post stroke.

Combining clinical and laboratory metrics could identify muscle strength impairments that contributions to motor regulation post stroke. With the use of maximal voluntary contractions (MVCs), researchers suggest stroke survivors have greater strength deficits due to less cortical input as compared to healthy controls (Horstman et al., 2008; Hyngstrom et al., 2012; Knorr et al., 2011). Similarly, lower extremity weakness is identified with clinical manual muscle testing (MMT) (Bohannon, 2001). There is evidence that MVCs have a relationship to walking speed post stroke (Kuhnen et al., 2015). However, these two tests do not provide insight into the relationship between MVC and force regulation post stroke.

Other laboratory tools could provide insight into stroke related force regulation by examining changes in the central nervous system (CNS) and specifically, the spinal cord circuitry. In this dissertation, central mechanisms

were investigated with voluntary activation (VA) measurements to indicate how well the general CNS drives voluntary movement (Gandevia, 2001). In stroke survivors, limited neural drive may reduce MVCs more as compared to healthy controls (Knorr et al., 2011).

More specifically, the neural dysfunction may be from impaired spinal cord circuitry, which was probed with the H-reflex technique and instrumented tendon taps (TT) in this dissertation. The H-reflex is an electrical analog to the stretch reflex. Similarly, it behaves like a manual TT that triggers monosynaptic sensory inputs, which cause muscle shortening. Both measures produce non-voluntary muscle activity and have different presynaptic inputs than a voluntary muscle contraction. The H-reflex EMG response appears to reduce less in stroke survivors as compared to healthy controls after repeated stimulation (Roche et al., 2012). In stroke, limited PSI may cause less H-reflex depression, which has correlated with greater spasticity (Roche 2012). Additionally, TT torque responses may increase and recruitment thresholds may lower post stroke when compared to healthy controls (Yang, Guo, Ren, Kang, & Zhang, 2013). However, neural impairments are not the only mechanism for impaired force regulation post stroke.

Muscle property integrity may be impaired post stroke, which could decrease force regulation (Toffola, Sparpaglione, Pistorio, & Buonocore, 2001). To understand peripheral contributions, we used resting twitches (RT) which are non-voluntary electrical evoked contractions. Resting twitches indicate the maximal muscle force that occurs through cross bridge formation regulated by

calcium availability (Gandevia, 2001). In healthy controls, RT torque reduces after fatigue, which suggests peripheral fatigue as a mechanism (Gandevia, 2001). However, post stroke publications rarely report RT reductions. Therefore, investigating these laboratory measures could enhance the knowledge that clinical metrics provide about stroke survivors' impairments and mobility.

1.3. MOTOR UNIT SYNAPTIC INPUT CONTRIBUTION TO MOTOR CONTROL REGULATION

To produce movement, the spinal cord's alpha motoneuron (MN) pool is activated (Cheney, 1985; Sherrington, 1906). The MN is a component of a motor unit, which includes the alpha motoneuron, its axon and the muscle fibers it innervates (Barkhaus & Lorenzo, 2011). Motoneurons can receive synaptic input from cortical descending pathways, brainstem pathways, interneuronal inputs and sensory feedback from muscles. The motoneuron integrates and transforms these inputs into action potentials that ultimately result in muscle contraction and force generation. Disruption in any one of the several synaptic inputs to spinal motoneurons may contribute to limited force regulation and motor output post stroke (Cheney, 1985; Sherrington, 1906). Therefore, the purpose of this dissertation is to explore how stroke-related changes in descending and spinal related inputs to motoneurons may contribute to deficits in force regulation and motor function post stroke.

1.3.1. Motor Unit Firing and Recruitment Changes Affect Motor Control Regulation in Stroke Survivors

Motor units facilitate movement; but post stroke, impaired motor unit behavior could hinder movement. Deficits in motor unit firing and recruitment may limit force post stroke as compared to healthy controls (Cengiz & Kuruoglu, 2004; Hu, Tong, & Hung, 2006; Lukacs, 2005; Lukacs, Vecsei, & Beniczky, 2008; Mottram, Suresh, Heckman, Gorassini, & Rymer, 2009; Mottram, Wallace, Chikando, & Rymer, 2010). The most often reported upper extremity motor unit

dysfunctions are firing rate reductions (Hu et al., 2006; Mottram et al., 2009; Sauvage et al., 2006), spontaneous firing (Mottram et al., 2010), M wave amplitude reductions (Lukacs, 2005), discharge rate deficits (Gemperline, Allen, Walk, & Rymer, 1995; Shahani, Wierzbicka, & Parker, 1991) and motor unit recruitment deficits (Cengiz & Kuruoglu, 2004; Lukacs et al., 2008). Lower extremity motor units deficits are reported less often, but show similar changes with reduced firing rates (McNulty, Lin, & Doust, 2014) and prolonged activation (Ivanova, Knorr, MacDonell, Pollock, & Garland, 2014). Therefore, stroke-related changes of motor unit firing or recruitment behavior could limit motor control regulation, and thus cause dysfunctional mobility.

1.3.1.1. Pre and Post Synaptic Mechanisms of Impaired Motoneuron Output Post Stroke

Impaired presynaptic excitatory and inhibitory inputs to motoneuron (MN) pools may cause abnormal MN firing behaviors post stroke (Mottram et al., 2009; Mottram et al., 2010). Abnormal MN firing may present as decreased, spontaneous or prolonged after a stroke. Presynaptic changes to the MN that cause reduce MN firing are as follows: vesicle depletion, an inhibitory neurotransmitter, depleted neurotransmitters, increased reciprocal inhibition of Renshaw interneurons, cortical inhibition or by antagonist co-activation (Hultborn, Brownstone, Toth, & Gossard, 2004; Kernell, 2006; Nussbaumer, Ruegg, Studer, & Gabriel, 2002). Alternatively, MN firing may increase via the following upstream changes: cortical disinhibition or excitatory neurotransmitters, excitatory

segmental neurons or amplified sensory afferents. As a result, synaptic changes prior to the MN receiving input could increase or decrease MN behavior.

In contrast, postsynaptic MN changes may cause abnormal MN firing behaviors post stroke (Mottram et al., 2009; Mottram et al., 2010). There is evidence from the cat model that reveals increased persistent inward current (PIC) activity may amplify or self-sustain MN firing (Heckman & Binder, 1988; Heckman, Lee, & Brownstone, 2003). Increased baseline synaptic excitability may cause premature activation of voltage sensitive Na channels, which would cause spontaneous MN firing (Kernell, 2006). On the other hand, depressed PIC activity could reduce MN firing (Kernell, 2006). Additionally, decreased MN receptors could reduce or delay MN firing, respectively (Kernell, 2006). Consequently, postsynaptic MN impairments could affect the output of the cell and limit force regulation.

1.3.1.2. Muscle Property Changes Effect on Motor Control Post Stroke

Motor unit muscle fiber changes may reduce force regulation post stroke. Current post stroke literature suggests lower limb muscles atrophy (Hachisuka, Umezu, & Ogata, 1997; Metoki, Sato, Satoh, Okumura, & Iwamoto, 2003; Ryan, Dobrovolny, Smith, Silver, & Macko, 2002) and slow twitch fibers predominant (Hachisuka et al., 1997). These types of muscle fiber changes could reduce conduction velocity post stroke (Toffola et al., 2001). These anatomical changes may be created by stroke related muscle disuse or synaptic impairments that could decrease force regulation.

Impaired muscle properties could reduce torque post stroke (Knorr et al., 2011). In healthy controls, impaired muscle properties (reduced resting twitches) have been indicated to reduce lower (Baudry, Klass, Pasquet, & Duchateau, 2006) and upper limbs torque after fatigue (Yoon, De-Lap, Griffith, & Hunter, 2008). A reduced RT is an indirect measure of a muscle's maximal force and could indicate changes in calcium availability needed for muscle contraction (Kent-Braun, Fitts, & Christie, 2012). Likewise, impaired neuromuscular propagation (reduced M waves) of stroke survivors are suggested to cause reduced torque in lower limb (Knorr et al., 2011) and upper limbs (Lukacs, 2005) after fatigue. A reduced M wave is an indirect measure of the decreased signal transmission at the neuromuscular junction (Gandevia, 2001). These impaired synaptic muscle property changes could cause slower muscle reaction times, which could reduce force regulation for balance or walking post stroke.

1.4. PURPOSE OF SPINAL STRETCH REFLEX IN HEALTHY POPULATIONS AND ITS ADAPTATION POST STROKE

Amplified stretch reflex gain may be a mechanism that contributes to deficits in force regulation and function post stroke. Typically, the stretch reflex maintains muscle length through activation of muscle spindles in a monosynaptic pathway (Walker, 1990). A muscle stretch activates muscle spindle Ia afferents, which then synapse onto the alpha MN pool. The alpha MN pools cause the homologous muscle to shorten (contract) and the heteronomous muscle to relax through the monosynaptic stretch reflex pathway. Gamma motoneuron activation prevents over-contraction by regulating Ia afferent muscle spindle excitability inside the intrafusal fibers. Supraspinal centers and intersegmental neurons can also control the alpha and gamma motoneurons' influence on the stretch reflex.

Stretch reflexes may assist or hinder movement. In the mesencephalic cat, soleus stretch reflexes appear to assist most during the stance phase of a walking task (Akazawa, Aldridge, Steeves, & Stein, 1982) implicated by H-reflex responses. Likewise, in healthy humans, rapid spinal stretch reflexes are suggested to assist during locomotion (Capaday & Stein, 1986) and limb proprioception (Dimitriou, 2014; Roll & Vedel, 1982), which minimizes cortical input use (Mukherjee & Chakravarty, 2010). After stroke, amplified stretch reflexes may hinder hip flexor contraction times (Hyngstrom, Onushko, Chua, & Schmit, 2010) or prolong quadricep muscle activity (Lewek, Hornby, Dhaher, & Schmit, 2007), which have shown to have a negative relationship with walking ability (Hyngstrom et al., 2010; Lewek et al., 2007). To explore stroke-related

reflex gain effect on force regulation, we used the H-reflex technique and instrumented tendon tap responses.

1.5. IDENTIFYING REFLEX GAIN EFFECT TO MOTOR UNITS POST STROKE WITH THE H-REFLEX AND TENDON TAP RESPONSES

H-reflex EMG responses can be used as a probe into the monosynaptic sensory pathway (Knikou, 2008; Toft, 1995) and indirectly identify hyperreflexia. The H-reflex technique can provide an understanding of MN behavior despite the presence of oligosynpatic inputs to the H-reflex response (Knikou, 2008; Misiaszek, 2003). In healthy controls, repeated stimuli depress H-reflex EMG amplitudes (Floeter & Kohn, 1997; Magladery & McDougal, 1950), but in stroke survivors, H-reflex responses depress less (Roche et al., 2012). Less H-reflex depression is assumed to be caused by less presynaptic inhibition (PSI) of the stretch reflex pathway (Aymard et al., 2000; Bhagchandani & Schindler-Ivens, 2012; Roche et al., 2012). Typically, PSI occurs because successive monosynaptic Ia excitatory postsynaptic potentials (EPSPs) reduce when activated repeatedly due to neurotransmitter depletion (Curtis & Eccles, 1960). In stroke survivors, amplified reflex gain may limit H-reflex depression. Additionally, reduced H-reflex depression and increased clinical spasticity relate (Roche et al., 2012), which is reported infrequently post stroke. Therefore, the H-reflex response may be a tool that reveals increased reflex gain contributes to impaired force regulation and clinical dysfunction post stroke.

Hyperreflexia can also be identified by using tendon tap (TT) responses. Tendon tap responses appear to have slower latencies than H-reflex responses in healthy humans (Burke, Gandevia, & McKeon, 1983; Morita, Petersen, Christensen, Sinkjaer, & Nielsen, 1998); possibly, because the H-reflex bypasses

muscle spindle activation and fusimotor drive. Stroke survivors' TT responses have larger torques and lower recruitment thresholds when compared to healthy controls (Yang et al., 2013); possibly due to increased reflex gain. In addition, after fatigue, TT EMG response may increase when MVC decreases given that healthy controls demonstrate these findings after fatigue (Biro, Griffin, & Cafarelli, 2007). However, the research reports infrequently the use of instrumented TT to assess how hyperreflexia affects force regulation post stroke.

1.6. MONOAMINES AND PICS POTENTIAL EFFECT ON REFLEX GAIN TO MOTOR UNITS POST STROKE

Brainstem monoamines along with PICs amplify motoneuron output; but post stroke, these neuromodulators may be unregulated and compound the effects of increased reflex gain. Reduced cortical drive to brainstem centers post stroke (Blicher et al., 2009; Schwerin et al., 2008; Swayne et al., 2008), may allow the uninhibited brainstem pathways to affect motor control by amplifying motoneuron pool excitation. In the intact nervous system, brainstem nuclei produce such neuromodulators as serotonin and norepinephrine. Neuromodulators amplify motoneuron firing responses to a given excitatory synaptic input (Heckman, Hyngstrom, & Johnson, 2008; Heckman, Lee, & Brownstone, 2003; Heckman, Mottram, Quinlan, Theiss, & Schuster, 2009). Neuromodulators initiate an intracellular cascade that activates the voltage sensitive channels. These channels allow persistent inward currents (PICs) to enter motoneuron cells (Lee, Kuo, Jiang, & Heckman, 2003). PICs can increase the motoneuron pools' gain by causing each cell's membrane potential to rest closer to depolarization. PICs cause a sustained depolarization of the motoneuron's membrane potential. This prolonged depolarization above the threshold for firing causes plateau potentials, which cause the motoneuron to self-sustain its firing. The self-sustained firing regenerates until a hyperpolarizing synaptic input inhibits it. In the cat model, there is evidence that monoaminergic inputs and PICs can amplify synaptic inputs (Hounsgaard, Hultborn, Jespersen, & Kiehn, 1988; Lee & Heckman, 2000). In stroke survivors, regulated

neuromodulators appear to improve function (Chollet, Acket, et al., 2013; Chollet, Cramer, et al., 2013). Likewise, studies in such other patient populations as spinal cord injured indicate that regulated neuromodulators can improve force generation (D'Amico et al., 2013; Gorassini, Knash, Harvey, Bennett, & Yang, 2004; Thompson & Hornby, 2013; Thompson, Jayaraman, Kinnaird, & Hornby, 2011). Therefore, it is plausible that these uninhibited neuromodulators affect increased reflex gain. To improve paretic muscle function, we may need to control uninhibited brainstem neuromodulators and stretch reflex gain.

1.7. NEUROMUSCULAR FATIGUE EFFECT ON PARETIC MOTOR REGULATION

Neuromuscular fatigue is the acute reduction in force or power after exercise (Gandevia, 2001). Increased stretch reflex gain may be one mechanism that limits motor control post stroke, but neuromuscular fatigue also may affect reflex gain. Data from our laboratory suggest that individuals with stroke have difficulty sustaining force and that stroke-related fatigue is primarily due to deficits in the nervous system's ability to activate the muscle (Hyngstrom et al., 2012; Kuhnen et al., 2015; Rybar et al., 2014). Neuromuscular fatigue is functionally relevant, as it would limit an individual's task endurance. In addition, understanding stroke-related muscle fatigue may reveal current physical therapy strengthening protocols are likely deficient because they work under the premise that the affected nervous system adequately excites the musculature. In this section, we will explore the mechanisms of central (neural) and peripheral (muscular) fatigue and the fatigue effects on healthy populations and individuals with a stroke. These differences will aid in investigating the influence fatigue has on motor control regulation post stroke.

1.7.1. Mechanisms of Neuromuscular Fatigue and Contributions to Motor Control

Central mechanisms of neural origin may play a greater role post stroke than peripheral (muscle property) changes when regulating motor output (Hyngstrom et al., 2012; Knorr et al., 2011; Riley & Bilodeau, 2002). Central fatigue is caused when the CNS reduces neural drive that activates a muscle

(Gandevia, 2001). Multiple CNS sites are suggested as potential sources of fatigue: upstream of the cortex, cortex, brainstem, spinal cord, spinal motoneuron and sensory afferents (Gandevia, 2001). There could be decreased excitatory spinal activity, decreased excitatory descending drive, increased cortical inhibition, inhibition of the motoneuron pool, and depression of excitatory feedback from peripheral afferents, increased inhibitory activity from spinal interneurons and/or intrinsic MN property changes (Gandevia, 2001). Any of these central impairments could alter the signal to produce an adequate amount of muscle force and thus cause muscle fatigue.

Peripheral mechanism may play a role in force production during fatiguing contractions for healthy populations (Bigland-Ritchie, Furbush, & Woods, 1986), but are suggested to affect stroke survivors to a lesser degree (Knorr et al., 2011). Peripheral fatigue is caused by alterations at or distal to the neuromuscular junction (NMJ) to the muscle (Gandevia, 2001). Decreased magnitudes of the potentiated (resting) twitch or reduced mean EMG power frequency after a fatiguing task are suggested to be caused by peripheral fatigue (Gandevia, 2001). Possible peripheral mechanisms of fatigue are as follows: decreased neural propagation, deactivated excitation contraction coupling, altered muscle metabolism, accumulated metabolites, reduced cross-bridge formation and/or decreased muscle perfusion (Gandevia, 2001; Kent-Braun et al., 2012). Alterations in these areas could lead to muscle fatigue and limit force production.

1.7.2. Differences in Fatigue Mechanisms of Stroke Survivors and Healthy Controls

Depending on the population investigated, central or peripheral mechanisms may primarily contribute to muscle fatigue. A person with stroke has CNS changes caused by cortical damage. This physiological change could affect force production by limiting descending excitatory drive to motoneuron pools. In healthy adults, peripheral mechanisms are suggested mainly to reduce maximal voluntary force and reduce evoked force after fatiguing quadriceps muscles contractions (Bigland-Ritchie et al., 1986).

However, central mechanisms are suggested to primarily affect muscle fatigue post stroke because stroke survivors have greater reductions in voluntary activation and MVC than healthy controls (Horstman et al., 2008; Knorr et al., 2011; Newham & Hsiao, 2001). In addition, it is suggested that E-C coupling failure may not limit paretic muscle work as compared to non-paretic muscles because mean power frequency does not decrease in the paretic muscle as compared to the non-paretic muscle (Svantesson, Sunnerhagen, Carlsson, & Grimby, 1999). The Svantesson group's results indicate paretic muscles' force reduction may not be primarily attributed to peripheral mechanisms (Svantesson et al., 1999). Therefore, muscle fatigue appears to be caused mainly by central impairments post stroke as opposed to peripheral mechanisms primarily affecting muscle fatigue for healthy controls.

Determining a single neuromuscular fatigue mechanism is difficult because it is likely not just one site in the central and peripheral areas (Knorr et

al., 2011; Riley & Bilodeau, 2002; Svantesson et al., 1999). Investigating multiple sites along the neural axis and within the muscle will enable researchers to identify mechanisms that limit force regulation; and thus improve functional mobility in stroke survivors.

1.8. ORIGIN OF SPASTICITY POST STROKE AND ITS EFFECT ON FORCE REGULATION POST STROKE

Spasticity is defined as velocity-dependent increase in spinal reflex responses (Lance, 1966).Researchers report extensively post stroke spasticity originates from increased excitatory synaptic inputs of the spinal cord's stretch reflex, (Kamper et al., 2014; Lance, 1966), which can impair force regulation. However, there is indirect evidence that the motor cortex may contribute to stretch reflex gain in healthy controls' transcranial magnetic stimulation (TMS) studies (Lewis, Polych, & Byblow, 2004; Perenboom, Van de Ruit, De Groot, Schouten, & Meskers, 2015) and stroke survivors' fMRI studies (Lindberg et al., 2009). Typically, researchers report cortical disinhibition of Ia afferents excitatory synaptic inputs, which permits amplified Ia EPSPs inputs to motoneuron pools (Lance, 1966). However, a conflicting TMS study suggests healthy controls' stretch reflex gain is controlled outside of the motor cortex (Fox & Shemmell, 2014). Likewise, electroencephalogram – electromyography (EEG-EMG) studies show little coherence with paretic muscle activity (Mima, Toma, Koshy, & Hallett, 2001). Therefore, researchers are not certain if the cortex contributes presynaptically to the Ia pathway changes that cause hyperreflexia.

Besides not knowing the contributing mechanisms of hyperreflexia, researchers are still debating if hyperreflexia actually limits force regulation post stroke. Reduced relaxation, increased co-activation and limited movement appear to arise from increased spasticity (Levin, Selles, Verheul, & Meijer, 2000). Spasticity appears to increase EMG activity when voluntarily moving the upper

and lower limb post stroke (Sahrmann & Norton, 1977). After stroke, amplified stretch reflexes may delay contraction times (Hyngstrom et al., 2010), which may impair function and posture (Sheean, 2002).

In contrast, amplified stretch reflexes may not affect motor control greatly post stroke (Dietz & Sinkjaer, 2007; Patten, Lexell, & Brown, 2004). Tonic reflexes were shown to be at the same intensity in stroke survivors and healthy controls during gait, indicating spasticity did not affect ambulation (Ada, Vattanasilp, O'Dwyer, & Crosbie, 1998) . Likewise, it was suggested spasticity did not affect postural sway during standing because lower limb muscles' EMG magnitudes did not increase with perturbations in stroke survivors as compared to healthy controls (Nardone, Galante, Lucas, & Schieppati, 2001). Additionally, it was suggested co-contraction tasks of the elbow muscles did not increase spasticity because scores of the Modified Ashworth test did not change before and after the co-contraction task (Miller & Light, 1997). Therefore, with this conflicting evidence, it is inconclusive if spasticity affects force regulation post stroke.

1.9. SPECIFIC AIMS

This dissertation proposes that amplified stretch reflex responses contribute to the mechanisms that cause impaired force regulation and leg mobility in chronic stroke survivors. Because of cortical damage post stroke, cortical disinhibition could permit amplified Ia EPSPs to motoneuron pools and their muscle fibers (motor units). As a result, there may be hyperreflexia that impairs force regulation. Impairments in force regulation could include spasticity, weakness, and reductions in muscle length, velocity and/or neuromuscular activation, and inability to control a sub-maximal force. Central mechanisms of impairment such as hyperreflexia may affect stroke survivors' motor control more than healthy controls. This dissertation examined the responsiveness of the nervous system in chronic stroke survivors to mechanisms of impairment in the central nervous system, spinal stretch reflex and muscle property and correlated these findings with clinical function. There is limited published research that identifies the central and peripheral structures that affect stroke survivor's force regulation and the relationship to clinical metrics. *The dissertation objective was to quantify stroke related changes of stretch reflex gain with and without a fatiguing task and relate those abnormalities with clinical leg impairment and walking function.* These findings may assist in improving stroke rehabilitation treatments.

1.9.1. Aim 1. Quantify stimulus frequency effects on soleus H-reflex responses and the relationship to walking speed in chronic stroke survivors

In Aim 1, we utilized the H-reflex technique as a probe to quantify stroke-related changes of the soleus H-reflex response to stimulus frequency. This technique gives insight into changes of the monosynaptic pathway of the Ia afferent to the motoneuron because it is an electrical analog to the stretch reflex. It is not understood well how the H-reflex EMG output responds to low and high frequency stimulus post stroke. In previous low frequency studies, stroke survivors demonstrate less H-reflex rate depression when compared to healthy controls. Subjects with the most severe spasticity also had the least amount rate H-reflex depression. Additionally, in previous studies the H-reflex rate of depression has shown an inverse relationship walking speed ability post stroke. Therefore, our goal was to quantify stroke-related changes of the H-reflex response via a stimulus train at varied frequencies and relate it to walking function. *We hypothesized that at low frequencies, individuals with stroke will have less H-reflex response depression as compared to controls and the level of H-reflex depression will negatively correlate with walking speed dysfunction.*

1.9.2. Aim 2. Quantify central and peripheral mechanisms of neuromuscular fatigue of paretic knee extensors

In Aim 2, we quantified differences in mechanisms of neuromuscular fatigue in the knee extensors of stroke survivors and healthy controls by measuring laboratory neuromuscular function. We measured MVC, voluntary activation (VA), resting twitch (RT) torque and tendon tap (TT) torque before and

after a fatiguing task. Fatigue affects healthy controls and individuals with stroke by reducing strength and task duration. However, fatigue may be more detrimental for stroke survivors because of central mechanisms primarily. Our goal was to implicate central mechanisms via reduced MVCs, reduced VA, larger TT responses and limited RT changes in stroke survivors as compared to healthy controls. Limited cortical input may reduce MVCs and VA. Furthermore, larger TT responses may indicate increased stretch reflex gain as one contributor of impairment post stroke when compared to healthy controls. Less RT reduction may imply peripheral mechanisms primarily affect force regulation post stroke. This project is novel because it included several techniques to understand the contributions of the CNS, spinal cord circuitry and muscle properties synaptic functions in one experiment. *We hypothesized that stroke survivors demonstrated knee extensor fatigue because of more central mechanisms as compared to healthy controls.*

1.9.3. Aim 3. Quantify the relationship of laboratory metrics of reflex response, paresis, voluntary activation and muscle properties to clinical leg metrics of function post stroke

In Aim 3, we examined tendon tap responses and other neuromuscular functions of the paretic knee extensors and related the findings to clinical mobility and leg impairment. We measured neuromuscular function in stroke survivors by measuring quantitatively tendon tap torque (spinal), voluntary activation (neural), MVC (neural), resting twitch (muscle) and strength symmetry of lower limbs. We correlated these laboratory neuromuscular function metrics to clinical functional

tests that measure leg impairment, balance and walking speed capabilities. We may be able to predict impairment and functional mobility post stroke by measuring these neuromuscular functions. The study's novelty is that we investigated several synaptic sites applicability to clinical function, which facilitates the bench to bedside importance of our research. The results could ultimately improve rehabilitation stroke treatments. *We hypothesized that stroke survivors with better neuromuscular function (larger RT, VA, MVC and less TT output) would have less leg impairment, better balance and walk faster. Additionally, central synaptic function may be a better prediction of clinical impairment and mobility instead of peripheral synaptic function for paretic knee extensors.*

CHAPTER 2: STIMULUS FREQUENCY EFFECTS ON SOLEUS H-REFLEX RESPONSES AND THE RELATIONSHIP TO WALKING SPEED IN CHRONIC STROKE SURVIVORS

2.1. INTRODUCTION

After stroke, motor deficits such as weakness and walking dysfunction may be caused by impairments in the spinal stretch reflex (Levin et al., 2000). The stretch reflex involves stretch-sensitive Ia afferents, which have monosynaptic connections to motoneuron (MN) pools (Sherrington, 1906). MN pools also receive inputs from a number of other sources, including corticospinal tracts; however, after stroke, cortical drive to MN pools is diminished (Blicher, Jakobsen, Andersen, & Nielsen, 2009; Schwerin et al., 2008; Swayne, Rothwell, Ward, & Greenwood, 2008), presumably because of stroke-related damage to the motor cortex or associated descending pathways. In addition, altered descending drive may impair Ia afferent pathways to MN pools (e.g. through changes in presynaptic inhibition), which could alter muscle excitation. In order to probe changes in the monosynaptic stretch reflex, the H-reflex technique, an electrical analog to the stretch reflex, can be used (Knikou, 2008; Toft, 1995). In the current study, we identified the temporal characteristics of repeated H-reflex stimuli to identify changes in stretch reflex pathways that might contribute to post stroke motor deficits.

Typically, a single electrical stimulus is used to elicit the H-reflex response in stroke and healthy populations; the response can then be used to test spinal inhibitory and facilitatory effects on the stretch reflex (Bhagchandani & Schindler-

Ivens, 2012; Dyer et al., 2009). In healthy populations, the H-reflex response adapts by depressing after either a single stimulus (Knikou, 2008) or repetitive stimuli (Floeter & Kohn, 1997; Magladery & McDougal, 1950); assumed to be caused by pre-synaptic inhibition (PSI). PSI causes successive monosynaptic Ia excitatory postsynaptic potentials (EPSPs) to reduce after repeated activation because of neurotransmitter depletion (Curtis & Eccles, 1960). PSI may subtly modify excitatory input to regulate force outputs for functional tasks (Mann, 2011); but after stroke, PSI may be altered (Aymard et al., 2000; Roche et al., 2012). Stroke-related changes of PSI could permit more EPSPs, which could increase stretch reflex gain, limit H-reflex depression and thus alter force. Amplified stretch reflexes could lead to prolonged muscle activity post stroke (Lewek et al., 2007).

To produce adequate force, many synaptic inputs are needed to regulate force, which could be simulated by a train of stimuli. Multiple stimuli depress H-reflex amplitudes at frequencies lower than 1 Hz in stroke survivors, but less in healthy populations; suggested to be related to underlying spasticity (Aymard et al., 2000; Roche et al., 2012). Also, stimulus frequency that increases from 0.1 Hz to 1 Hz are implied to cause greater H-reflex depression in stroke survivors more than healthy controls (Roche et al., 2012). Despite a 1 Hz stimulus train diminishing the H-reflex amplitude, there is information to gain from higher frequency, repetitive stimuli. The H-reflex response from varying stimulus frequencies may give insight into how rate modulation limits force and causes functional deficits post stroke.

The most clinically impaired stroke survivors have less H-reflex depression (Bhagchandani & Schindler-Ivens, 2012; Roche et al., 2012). Less H-reflex reduction caused by less disynaptic inhibition may be related to spasticity (measured with use of the Modified Ashworth clinical test) post stroke (Roche et al., 2012). Likewise, reduced reciprocal inhibition that limits H-reflex depression may be inversely related to movement impairments (measured with the Fugl-Meyer and 8-m walk test) (Bhagchandani & Schindler-Ivens, 2012), indicating limited H-reflex depression responses may predict clinical function. These deficits could hinder a stroke survivor from walking quickly across a street. Additionally, impaired walking speed (measured with the 10-meter walk test) may correlate with the H-reflex adaption response post stroke at higher stimulation frequencies, which could further identify this relationship beyond Bhagchandani and Schindler-Ivens' (2012) work.

The study purpose is to quantify stimulus frequency effects on the soleus H-reflex response and its implications to walking speed post stroke. Repetitive stimuli at low and high frequencies were used to investigate the stimulus frequency effects on H-reflex EMG amplitudes. To identify if there is a relationship between the H-reflex adaptation responses and walking speed post stroke, the 10-m walk test was correlated the responses with H-reflex amplitude changes. H-reflex adaptation responses may predict walking speed. This H-reflex response may give insight into the amount of spasticity a stroke survivor has that would hinder functional walking. This study's hypothesis is that the H-reflex adaptation response post stroke would depress less than the control group after

use of a low frequency train of stimuli and stroke survivors' H-reflex response would negatively correlate with walking speed.

2.2. METHODS

2.2.1. Subjects

Ten stroke survivors (61.4 ± 7.6 years; 6 females, 4 males) and 10 neurologically intact (61.2 ± 7.6 years) subjects participated in the study, (*Table* 2.1. and *Table* 2.2.). The subjects were gender and age matched. Self-selected walking speed was measure with the 10-m walk test (Mudge & Stott, 2009) for stroke survivors. Subjects were excluded as follows: stroke occurred less than 6 months ago, unable to follow two-step commands, had low back pain and/or had more than one stroke. Subjects gave written consent to participate in the study, which the Institutional Review Board of Marquette University approved.

Table 2.1. Subject Characteristics of Stroke Survivors

Participants Post Stroke	**Age (yrs)**	**Sex**	**Affected Side**	**Self-Selected 10 m Walk Test (m/s)**	**MVC of Plantarflexors (Nm)**
101	62	M	Right	1.37	47
102	59	M	Right	1.26	25
103	62	F	Left	0.6	6.4
104	55	F	Right	1.27	35
105	55	M	Left	1.05	24
106	61	F	Left	0.9	22
107	56	F	Left	0.67	18
108	65	F	Left	0.38	7.7
109	54	M	Left	0.99	15
110	81	F	Left	0.19	12
111	65	F	Left	1.4	23
Mean	61.36			0.87	21.37
Standard Deviation	7.63			0.38	11.9

Note: F = female, M = male, MVC = maximal voluntary contraction, Nm = newton meters, yrs = years

Table 2.2. Subject Characteristics of Healthy Controls

Healthy Controls	Age (yrs)	Sex	MVC of Plantarflexors (Nm)
204	62	M	39
206	61	F	20
207	54	F	14
208	59	F	19
209	57	F	21
210	60	M	27
212	80	F	28
213	57	M	20
214	55	M	43
215	67	F	22
Mean	61.2		25.3
Standard Deviation	7.6		9.21

Note: F = female, M = male, MVC = maximal voluntary contraction, Nm = Newton meters, yrs = years

2.2.2. Experiment Set-Up

Subjects were positioned supine with legs securely fastened into a custom built apparatus instrumented with load cells (JR3, Inc., Woodland, CA) at the ankle joints. The soleus H-reflex EMG response was elicited by stimulating the posterior tibial nerve in the popliteal fossa area. A monopolar bar electrode was utilized with a 1-ms pulse generated by a constant current stimulator (DS7A; Digitimer Ltd., UK). The ground electrode was placed on the patella. LabVIEW (National Instruments, Austin, TX) programs were used to trigger an electrical stimulator and acquire all data. Prior to acquisition, torque signals were low-pass filtered (500 Hz) and then sampled at 1 kHz.

Three to five baseline maximal voluntary contractions (MVC) were obtained from each subject's tested plantarflexor. Subjects were given a 1-minute rest period after each MVC as not to cause fatigue. Thresholds and

recruitment curves for the maximal M wave (Mmax) and H-reflex (Hmax) were quantified. The H-reflex intensity during the experiment was 20-30% of Mmax; within the ascending part of the recruitment curve (Knikou, 2008).

A single control pulse was given and then a 1-minute wait period occurred before the train of 10 pulses. Subjects were given a train of stimuli at 0.1 Hz, 1 Hz, 5 Hz, 10 Hz or 15Hz (single subject example at 15 Hz, *Fig* 2.1). Each frequency condition was repeated (15 trials) and frequency conditions were randomized. Subjects rested 1 minute before starting a new trial and MVCs were repeated at the end of testing as not to cause neuromuscular fatigue. Peak to peak amplitudes of the H-reflex response were measured. Pulses 6-10 were normalized by the first pulse and then averaged.

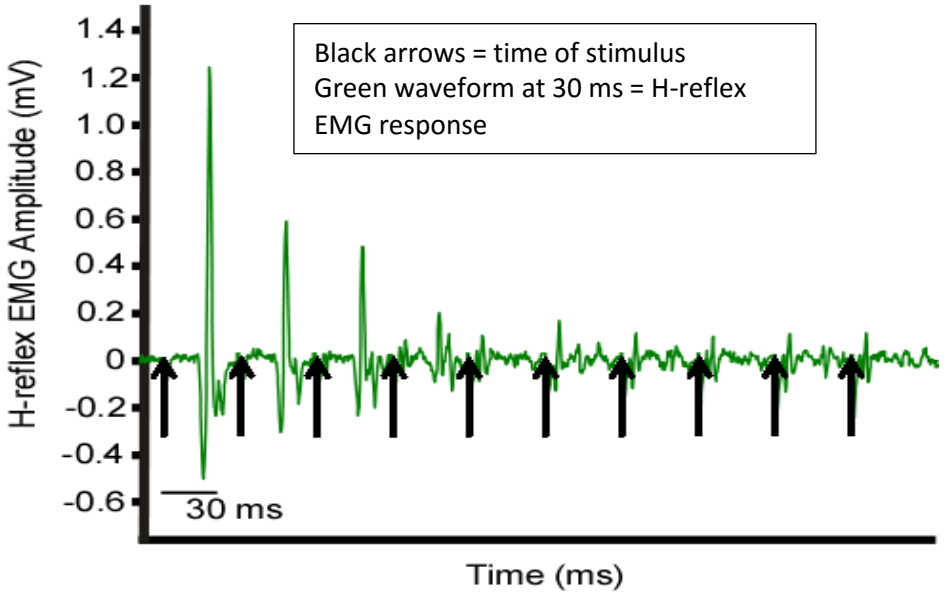


Figure 2.1. H-reflex Response at 15 Hz Stimulation of a Single Stroke Subject. This example shows a 15 Hz stimulus train and its effect on soleus H-reflex EMG amplitude for a single stroke subject.

2.2.3. Data Analysis

Separate mixed-model ANOVAs detected differences between subject groups for the following variables: H-reflex adaptation responses of the five frequencies and MVCs. Scheffe post hoc tests ($\alpha = 0.05$) were utilized to compare means. Data are represented as mean ± SD. Squared Pearson product-moment correlation coefficient (r^2, $\alpha = 0.05$) detected correlations in H-reflex adaptation responses to walking function.

2.3. RESULTS

A significant decrease occurred in the H-reflex EMG amplitude as the frequency stimulation increased with the stroke and control groups ($P < 0.001$). Stroke survivors demonstrated less rate depression as compared to the control group at stimulation frequencies of 1 Hz and 5 Hz (*Fig.* 2.2; $P < 0.05$). There was no significant difference in H-reflex depression response between subject groups at the stimulation frequencies of 1 Hz, 10 Hz and 15 Hz ($P > 0.05$).

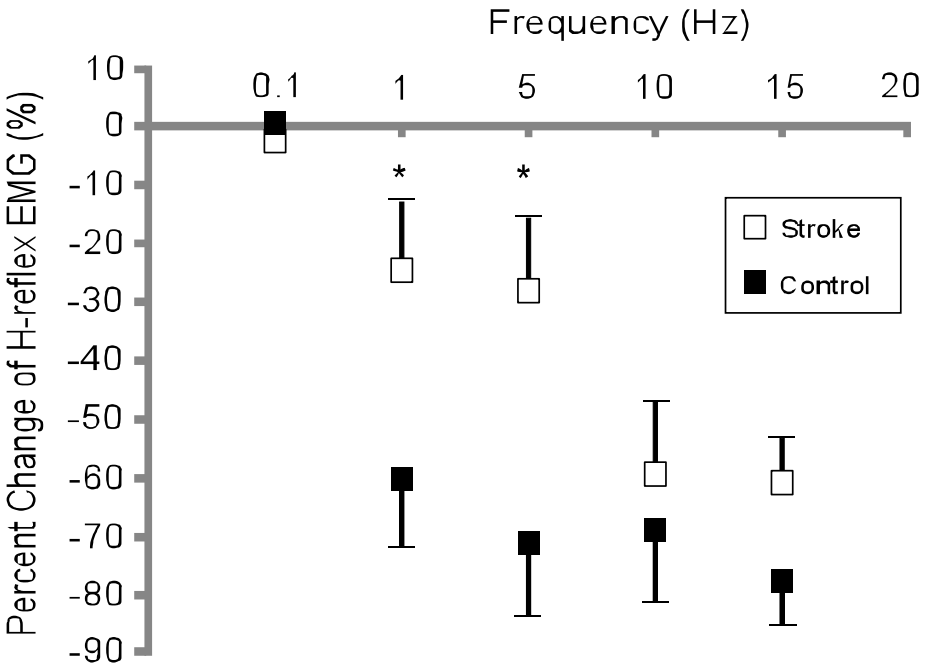


Figure 2.2. Stimulation Frequency Differences Between Subject Groups. The percent change in H-reflex amplitudes for stroke (open squares) and control groups (closed squares). There was a group effect at 1 Hz and 5 Hz stimulation frequency ($P < 0.05$), whereby stroke subjects had less H-reflex depression. Data are represented as mean ± SD.

No significant difference was shown between the average plantarflexor MVC for the control (25.3 Nm ± 9.3) and stroke (21.4 Nm ± 11.9) groups (P = 0.13).

Walking speeds of stroke survivors inversely correlated with the H-reflex adaptation response at 5 Hz stimulation, (*Fig.* 2.3; P = 0.046). Walking speeds of the stroke survivors did not correlate with the H-reflex adaptation response at 0.1 Hz (r^2 = 0.004, P = 0.86), 1 Hz (r^2 = 0.16, P = 0.26), 10 Hz (r^2 = 0.08, P = 0.42) or 15 Hz (r^2 = 0.37, P = 0.06).

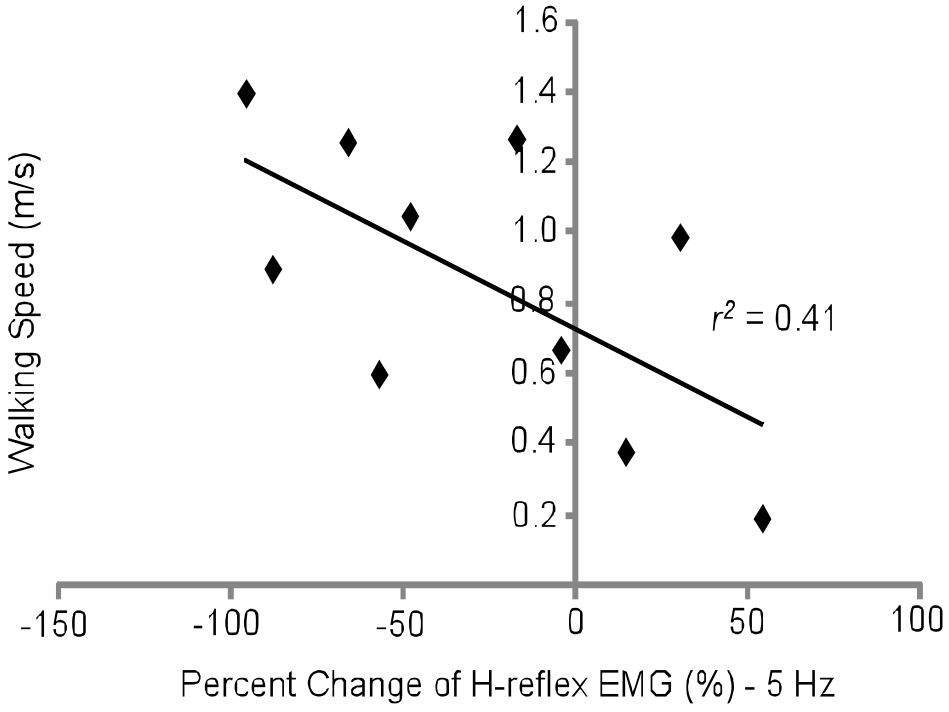


Figure 2.3. Correlation of H-reflex Adaptation Response and Walking Speed Post Stroke. Walking speed was negatively correlated with percent change of H-reflex amplitudes at the 5 Hz stimulation frequency (r^2 = 0.41; P = 0.046).

2.4. DISCUSSION

After repetitive stimulation to elicit the H-reflex EMG response, stroke survivors' adaptation responses depressed less when compared to healthy controls. At the 0.1 Hz stimulation frequency, there was no difference between the adaptation responses of the subject groups. There was a significant difference between the two subject groups' H-reflex responses at the 1 Hz and 5 Hz stimulation frequencies. The H-reflex response of the stroke survivors depressed less than the control group at the 10 Hz and 15 Hz stimulation frequencies, but it was not statistically significant. These results demonstrate the typical H-reflex rate depression seen in other literature of stroke survivors and healthy controls (Roche et al., 2012).

Stroke survivors had less H-reflex response depression as compared to healthy controls after repetitive stimulation. These results are comparable to healthy control data that shows the H-reflex adaption response depresses after repeated stimulation (Floeter & Kohn, 1997; Magladery & McDougal, 1950). The H-reflex response depressed at 1 Hz frequency when given a train of 10 pulses (Floeter & Kohn, 1997). Healthy controls' H-reflexes responses depress at low and high frequencies in the lower and upper limb muscles (Lamy et al., 2005; Rossi-Durand, Jones, Adams, & Bawa, 1999; Van Boxtel, 1986). Lamy and colleagues saw greater reduction of the H-reflex when pulses were given every 1-2 s vs every 6-8s in a variety of upper and lower extremity muscles (Lamy et al., 2005). In the flexor carpi radialis, the H-reflex depression steadily decreased starting at 0.5 Hz (ranging from 0.5 Hz to 10 Hz) (Rossi-Durand et al., 1999).

Another research group saw this same reduction in the soleus from .6 Hz to 2 Hz stimulation of the soleus H-reflex (Van Boxtel, 1986). These results demonstrate the H-reflex adaptation response seen at 1 Hz in this dissertation study is plausible.

The H-reflex rate depression response appears to depress after repeated stimulation in subjects with spasticity (Aymard et al., 2000; Roche et al., 2012; Schindler-Ivens & Shields, 2000). Chronic spinal cord injured (SCI) soleus muscle when using stimulation frequencies at 0.1 Hz, 0.2 Hz, 1 Hz, 5 Hz and 10 Hz and the adaption is less reduced when compared to healthy controls (Schindler-Ivens & Shields, 2000). The SCI group's H-reflex depressed less when compared to healthy controls at the 0.2 Hz stimulation (measured from 0.1 Hz to 0.2 Hz). The stroke survivors in this dissertation study did not have a significant difference in rate depression until the 1 Hz stimulation (where the patient group showed less H-reflex depression), when compared to healthy controls. Likewise, this same result in rate modulation was seen between stroke survivors and healthy controls at 0.16 Hz and 1 Hz stimulation, which may was suggested to be caused by presynaptic inhibition (Roche et al., 2012). The greatest decline was at the 1 Hz stimulation and the difference in subject groups was attributed to reduced PSI in stroke survivors (Roche et al., 2012). Aymard et. al. saw a difference in H-reflex rate depression between pulses given every 2 s versus every 8s (Aymard et al., 2000). The faster rate had greater H-reflex depression responses. Therefore, it appears increasing frequency stimulation

causes H-reflex reduction in patients with spasticity, but there is less depression of the H-reflex response when compared to healthy controls.

The H-reflex response is believed to reduce after repetitive stimulation because of presynaptic inhibition (PSI) to the stretch reflex (Floeter & Kohn, 1997; Magladery & McDougal, 1950). In the cat model, repetitive stimulation is assumed to mainly result in neurotransmitter depletion at the presynaptic terminals which would limit an action potential (Curtis & Eccles, 1960). An alternative mechanism may be the action potential is blocked at sites in the presynaptic pathway (Curtis & Eccles, 1960). In neurological intact humans, the former PSI explanation is suggested to reduce H reflex responses after repetitive stimulation (Floeter & Kohn, 1997; Magladery & McDougal, 1950). This same presynaptic mechanism response is suggested to be a mechanism that reduces H-reflex amplitudes post stroke (Aymard et al., 2000; Dyer et al., 2009; I. Milanov, 1992a; Nakashima et al., 1989; Roche et al., 2012). Even though, PSI is a likely explanation for the frequency dependence of the H-reflex response, postsynaptic motoneuron (MN) changes cannot be ruled out as a cause for rate depression (Misiaszek, 2003).

Postsynaptic mechanisms are not published often as the cause for H-reflex rate depression (Misiaszek, 2003). Intracellular recordings in the cat's MN suggest there is a decrease in the EPSP size of the during the after-hypolarization phase after repetitive stimulation (Curtis & Eccles, 1960). Alternatively, desensitized receptor sites may not accept a neurotransmitter to activate MN pools (Curtis & Eccles, 1960). In the human model, EMG recordings

of motor units (MN and its muscle fibers) suggest that the MN demonstrates spontaneous or irregular firing and recruitment ability post stroke as compared to healthy controls (Cengiz & Kuruoglu, 2004; Hu et al., 2006; Lukacs, 2005; Lukacs et al., 2008; Mottram et al., 2009; Mottram et al., 2010). It is plausible amplified stretch reflexes could cause spontaneous or irregular MN behaviors. This amplified MN activity could limit H-reflex rate depression.

Another two parameters to consider on how hyperreflexia is caused by postsynaptic MN changes is to distinguish differences between threshold and gain changes of the stretch reflex (Katz & Rymer, 1989). A lowered threshold at the receptor site would activate the stretch reflex with minimal synaptic input, which indicates the Ia afferent's membrane potential is at a lower level of recruitment (Katz & Rymer, 1989). Increased reflex gain means that for a given input there is a larger output. The force of the stretch reflex is above normal with little change to the reflex threshold (Katz & Rymer, 1989). Both threshold and gain changes at the Ia afferent could cause hyperreflexia, but it is suggested that threshold of the Ia afferent is mainly altered (Katz & Rymer, 1989). Therefore, it is possible there may be postsynaptic mechanisms that affect the stretch reflex, it is not suggested to primarily be caused by postsynaptic MN impairments(Lance, 1966).

Taken together, the evidence suggests there is a relationship between the H-reflex adaptation response and clinical spasticity post stroke (Masakado et al., 2005; Milanov, 1992a; Nakashima et al., 1989; Roche et al., 2012). The most impaired stroke survivors with clinical spasticity are suggested to have the least

amount of depression of the H-reflex response due to limited presynaptic stretch reflex changes (Masakado et al., 2005; Milanov, 1992a; Nakashima et al., 1989; Roche et al., 2012). This evidence indicates that spasticity and H-reflex responses are related and spasticity may be predictive of the H-reflex response. This finding may lead to understanding how spasticity limits clinical function. In this dissertation study, high frequency stimulation may have reduced the H-reflex response, but less reduced when compared to controls. This difference may be attributed to spasticity. Furthermore, the stroke survivors with the least amount of H-reflex depression were the slowest walkers, which may indicate spasticity limited walking speed post stroke This is consistent with other studies looking at low frequency stimulation of the H reflex response (Bhagchandani & Schindler-Ivens, 2012).

The H-reflex response has been correlated with walking speed with stroke survivors whom have the most clinical spasticity (Bhagchandani & Schindler-Ivens, 2012). This finding is in agreement with the correlation result of this study, which revealed that the stroke subjects with the least amount of H-reflex depression also, were the slowest walkers. This relationship shows that spasticity may hinder walking (Hyngstrom, Onushko, Chua, & Schmit, 2010; Lewek et al., 2007), which contradicts studies that report spasticity may not limit function (Di Fabio, Badke, & Duncan, 1986; Dietz & Sinkjaer, 2007). Walking ability is important for daily routines of crossing a street, which may be impaired when limb spasticity is present (Hyngstrom et al., 2010; Lewek et al., 2007). Furthermore, spasticity may be most present during activity since studies in

healthy controls have shown that the soleus H-reflex amplitude is the greatest during the stance phase of ambulation (Capaday & Stein, 1986) as is similarly been documented in the biceps femoris during gait (Faist, Blahak, Duysens, & Berger, 1999). Likewise, during sit to stand, the H-reflex demonstrates less depression in SCI (who have increased spasticity) as compared to healthy controls (Field-Fote, Brown, & Lindley, 2006). These studies indicate the H-reflex is most responsive during extension activity. Additionally, it is possible that limited ambulation post stroke is attributed to spasticity that causes muscle co-contraction, reduced muscle relaxation and reduced limb movement (Levin et al., 2000).

The novelty of this study is that H-reflex adaptation response is dependent on the frequency stimulation and may be related to limited walking speed post stroke. Underlying spasticity may interfere by hindering H-reflex depression, since other stroke literature revealed Ashworth scores were inversely related to H-reflex adaption responses at lower frequencies (Bhagchandani & Schindler-Ivens, 2012). This spasticity and H-reflex relationship may suggest how stroke survivors' in this study who walk slower, also had less soleus H-reflex depression at the 5 Hz stimulation. Furthermore, less reciprocal inhibition may limit PSI of the soleus H-reflex response in the slower walkers post stroke (Bhagchandani & Schindler-Ivens, 2012). Therefore, spasticity may have affected this study's frequency dependent H-reflex response and walking speed post stroke. Future studies will need to examine which presynaptic pathway sites need to be treated to limit hyperreflexia and thus improve clinical function post stroke. As well as,

future studies are needed to examine how manipulating the H-reflex response could minimize hyperreflexia that limits walking speed post stroke.

CHAPTER 3: CENTRAL AND PERIPHERAL MECHANISMS OF NEUROMUSCULAR FATIGUE IN PARETIC KNEE EXTENSORS

3.1. INTRODUCTION

Neuromuscular fatigue is an acute reduction in force or power after exercise (Gandevia, 2001). As a result of neuromuscular fatigue, stroke survivors demonstrate reduced strength and shorter task duration times as compared to healthy controls (Hyngstrom et al., 2012; Knorr et al., 2011). Multiple nervous system sites may cause these impairments. Stroke-related cortical damage may affect the central nervous system to neurally drive a muscle to fully contract (Knorr et al., 2011). Central mechanisms are assumed to affect stroke survivors more because stroke survivors have greater reductions of VA and MVC when compared to healthy controls (Horstman et al., 2008; Knorr et al., 2011; Newham & Hsiao, 2001). In healthy adults, peripheral (muscle property) mechanisms are primarily suggested to reduce maximal voluntary force after a fatiguing task because of reduced evoked force (Bigland-Ritchie et al., 1986; Yoon et al., 2008). However, determining which mechanism is the cause for neuromuscular fatigue is difficult because it is most likely not one site contributing from central and peripheral areas of impairment (Hyngstrom et al., 2012; Knorr et al., 2011; Riley & Bilodeau, 2002).

Central nervous system changes post stroke may affect motor control more as compared to healthy populations after fatigue (Horstman et al., 2008; Knorr et al., 2011; Newham & Hsiao, 2001). Voluntary activation and MVC were

lower after a fatiguing knee extensor task in stroke survivors when compared to healthy controls (Horstman et al., 2008; Newham & Hsiao, 2001). This finding suggests reduced neural drive may affect paresis post stroke. Similarly, stroke survivors had reduced MEPs and shorter times to task failure after a fatiguing dorsiflexor task when compared to healthy controls (Knorr et al., 2011). This result may indicate stroke survivors' may have an inability to cortically modulate excitability to paretic dorsiflexors. Therefore, central mechanisms may primarily contribute neuromuscular fatigue post stroke.

Another potential neural contributor to impaired force regulation during fatigue is spasticity. Due to motor cortex damage, a person with stroke could have cortical disinhibition that causes increased stretch reflex gain of Ia afferents (Lance, 1966), which can decrease force regulation. Amplified reflex gain from changes in spinal cord circuitry may be one issue that limits force regulation post stroke when compared to healthy controls. Stroke survivors have larger TT responses and lower recruitment thresholds when compared to healthy controls (Yang et al., 2013); possibly due to increased reflex gain. In addition, after fatigue, TT EMG responses may reduce while MVC magnitudes decrease in stroke since healthy controls are revealed to have decreased TT EMG outputs after fatigue (Biro et al., 2007). However, instrumented tendon taps are not reported often to be used to assess reflex gain post stroke. Tendon tap responses are an accessible measure in the clinical setting and could translate bench science to bedside use. Hyperreflexia along with other nervous system impairments may decrease force regulation during fatigue. Therefore,

hyperreflexia and other central mechanisms were investigated to explore their effects on force regulation during fatigue post stroke.

This study quantified differences in mechanisms of neuromuscular fatigue in paretic and neurologically intact knee extensors by measuring central and peripheral sites of impairments. Maximal voluntary contractions, VA, RT torque and TT torque were measured before and after a fatiguing task. These metrics allow one study to include several techniques to explore the contribution of the CNS, spinal cord circuitry and muscle properties impairment effects on force regulation post stroke. In particular, hyperreflexia may contribute to post stroke impairments more when compared to healthy controls. Therefore, the hypothesis was that stroke survivors would demonstrate knee extensor fatigue because of more central mechanisms dysfunctions as compared to healthy controls.

3.2. METHODS

3.2.1. Subjects

Ten stroke survivors (61.8 ± 10.9.6 years; 6 females, 4 males) and 10 neurologically intact (61.1 ± 8.6 years) subjects participated in the study; were gender and age matched (*Table* 3.1. and *Table* 3.2.). Subjects were excluded as follows: stroke was less than 6 months ago, unable to follow two-step commands, had low back pain, had more than one stroke, had exercise associated health risk, and/or had an acute history of knee soreness or knee surgery. Subjects gave written consent to participate in the study, which the Institutional Review Board of Marquette University approved. Participants were familiarized with the testing set-up and practiced maximal and sub-maximal knee extensor contractions. All subjects participated in a familiarization and one fatigue session.

Table 3.1. Subject Characteristics of Stroke Survivors

Stroke Survivors	Age (yrs)	Sex	Affected Side	Time Post Stroke (yrs)	MVC of Knee Extensors (Nm)
101	55	M	Left	9.5	49.55
103	66	F	Left	7.5	38.48
104	62	F	Right	22.5	64.6
107	56	M	Left	4.5	62.52
108	48	M	Right	16	110.3
109	57	F	Left	36	23.3
110	76	F	Right	4	40.73
111	67	M	Left	1.5	10.76
112	48	M	Left	11	35.14
113	79	F	Right	5	133.9
114	55	M	Left	4	45.63
115	67	M	Right	9	62.86

Table 3.1. Continued

Stroke Survivors	Age (yrs)	Sex	Affected Side	Time Post Stroke (yrs)	MVC of Knee Extensors (Nm)
Mean	61.33			10.88	56.48
Standard Deviation	9.98			9.85	34.93

Note: F = female, M = male, MVC = maximal voluntary contraction, Nm = Newton meters, yrs = years

Table 3.2. Subject Characteristics of Healthy Controls

Healthy Controls	Age (yrs)	Sex	MVC of Knee Extensors (Nm)
201	62	F	58.44
202	63	M	175.8
204	72	F	74.53
205	54	M	223.2
206	55	M	136.14
208	51	F	69.9
211	74	F	80.5
212	67	M	142.45
213	49	M	179.63
214	66	M	169.97
Mean	61.3		131.06
Standard Deviation	8.72		57.04

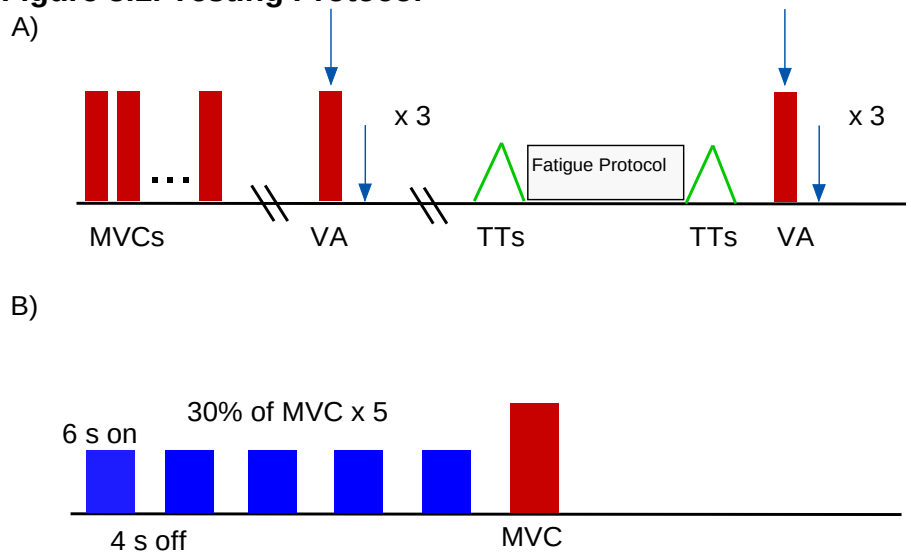
Note: F = female, M = male, MVC = maximal voluntary contraction, Nm = Newton meters, yrs = years

3.2.2. Experimental Set-Up

During the neuromuscular fatigue session, subjects sat with the test leg positioned in 70° of flexion into a Biodex dynamometer chair. A load cell (JR3 Inc., Woodland, CA) was used to measure knee extensor torques during the testing session. Subjects performed 3 to 5 baseline strength measurements of isometric MVCs of the knee extensors. The subjects increased knee extension force from zero to maximum over 1-2 s and observed the exerted force on a

monitor. The researchers verbally encouraged the subjects during all tasks. Subjects rested for 60 s between trials as minimize neuromuscular fatigue during baseline measurements. Trials were repeated until peak forces from 2 of the 5 trials were within 5% of each other. The MVC was the peak torque generated. A protocol example can be seen in *Fig.* 3.1.

Figure 3.1. Testing Protocol



A) The complete testing protocol includes MVCs, voluntary activation, tendon tap responses and the fatigue session. Testing protocol includes MVCs (red rectangles), resting twitch (2nd blue arrow), voluntary activation (MVCs with superimposed and resting twitches (1st pair of blue arrows), and tendon tap responses (green triangles).
B) The fatigue protocol includes 5 intermittent submaximal contractions and 1 MVC). Submaximal contractions (blue boxes) are 30% of MVC.
Note: MVCs = maximal voluntary contractions, VA = voluntary activation, TTs = tendon tap responses.

During the last 3 MVC attempts, VA was quantified using the interpolated twitch technique (Gandevia, 2001). Determination of voluntary activation using the interpolated twitch technique provides a metric of the nervous system's ability to activate fully the knee extensor musculature. For the paretic and control legs, VA was made before and after the fatigue protocol. A VA example can be seen in

Fig. 3.2. A brief constant-current stimulator (Digitimer DS7AH, Welwyn Garden City, UK) delivered a rectangular pulse of 100 µs duration with maximum amplitude of 400 V, which was used to stimulate the quadriceps muscle. The stimulation intensity (usually 200 mA to 500 mA) was set at 20% above the level required to produce a maximal resting twitch amplitude that caused a supramaximal stimulation. When the muscle was potentiated, resting twitches were obtained about 5 s after the MVC task. An interpolated twitch was given at the plateau of the MVC task to assess voluntary activation (VA). The formula to determine percent voluntary activation was ((1- (magnitude of the interpolated twitch)/ (magnitude of the resting twitch))*100) (Gandevia, 2001). To determine if fatigue was related to changes in muscle contractile properties, we quantified changes in the RT magnitude.

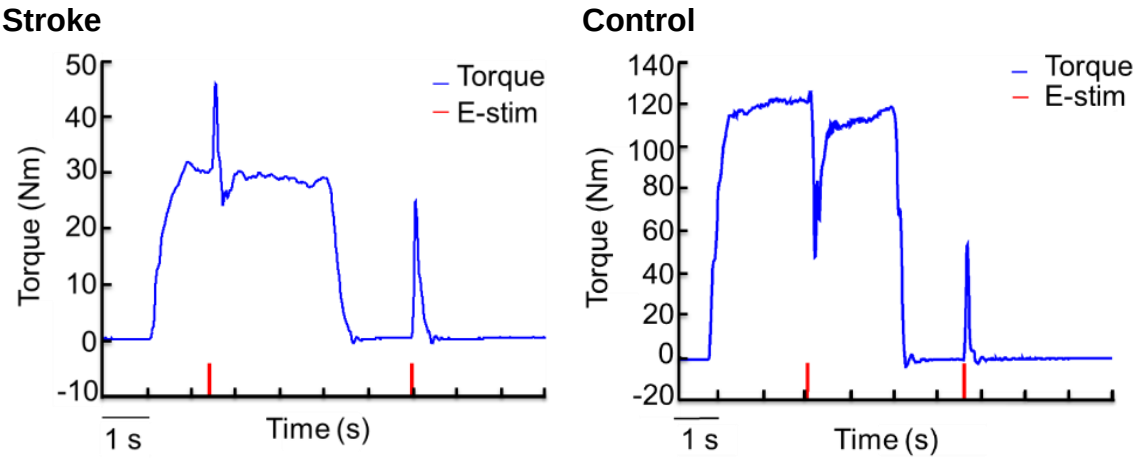


Figure 3.2. Voluntary Activation Example. Examples represent the knee extensors' baseline voluntary activation for a single stroke survivor (1st graph) and single control subject (2nd graph). The 1st twitch response in each graph is the superimposed twitch. The 2nd twitch response in each graph is the baseline resting twitch.

Spinal reflex responses were measured using an instrumented tendon tapper. A Linmot linear motor (model # PSo1-23x 160) gave 5 taps (2 Hz) to the knee extensors (Lance, 1966; Shinohara, Moritz, Pascoe, & Enoka, 2005) before and after the fatiguing task. Changes in the knee extensor's reflex magnitude to the tendon tapping provided information on spinal reflex pathways' contribution to force generation post fatigue.

Following baseline MVC and VA measurements, each subject performed sets of 5 isometric intermittent fatiguing knee extension contractions at 30% of MVC force until task failure. Each submaximal contraction was maintained for 6 s followed by a 4 s rest period. Subjects generated an MVC immediately following the fifth submaximal contraction. This contraction series was repeated until the MVC force fell below 30% of the baseline MVC measurement. Task failure criteria was measured as follows: the time until the subject could not maintain the target torque for at least 3 s or when the force generated fell below a 5% error window greater than 3 times during the 6 s contractions. The intermittent fatiguing contraction is appropriate because many activities of daily living require repetitive contractions (Enoka & Duchateau, 2008; Enoka & Stuart, 1992) and they limit contributions to neuromuscular fatigue from muscle ischemia (Hogan, Richardson, & Kurdak, 1994). Final metrics of MVC, VA and TT responses were measured within 5 s of task failure.

Custom-written LabVIEW (National Instruments, Austin, TX) programs triggered the electrical stimulator and acquired all data. Prior to acquisition, torque signals were low-pass filtered (500 Hz) and then sampled at 1 kHz.

3.2.3. Data Analysis

Squared Pearson product-moment correlation coefficient (r^2, $\alpha = 0.05$) detected correlations in MVC, VA, RT torque and TT torque within subject groups. A repeat measures ANOVA analysis measured differences and interactions in MVCs, VAs, RTs and TTs before and after fatigue, and between subject groups.

An independent samples T-test measured differences in means of task failure times, baseline MVCs, VA, RT and TT; and change in MVC, VA, RT and TT between subject groups. Data are represented as mean ± SD. Sidak post hoc tests ($\alpha = 0.05$) were utilized to compare means.

3.3. RESULTS

Stroke survivors had significantly lower MVC values as compared to healthy controls at baseline and after the fatiguing knee extensor task, (*Fig.* 3.3 and *Fig.* 3.4). In *Fig.* 3.3, there was a main effect of time that demonstrates the MVC value reduced significantly from baseline to post-fatigue (*P* = 0.0001). There was also a main effect between subject groups that showed there was a significant difference between MVC values between the subject groups (*P* = 0.001). Additionally, there was an interaction effect that revealed the MVC value reduced differently for each subject group (*P* = 0.002). In *Fig.* 3.4, healthy controls had a greater difference in MVC when compared to stroke survivors (*P* = 0.002).

Baseline MVC of Both Subject Groups' Knee Extensors

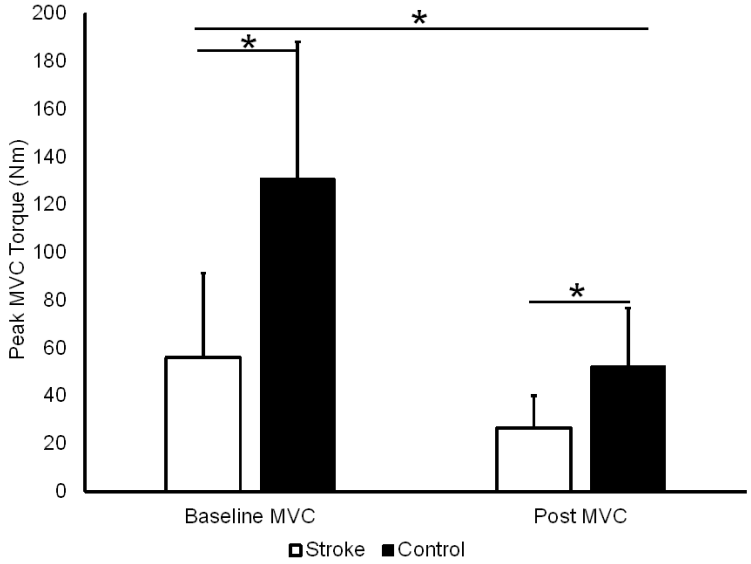


Figure 3.3. MVC differed between subject groups. MVC reduced significantly from pre- and post- fatigue (*P* = 0.001). There was a significant difference between MVC values between the subject groups as a main effect (*P* = 0.001). MVCs reduced differently in the stroke survivors and control subjects (*P* = 0.002). Data are represented as mean ± SD.

The Effect of Fatigue on MVC of Both Subject Groups' Knee Extensors

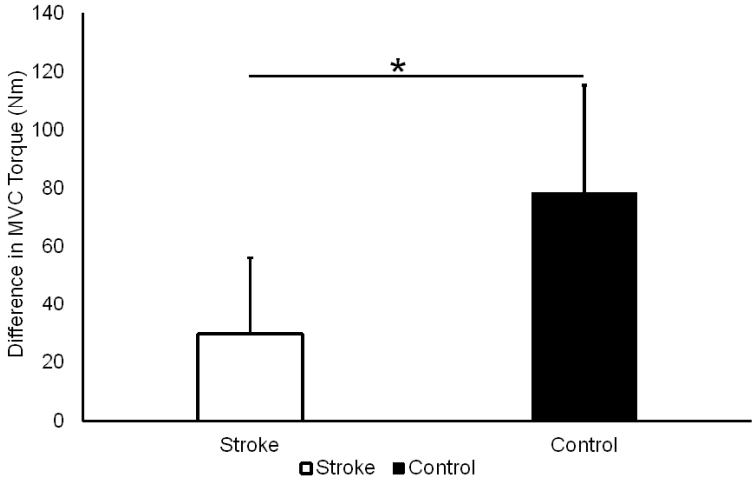


Figure 3.4. MVC differed between subject groups. Healthy controls had a greater difference in MVC when compared to stroke survivors (*P* = 0.002). Data are represented as mean ± SD.

With limited MVCs, stroke survivors fatigued earlier (shorter time to task failure) than controls, but it was not significantly different from controls (*P* = 0.31), (*Fig*. 3.5). Although, individuals with stroke demonstrated significantly shorter task duration times when analyzed in a superset group of 19 stroke survivors and 23 healthy controls (*P* = 0.02), (*Fig.* 3.6).

Task Duration Differences Between Subject Groups' Knee Extensors

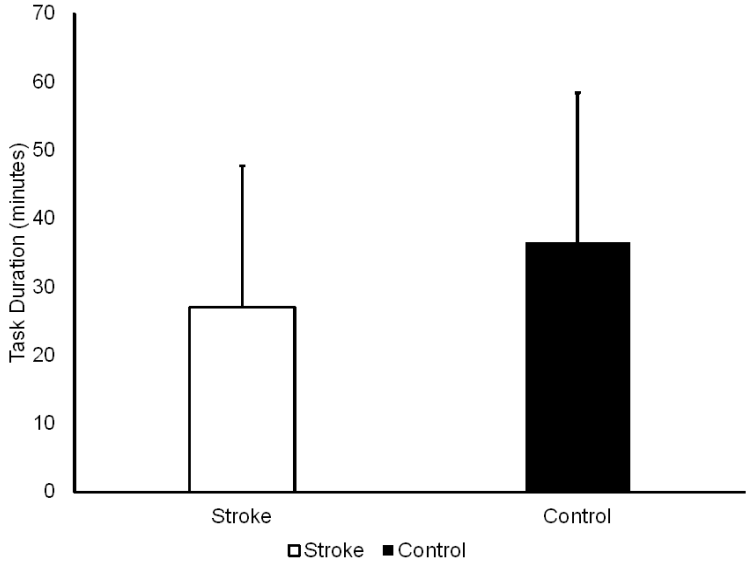


Figure 3.5. Stroke survivors fatigued sooner than healthy controls. Stroke survivors fatigued sooner, but it was not significantly different from controls (*P* = 0.31). Data are represented as mean ± SD.

Task Duration Differences Between Subject Groups' Knee Extensors of Superset

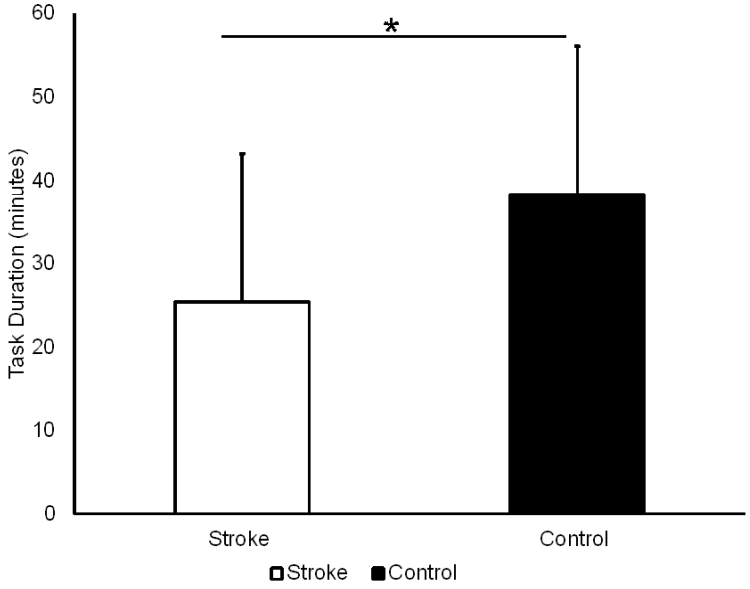


Figure 3.6. Stroke survivors fatigued sooner than healthy controls. Stroke survivors fatigued significantly sooner when analyzed in a superset group of 19 stroke survivors and 23 healthy controls (*P* = 0.02). Data are represented as mean ± SD.

Resting twitch torque reduced after a fatiguing knee extensor task and healthy controls had a greater RT reduction, (*Fig.* 3.7 and *Fig.* 3.8). In *Fig.* 3.7, there was a main effect of time that demonstrates the RT value reduced significantly from baseline to post-fatigue ($P = 0.0001$). There was not a main effect between subject groups that shows there was a significant difference between RT values between the subject groups ($P = 0.06$). However, there was an interaction effect that revealed the RT value reduced differently for each subject group ($P = 0.05$). In *Fig.* 3.8, healthy controls had a greater percent reduction of RT when compared to stroke survivors ($P = 0.05$).

Baseline Resting Twitch Torque of Both Subject Groups' Knee Extensors

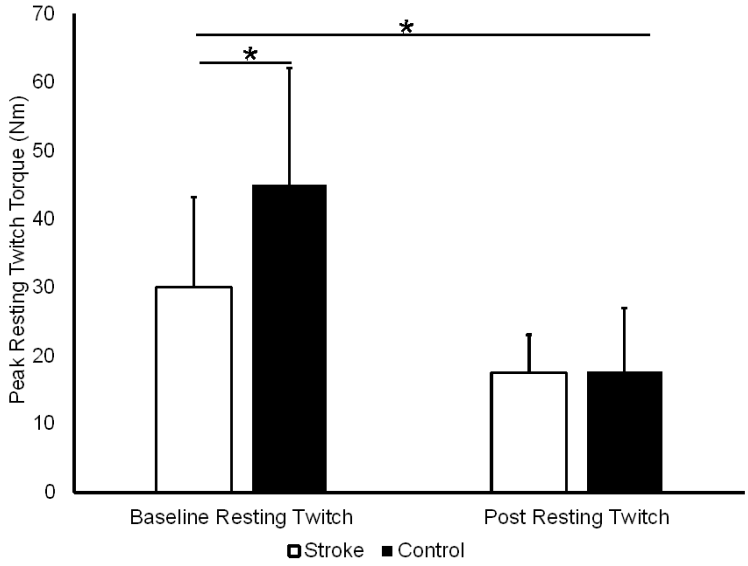


Figure 3.7. Resting twitch torque reduced after fatigue and differed between subject groups. RT reduced significantly from pre- and post- fatigue ($P = 0.0001$). There was not a significant difference between RT values between the subject groups as a main effect ($P = 0.06$). RTs reduced differently in the stroke survivors and control subjects ($P = 0.05$). Data are represented as mean ± SD.

The Effect of Fatigue on Resting Twitch Torque of Both Subject Groups' Knee Extensors

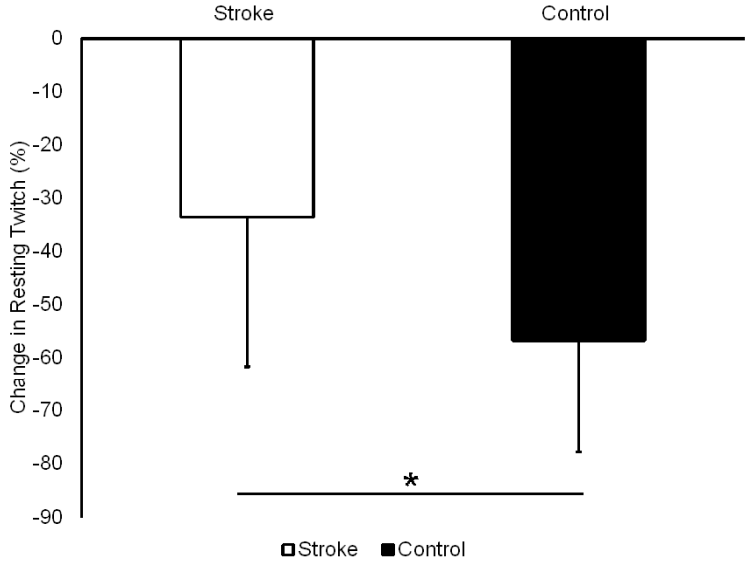


Figure 3.8. Resting twitch torque differed between subject groups after fatigue. Healthy controls had a greater percent RT reduction when compared to stroke survivors (*P* = 0.05). Data are represented as mean ± SD.

Voluntary activation reduced after fatigue in each subject group, but more in stroke survivors, (*Fig.* 3.9 and *Fig.* 3.10). In *Fig.* 3.9, there was a main effect of time that demonstrated the VA value reduced significantly from baseline to post-fatigue (*P* = 0.0001). There was not a main effect between subject groups that shows there was no significant difference between VA values between the subject groups (*P* = 0.09). Likewise, there was no interaction effect that revealed the VA value reduced similarly for each subject group (*P* = 0.24). In *Fig.* 3.10, stroke survivors had a greater percent reduction of VA when compared to healthy controls, but it was not significant (*P* = 0.17).

Baseline Voluntary Activation of Both Subject Groups' Knee Extensors

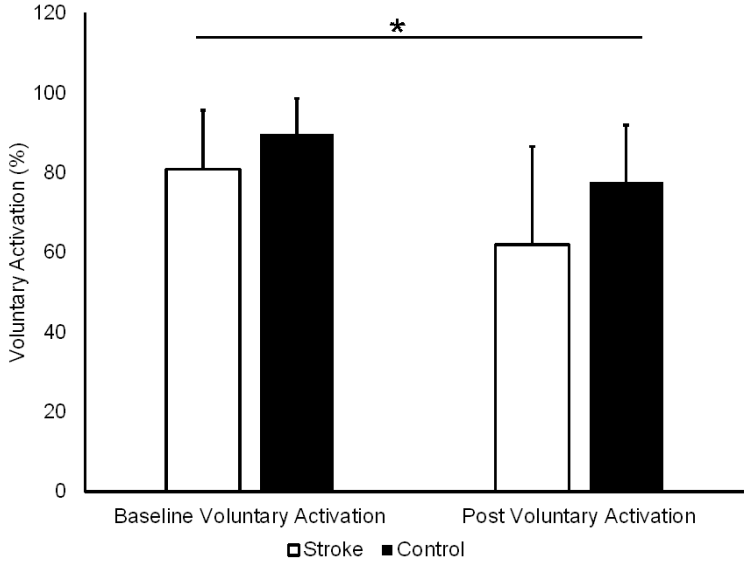


Figure 3.9. Voluntary activation reduced after fatigue in each subject group. **A)** VA reduced significantly from pre- and post- fatigue (P = 0.0001). There was not a significant difference between VA values between the subject groups as a main effect (P = 0.09). VA reduced similarly in the stroke survivors and control subjects (P = 0.24). Data are represented as mean ± SD.

The Effect of Fatigue on Voluntary Activation of Both Subject Groups' Knee Extensors

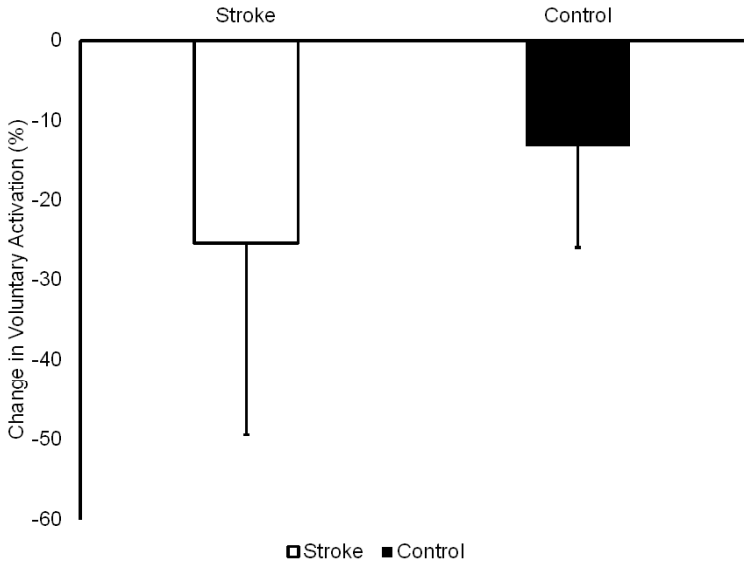


Figure 3.10. Voluntary activation differed between subject groups after fatigue. Stroke survivors had a greater percent reduction of VA when compared to healthy controls, but not significantly (P = 0.17). Data are represented as mean ± SD.

Stroke survivors have greater tendon tap torque responses as compared to healthy controls, (*Fig.* 3.11 and *Fig.* 3.12). In *Fig.* 3.11, there is a main effect of time that demonstrates the TT value reduced significantly from baseline to post-fatigue ($P = 0.0001$). There was a main effect between subject groups that showed there was a significant difference between TT values between the subject groups ($P = 0.001$). The difference was that TT values were different between subject groups regardless of TT timing. However, there was no interaction effect that revealed the TT value reduced similarly for each subject group ($P = 0.12$). In *Fig.* 3.12, healthy controls had a greater percent reduction of TT when compared to stroke survivors ($P = 0.05$).

Baseline Peak Tendon Tap Torque of Both Subject Groups' Knee Extensors

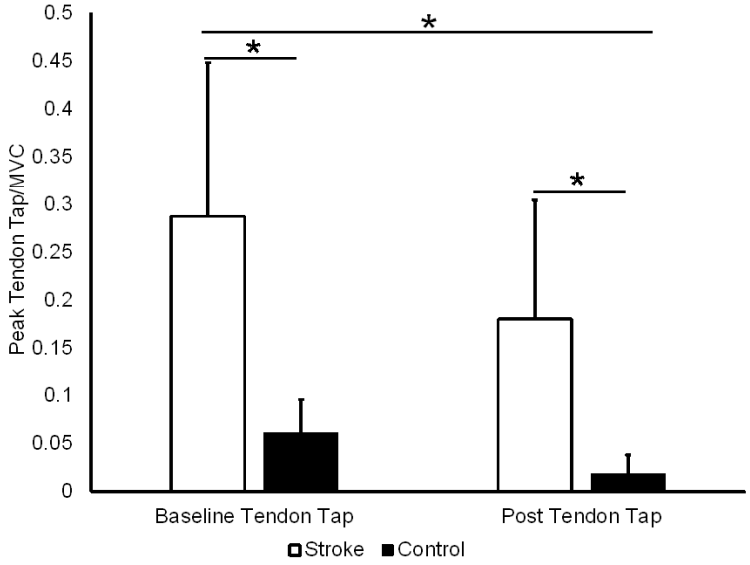


Figure 3.11. Tendon tap torque reduced after fatigue differed between subject groups. TT torque reduced significantly from pre- and post- fatigue ($P = 0.0001$). There was a significant difference between TT torque values between the subject groups as a main effect ($P = 0.001$). TT reduced similarly in the stroke survivors and control subjects ($P = 0.12$). Data are represented as mean ± SD.

The Effect of Fatigue on Tendon Tap Responses of Both Subject Groups' Knee Extensors

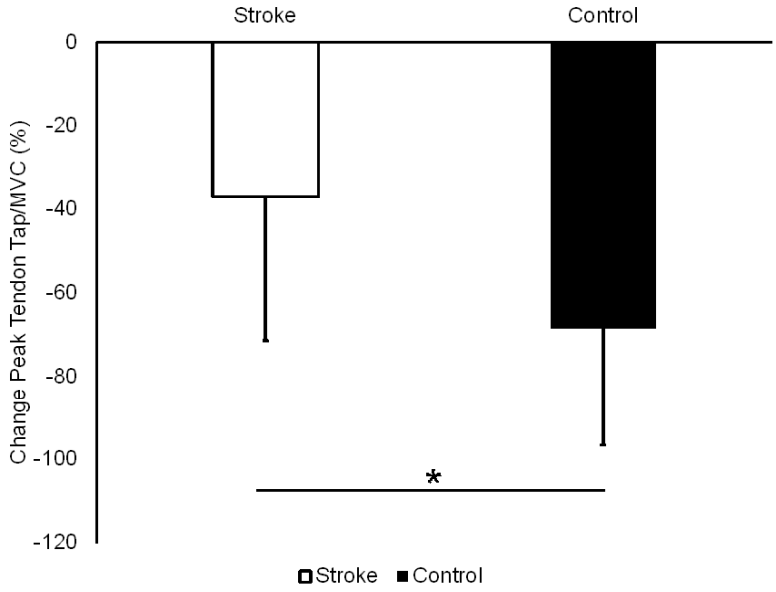


Figure 3.12. Tendon tap torque differed between subject groups after fatigue. Healthy controls had a greater percent reduction of TT torque when compared to stroke survivors (P = 0.05). Data are represented as mean ± SD.

Strength negatively correlated with task duration for healthy controls only in the superset group, (*Fig*. 3.13). MVC values related to shorter task duration times for controls only (r^2 = 0.22, P = 0.03), not for stroke survivors (r^2 = 0.13; P = 0.12).

Relationship Between MVC and Task Duration of Both Subject Groups in Superset Group

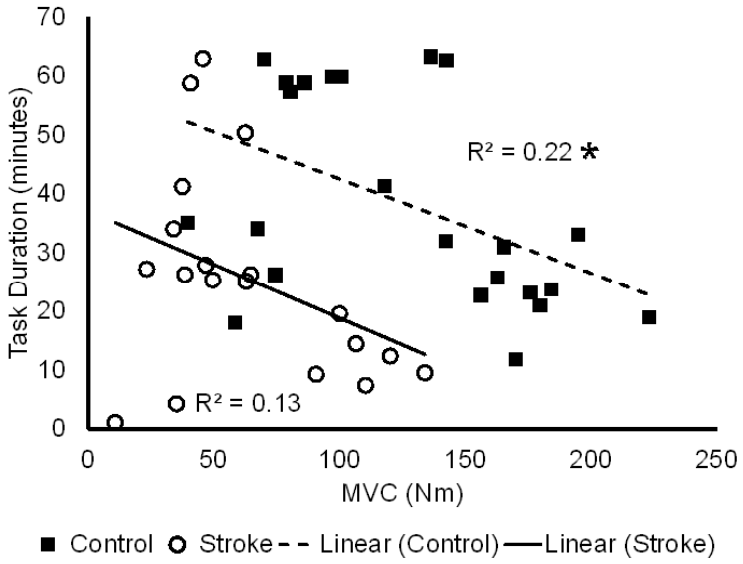


Figure 3.13. Baseline MVC inversely correlated with task duration for healthy controls. Open circles with solid trend line represent the data of stroke survivors. Black squares with dashed trend line are the data of the control group. MVC magnitudes negatively correlated to shorter task duration for controls only, (*P* = 0.03 for controls and *P* = 0.12 for stroke survivors).

Resting twitch reduction correlated to MVC reduction for healthy controls only, (*Fig*. 3.14). Greater RT reduction related to greater MVC reduction for controls only (r^2 = 0.53, *P* = 0.02), and not stroke survivors (r^2 = 0.04; *P* = 0.56).

Relationship Between Change in Resting Twitch and Change in MVC of Both Subject Groups

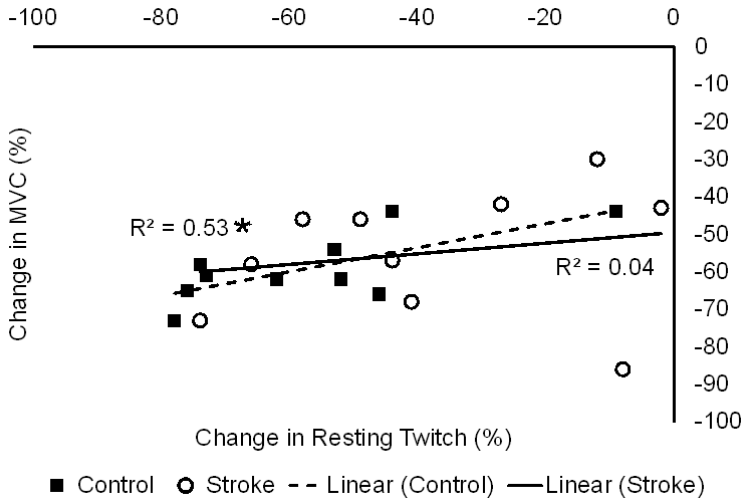


Figure 3.14. Change in RT correlated with change in MVC for healthy controls (squares) and stroke participants (circles). There was a positive correlation between reduction in RT magnitude and reduction in MVC. (P = 0.02 for controls and P = 0.56 for stroke survivors).

3.4. DISCUSSION

The primary findings of this study were that central mechanisms may primarily affect neuromuscular fatigue post stroke. The stroke survivors had less RT reduction, higher post-TT responses, less change of TT output and less MVC difference as compared to healthy controls. This evidence suggests that neural mechanisms contributed greater to neuromuscular fatigue as compared to peripheral mechanisms. Other stroke literature suggests reductions in voluntary activation (neural drive measure) may cause reductions in MVC (paresis measure) which would limit force regulation (Horstman et al., 2008; Riley & Bilodeau, 2002). Therefore, central mechanisms of impairment may mainly affect stroke survivors force regulation.

In our study, the reduction in RT amplitude in stroke subjects was less than for the controls. This suggests that the stroke subjects had less peripheral fatigue as compared to controls. This is a comparable finding seen in other stroke research (Riley & Bilodeau, 2002; Svantesson et al., 1999). Stroke survivors were revealed to have lower voluntary activation values and no reduction of EMG median frequencies in the paretic biceps when compared to the non-paretic biceps after a fatiguing task (Riley & Bilodeau, 2002). These finding shows no change in a peripheral impairment measure may indicate limited peripheral contributions to paretic bicep fatigue, while a neural impairment is suggested because VA reduced. The Svantesson group's results indicate that peripheral mechanisms may not affect primarily reduce force in the paretic plantarflexors because EMG mean power frequencies (indicator of E-C coupling

failure) did not decrease in the paretic muscle as compared to the non-paretic muscle (Svantesson et al., 1999). Also, in this dissertation study greater RT reduction related to greater MVC reduction for healthy controls only, which may indicate peripheral mechanism do not primarily contribute to post stroke fatigue. Although, peripheral mechanisms cannot be ruled out because both subject groups' RT reduced (Knorr et al., 2011; Riley & Bilodeau, 2002). Therefore, fatigue appears to be mainly attributed to central changes post stroke as opposed to peripheral mechanisms.

A possible central mechanism is suggested to affect muscle fatigue because the stroke survivors in this study had reduced MVC values after a fatiguing task as compared the healthy controls. This difference may suggest stroke survivors have a MVC reserve that still could be activated; thus central mechanisms are likely to be involved. In other words, controls have a larger difference in MVC because they are better able to activate their knee extensors fully to reach fatigue (Horstman et al., 2008; Hyngstrom et al., 2012; Knorr et al., 2011). Additionally, stroke survivors had higher VA reduction than controls even though the result was not significant. A larger VA reduction implies stroke survivors are not able to neurally drive the muscle activate fully; therefore, central mechanisms may be involved (Knorr et al., 2011; Riley & Bilodeau, 2002). Therefore, central mechanisms may primarily affect neuromuscular fatigue post stroke (Horstman et al., 2008; Hyngstrom et al., 2012; Knorr et al., 2011; Riley & Bilodeau, 2002).

More specifically, the changes in the spinal cord's stretch reflex may be one neural mechanism that contributes to decreased force regulation post stroke during fatigue. The stroke survivors in this study had higher post-TT and less change of TT responses post fatigue as compared to controls, which indicates hyperreflexia may cause decreased force regulation post stroke. Stroke survivors have larger TT responses and lower recruitment thresholds when compared to healthy controls (Yang et al., 2013); possibly due to hyperreflexia. Additionally, it was demonstrated that MVC magnitudes decreases and EMG activity increases post fatigue in healthy controls (Biro et al., 2007), which may suggest central mechanisms are involved to maintain force post fatigue. As result, amplified stretch reflexes (a neural mechanism of impairment) and neuromuscular fatigue may limit force regulation post stroke.

There are several limitations to this sutdy. Investigating central and peripheral mechanisms of neuromuscular fatigue for this study may have been affected by the design of this study. First, peripheral mechanisms of impairment were investigated using resting twitches only, which was assumed that peripheral mechanisms are only measured by one method. Other measurements of peripheral impairment may test muscle fatigue better. Using blood flow measures may have revealed that ischemia of the knee extensors could exacerbate muscle fatigue and reduce force regulation (Russ & Kent-Braun, 2003; Sjogaard, Kiens, Jorgensen, & Saltin, 1986; Sjogaard, Savard, & Juel, 1988). Second, there was a small sample size, which may affect generalization to the population (Green, 1981; Koch, Gillings, & Stokes, 1980; Pastides & Moore-Pastides, 1986). Third,

the tester bias may have affected the results because subjects were not randomized before testing (Green, 1981; Koch et al., 1980; Pastides & Moore-Pastides, 1986). Generalization to muscle fatigue may be limited as only one type of contraction was examined. Sustained versus intermittent contractions stress the neural muscular system differently (Hunter, Butler, Todd, Gandevia, & Taylor, 2006; Russ & Kent-Braun, 2003). Intermittent contractions allow for a rest period between contractions, which provides an opportunity for better muscle perfusion to produce adequate force (Russ & Kent-Braun, 2003). Also, isometric contractions were used instead of dynamic contractions for this study. Typical daily movements of the knee require dynamic contractions. Fatiguing maximal dynamic contractions show stroke survivors have shorter times to task failure and have reduced MVCs post stroke as compared to healthy controls (Rybar et al., 2014). Therefore, this study cannot rule out the possibility of greater contribution from muscle mechanisms and future studies should examine contraction types, load and test bias.

This study reveals neuromuscular fatigue may be caused by central mechanisms of impairments more than peripheral changes post stroke, which is comparable to other studies (Horstman et al., 2008; Hyngstrom et al., 2012; Knorr et al., 2011; Riley & Bilodeau, 2002). Additionally, stroke survivors' neuromuscular fatigue may be predicted by testing changes in TT responses (Biro et al., 2007) because reduced TT torque during fatigue may imply that the paretic muscle fatigued adequately to cause muscle hypertrophy needed for strengthening. Additionally, reductions in TT torque may correlate with lower limb

function during standing balance, which may imply that a central mechanism is predictive of balance post stroke. Therefore, clinical testing of these metrics could assist in predicting function and assessing the effectiveness of treatments post stroke that could improve force regulation.

CHAPTER 4: THE RELATIONSHIP OF REFLEX RESPONSES, PARESIS, VOLUNTARY ACTIVATION AND MUSCLE PROPERTIES TO CLINICAL METRICS OF LEG FUNCTION POST STROKE

4.1. INTRODUCTION

Central mechanisms of motor impairments may aid in understanding how force regulation and strength limit activities of daily living for stroke survivors. Limited function following stroke is multifactorial and could be from impairments or pathologies at several sites within the neuromuscular system. Central mechanism are changes in the central nervous system sites upstream of the NMJ and peripheral mechanisms are caused by changes in muscle properties (Gandevia, 2001). Therefore, there is a need to understand how stroke survivors continue to have deficits of strength and force regulation in order that physical therapists (PTs) may better treat these problems. Current clinical tests do not give an idea of the mechanism for deficits such as weakness or impaired force regulation. For instance, physical therapists assess muscle strength during brief maximal effort contractions called MMT (Bohannon, 2001). This test does not indicate which nervous system sites have changed to cause strength deficits – it only tells the tester, the subject is weak. Unfortunately, there is little evidence on what specific mechanisms cause weakness so it can be treated effectively. Central mechanisms may play a primary role in affecting motor impairments since there is cortical damage post stroke (Lance, 1966). Therefore, this study's goal is to investigate central mechanisms as a cause for these motor deficits post stroke.

To measure these central mechanisms involvement in weakness and sub-maximal force regulation, quantitative laboratory measures can be used. Load cells in dynamometers measure force and torque generation (Bohannon, 2005; Escolar et al., 2001). Many studies have demonstrated that the MVC measures indicate stroke survivors are weaker than healthy controls (Horstman et al., 2008; Hyngstrom et al., 2012; Knorr et al., 2011). Biodex dynamometers are accessible to many physical therapy clinics. Therefore, a quantitative metric may be more reliable than a subjective measure to examine muscle strength post stroke.

Furthermore, the mechanism for this post stroke weakness could be discovered by measuring voluntary activation. Voluntary activation metrics indicate how well the central nervous system neural drives a muscle to fully activate. Voluntary activation is measured by using the interpolated twitch technique, which involves obtaining MVC values. Having both deficits of voluntary activation and MVC may suggest that stroke survivors demonstrate muscle weakness because of impairments in the central nervous systems ability to excite motoneuron pools and ultimately muscle (Horstman et al., 2008; Knorr et al., 2011; Riley & Bilodeau, 2002). This impairment may be why stroke survivors are unable to regulate their force for basic functional tasks such as balance with walking.

Balance has been shown to be related muscle weakness (Gerrits et al., 2009; Horstman et al., 2008; Kim & Eng, 2003) and impaired force regulation (Hyngstrom et al., 2014) post stroke. Measures of MVCs have been correlated to clinical tests to reveal a better understanding of how muscle weakness impacts

function post stroke. For instance, there is a correlation between paretic knee extensor strength (measured by MVC) and limited clinical balance (Gerrits et al., 2009; Horstman et al., 2008). This relationship indicates that stroke survivors, who demonstrated the most knee extensor weakness, were also the same subjects who had the most impaired balance. Likewise, hip flexor dynamic maximal voluntary contractions (MVCs) magnitudes demonstrated a relationship with self-selected walking speed post stroke (Kuhnen et al., 2015). In other words, neuromuscular weakness of the paretic hip flexors may predict walking speed. Therefore, using laboratory and clinical measures together may provide a better understanding of what impairments affect clinical mobility post stroke.

Moreover, laboratory measures may provide further insight into the muscle (peripheral) and spinal cord mechanisms of post stroke impairments and functional mobility. To understand other mechanisms of impairments and how they may contribution to post stroke deficits, researchers can investigate RT and TT responses and relate the results to clinical function.

Resting twitch changes give an understanding of maximal muscle strength and calcium availability for cross bridge formation needed for muscle contraction (Baudry et al., 2006; Gandevia, 2001). Typically, in the healthy controls, the RT reduces after a fatiguing task, which indicates muscle integrity changes as the cause for muscle fatigue (Baudry et al., 2006; Bigland-Ritchie et al., 1986; Gandevia, 2001). In stroke survivors, there are limited studies that indicate what happens to the resting twitch magnitude when paretic muscles are shown to be weak (reduced MVC). However, half-relaxation times elicited by electrical evoked

contractions have shown to be longer in duration for the paretic limb when compared to the healthy control's limb (Horstman et al., 2009; Horstman et al., 2010). This result may indicate that there are changes in the muscle properties that contribute to muscle weakness post stroke and could decrease force regulation. However, this peripheral mechanism may not be the main mechanism for poor force regulation post stroke.

Central mechanism may be related to cortical damage post stroke, which may primarily affect force regulation post stroke. Due to cortical disinhibition, stroke survivors amplified Ia EPSPs (Lance, 1966). Tendon tap responses can be used to measure the monosynaptic stretch reflex pathway activity. Stroke survivors' demonstrate larger TT torque responses and lower recruitment thresholds when compared to healthy controls (Yang et al., 2013); possibly due to increased reflex gain. However, the research has been limited in using instrumented TT to assess reflex gain post stroke. Therefore, the one study goal is to probe changes at the spinal cord level with the use of TTs to indicate central mechanisms may affect force regulation post stroke.

The purpose of this dissertation study was to quantify baseline neuromuscular function in peripheral and central sites and investigate the relationship to clinical impairment and dysfunction post stroke. It may be possible to predict impairment and functional mobility by measuring neuromuscular function post stroke. Baseline neuromuscular function (TT, MVC, VA and RT responses) of the paretic knee extensors were examined. The findings were related to leg impairment, balance and walking speed capabilities. The

hypothesis was that stroke survivors with better central neuromuscular function would have less leg impairment, better balance and be faster walkers. Additionally, central synaptic function may be a better prediction of clinical function instead of peripheral synaptic function for paretic knee extensors. Investigating several synaptic sites applicability to clinical function may facilitate the bench to bedside importance of research. Ultimately, these findings could improve rehabilitation stroke treatments.

4.2. METHODS

4.2.1. Subjects

Ten stroke survivors (61.8 ± 10.9 years; 6 females, 4 males) participated in the study; (*Table* 4.1.). The Fugl Meyer (de Oliveira, Cacho, & Borges, 2006), Berg Balance Scale, Dynamic Gait Index and 10-m walk test (Mudge & Stott, 2009) (self-selected walking speed) were measured for stroke survivors. Subjects were excluded as follows: stroke was less than 6 months ago, unable to follow 2 step commands, had low back pain, had more than 1 stroke, had exercise associated health risk, and/or had an acute history of knee soreness or knee surgery. Subjects gave written consent to participate in the study, which the Institutional Review Board of Marquette University approved. In a familiarization session, participants practiced maximal and sub-maximal knee extensor contractions. All subjects participated in a familiarization and functional testing session and one experimental protocol session.

Table 4.1. Subject Characteristics and Clinical Metric Scores

Subject	Age (yrs)	Sex	Paretic Side	Time Post CVA (yrs)	FM Score	DGI Score	10 m Walk Test (m/s)	Berg Score	MVC of Knee Extensors (Nm)
101	55	M	Left	9.5	29	16	0.96	45	49.55
103	66	F	Left	7.5	17	13	0.28	38	38.48
104	62	F	Right	22.5	30	19	1.22	47	64.6
107	56	M	Left	4.5	30	22	0.94	55	62.52
108	48	M	Right	16	23	22	1.35	55	110.3
109	57	F	Left	36	14	15	0.4	46	23.3
110	76	F	Right	4	30	23	1.1	48	40.73
111	67	M	Left	1.5	11	5	0.14	24	10.76
112	48	M	Left	11	21	16	0.34	43	35.14
113	79	F	Right	5	22	16	0.83	42	133.9
114	55	M	Left	4	27	15	0.66	49	45.63
115	67	M	Right	9	19	18	0.67	48	62.86

Table 4.1. Continued

Subject	Age (yrs)	Sex	Paretic Side	Time Post CVA (yrs)	FM Score	DGI Score	10 m Walk Test (m/s)	Berg Score	MVC of Knee Extensors (Nm)
Mean	61.33			10.88	22.76	16.67	0.78	44.42	56.48
Standard Deviation	9.98			9.85	6.61	4.87	0.43	7.67	34.93

Note: Berg = Berg Balance Scale, CVA = cerebrovascular accident, DGI = Dynamic Gait Index, FM = Fugl – Meyer 10 m Walk test = Self-selected 10 meter walk test, F = female, M = male, MVC = maximal voluntary contraction, Nm = Newton meters, yrs = years

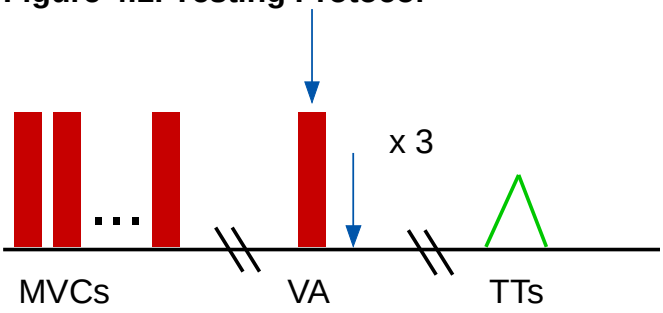
4.2.2. Experiment Set-Up

During the experimental session, subjects sat with the test leg positioned in 70° of flexion into a Biodex dynamometer chair. A load cell (JR3 Inc., Woodland, CA) was used to measure knee extensor torques during the testing session. Subjects performed 3 to 5 baseline strength measurements of isometric MVCs of the knee extensors. The subjects increased knee extension force from zero to maximum over 1-2 s and observed the exerted force on a monitor. The researchers verbally encouraged the subjects during all tasks. Subjects rested for 60 s between trials as not to cause neuromuscular fatigue during testing. Trials were repeated until peak forces from 2 of the 5 trials were within 5% of each other. The MVC was the peak torque generated. A protocol example can be seen in *Fig*. 4.1.

During the last three MVC attempts, VA was quantified using the interpolated twitch technique (Gandevia, 2001). Determination of VA using the interpolated twitch technique provides a metric of the nervous system's ability to activate fully the knee extensor musculature. A VA example can be seen in *Fig.*

4.2. A brief constant-current stimulator (Digitimer DS7AH, Welwyn Garden City, UK) delivered a rectangular pulse of 100 µs duration with maximum amplitude of 400 V, which was used to stimulate the rectus femoris muscle. The stimulation intensity (usually 200 mA to 500 mA) was set at 20% above the level required to produce a maximal resting twitch amplitude. To determine muscle contractile property contributions, changes in resting twitch magnitudes were quantified. When the muscle was potentiated, resting twitches were obtained about 5 seconds after the MVC task. An interpolated twitch was given at the plateau of the MVC task to assess VA. The formula to determine percent voluntary activation was ((1- (interpolated twitch magnitude)/ (RT magnitude))*100) (Gandevia, 2001).

Figure 4.1. Testing Protocol



The testing protocol includes MVCs (red rectangles), resting twitch (2nd blue arrow), voluntary activation (MVCs with superimposed and resting twitches (blue arrows)), and tendon tap responses (green triangle).
Note: MVCs = maximal voluntary contractions, VA = voluntary activation, TTs = tendon tap responses.

Stroke

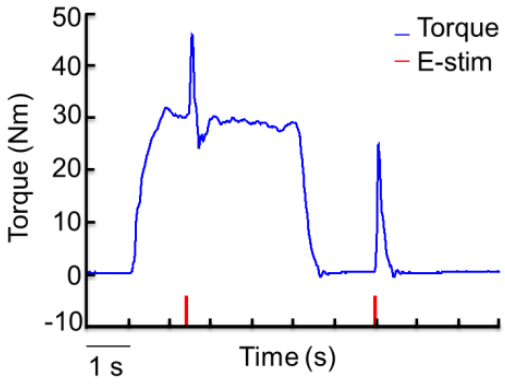


Figure 4.2. Voluntary Activation Example. This example represents a knee extensors' baseline voluntary activation for a single stroke survivor. The 1st twitch response is the superimposed twitch. The 2nd twitch response is the baseline resting twitch.

Spinal reflex responses were measured. A Linmot linear motor (model # PSo1-23x 160) gave 5 taps (2 Hz) to the knee extensors (Lance, 1966; Shinohara et al., 2005). The knee extensor reflex magnitude provided information on spinal reflex pathways contribution to force generation.

Custom-written LabVIEW (National Instruments, Austin, TX) programs triggered the electrical stimulator and acquired all data. Prior to acquisition, torque signals were low-pass filtered (500 Hz) and then sampled at 1 kHz.

4.2.3. Data Analysis

Squared Pearson product-moment correlation coefficient (r^2, $\alpha = 0.05$) detected correlations in resting twitch torque, MVC, tendon tap and voluntary activation with clinical metric scores from the Fugl Meyer, Berg Balance Scale, Dynamic Gait Index and Ten Meter Walk Test. A forward step regression analysis was used to identify a single best predictor from a group of variables.

4.3. RESULTS

Bivariate correlation analyses revealed baseline VA and peak TT responses were related to clinical measures of balance in stroke survivors *(Fig.* 4.3, *Fig*. 4.4, *Fig.* 4.5 and *Fig.* 4.6*)*. In other words, stroke survivors with higher voluntary activation and lower tendon tap responses were the higher functioning participants. VA activation percentages positively correlated with higher Dynamic Gait Index (DGI) scores, (r^2 = 0.44, P = 0.04) and with higher Berg Balance Scale (BBS) scores, (r^2 = 0.42, P = 0.04). In contrast, TT output negatively correlated with DGI scores, (r^2 = 0.76, P = 0.0001) and correlated with BBS scores, (r^2 = 0.69, P = 0.001).

Voluntary Activation Relationship to Dynamic Balance Post Stroke

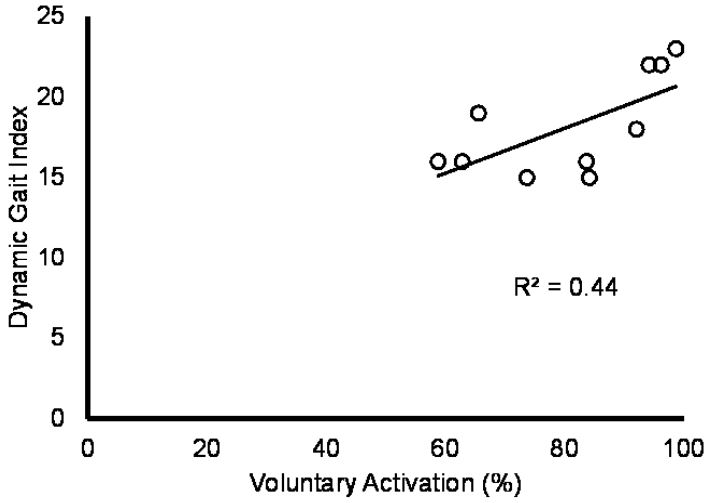


Figure 4.3. Baseline voluntary activation responses are related to clinical measures of balance in stroke survivors. Voluntary activation positively correlated with higher Dynamic Gait Index (DGI) score, (r^2 = 0.44, P = 0.04).

Voluntary Activation Relationship to Balance Post Stroke

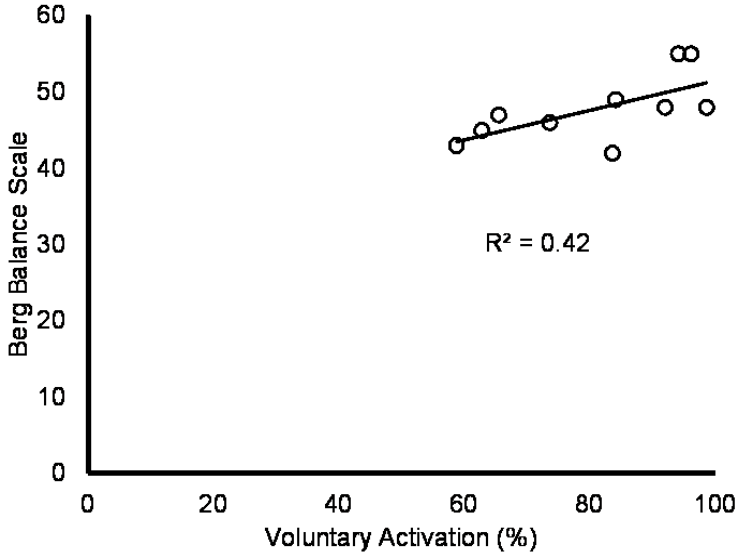


Figure 4.4. Baseline voluntary activation responses are related to clinical measures of balance in stroke survivors. Voluntary activation positively correlated with Berg Balance Scale (BBS) score (r^2 = 0.42, P = 0.04).

Tendon Tap Response Relationship to Dynamic Balance Post Stroke

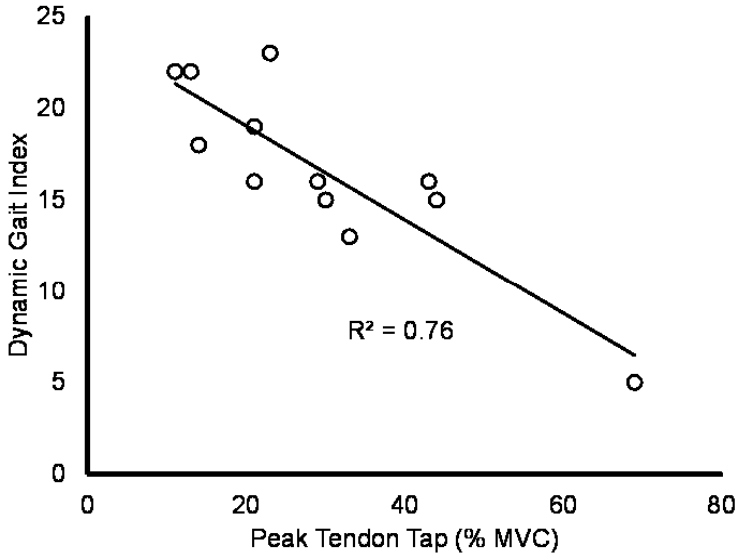


Figure 4.5. Baseline peak tendon tap responses are related to clinical measures of balance in stroke survivors. Tendon tap output negatively correlated with DGI score, (r^2 = 0.76, P = 0.0001).

Tendon Tap Response Relationship to Balance Post Stroke

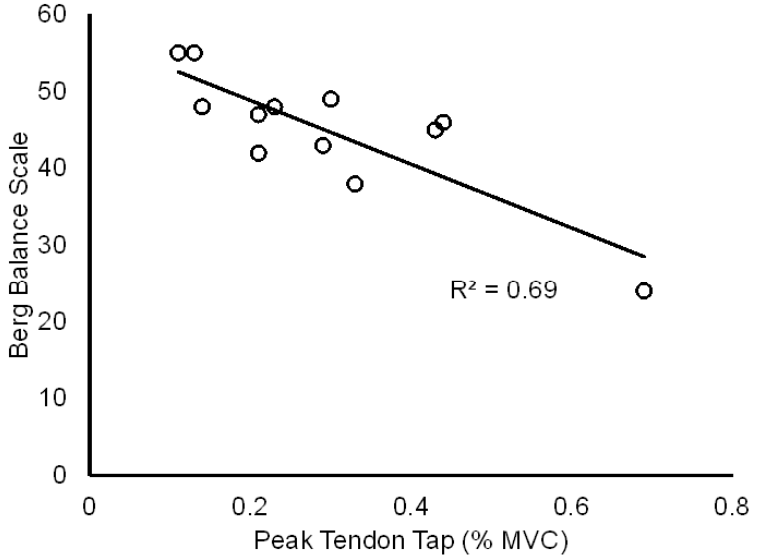


Figure 4.6. Baseline peak tendon tap responses are related to clinical measures of balance in stroke survivors. Tendon tap output negatively correlated with BBS score (r^2 = 0.69, P = 0.001).

Baseline peak TT responses and MVC were related to clinical measures of leg impairment and walking speed in stroke survivors (*Fig.* 4.7., *Fig.* 4.8. and *Fig.* 4.9)., Stroke survivors with lower tendon tap responses and higher MVC values were the higher functioning participants. Tendon tap output inversely correlated with higher Fugl-Meyer (FM) scores, (r^2 = 0.35, P = 0.04). Additionally, TT output negatively correlated with faster walking speeds, (r^2 = 0.44, P = 0.02). However, MVCs of knee extensor positively correlated with faster walking speeds, (r^2 = 0.39, P = 0.03).

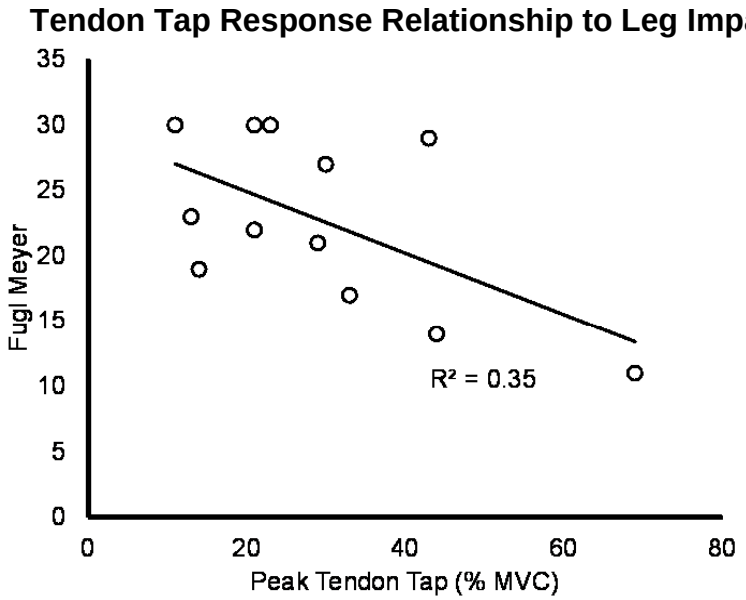


Figure 4.7. Baseline peak tendon tap responses are related to clinical measures of leg impairment in stroke survivors. Tendon tap output negatively correlated with higher Fugl-Meyer (FM) score (e.g. less leg impairment), (r^2 = 0.35, P = 0.04).

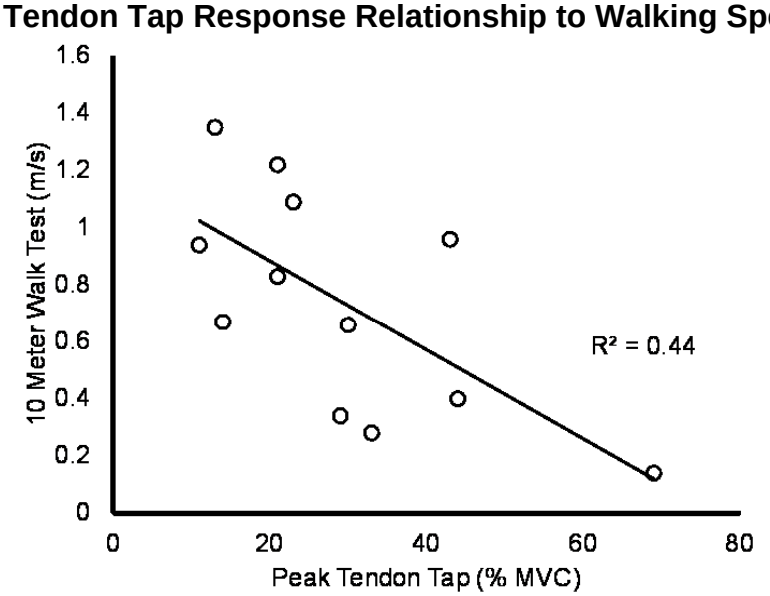


Figure 4.8. Baseline peak tendon tap responses are related to walking speed in stroke survivors. Tendon tap output negatively correlated with faster walking speed (r^2 = 0.44, P = 0.02).

MVC Relationship to Walking Speed Post Stroke

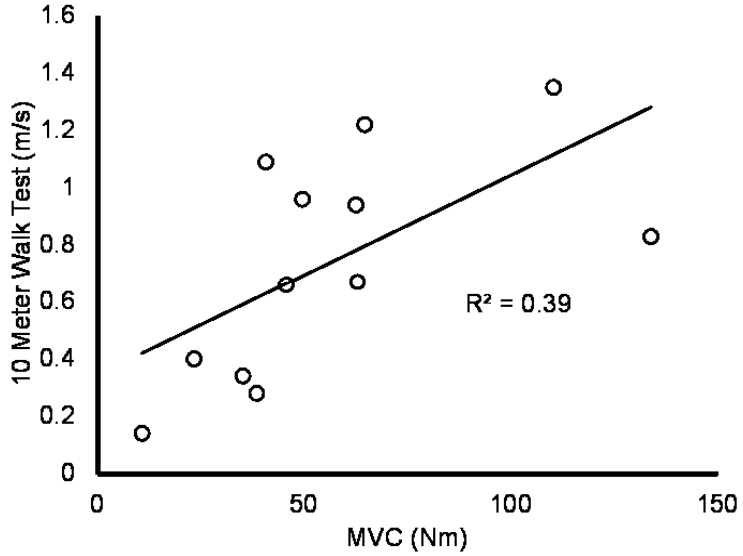


Figure 4.9. Baseline MVC responses are related to clinical measures of leg impairment and walking speed in stroke survivors. MVC (stronger) of knee extensors positively correlated with faster walking speed (r^2 = 0.39, P = 0.03).

Stroke survivors with better limb muscle strength symmetry were the higher functioning participants. *(Fig.* 4.10., *Fig.* 4.11. and *Fig.* 4.12.*)*. A ratio of paretic MVC/non-paretic MVC was utilized to understand the muscle strength symmetry of the two limbs. A higher MVC Ratio correlated with faster walking speeds, (r^2 = 0.55, P = 0.01), with higher DGI scores, (r^2 = 0.41, P = 0.03) and with higher FM scores, (r^2 = 0.64, P = 0.002).

Leg Strength Symmetry Related to Walking Speed Post Stroke

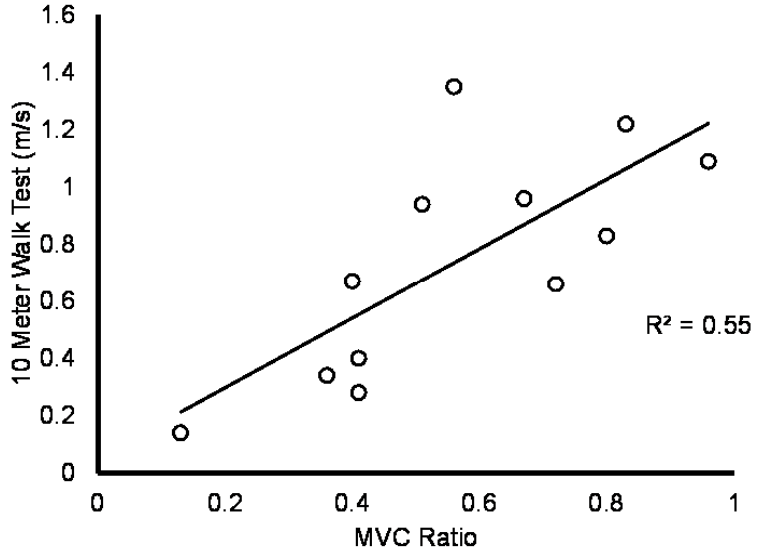


Figure 4.10. Lower limb baseline MVC (strength) symmetry related to walking speed post stroke. MVC Ratio (better leg strength symmetry) positively correlated with faster walking speed, (r^2 = 0.55, P = 0.01).

Leg Strength Symmetry Related to Balance Post Stroke

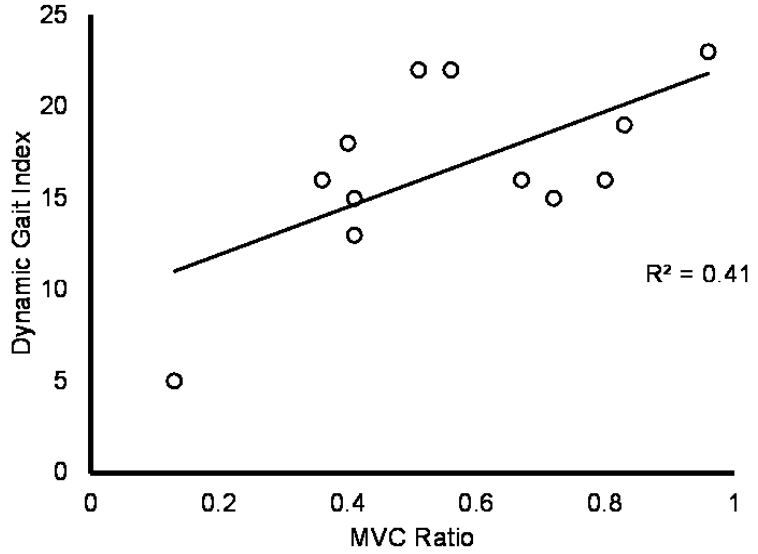


Figure 4.11. Lower limb baseline MVC (strength) symmetry related to balance post stroke. MVC Ratio positively correlated with higher DGI score (better balance), (r^2 = 0.41, P = 0.03).

Leg Strength Symmetry Related to Leg Impairment Post Stroke

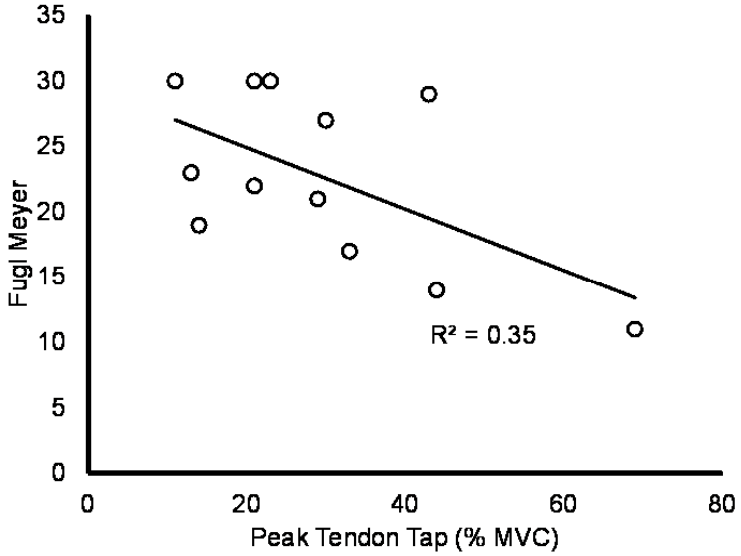


Figure 4.12. Lower limb baseline MVC (strength) symmetry related to leg impairment post stroke. MVC Ratio negatively correlated with higher FM score (less leg impairment), (r^2 = 0.64, P = 0.002).

There was no significant relationship seen with RT and the clinical measures *(Table* 4.2.). The RT magnitude correlated with the clinical measures as follows: FM score, (r^2 = 0.001, P = 0.91); DGI score, (r^2 = 0.02, P = 0.69); self-selected Ten Meter Walk Test (m/s), (r^2 = 0.10, P = 0.34); and BBS score, (r^2 = 0.001, P = 0.93).

Table 4.2. Baseline Resting Twitch Relationship to Clinical Leg Impairment and Function

Resting Twitch vs Clinical Test	**r^2 correlation**
Resting Twitch vs Fugl Meyer	0.001
Resting Twitch vs Dynamic Gait Index	0.02
Resting Twitch vs Ten Meter Walk	0.10
Resting Twitch vs Berg Balance Scale	0.001

A forward regression analysis revealed the single best predictor of each clinical test (*Table* 4.3). The Fugl Myer score was best predicted by the MVC ratio, (r^2 = 0.64). The DGI score was predicted by the peak tendon tap response,

(r^2 = 0.48). The BBS score was predicted by the voluntary activation percentage, (r^2 = 0.43). The Ten Meter Walk Test was best predicted by the MVC ratio, (r^2 = 0.55).

Table 4.3. Regression Analysis – Single Best Predictor of Each Clinical Measure

Clinical Test	Lab Measurement
Fugl Myer	MVC Ratio (r^2 = 0.64)
Dynamic Gait Index	Peak Tendon Tap Response (r^2 = 0.48)
Berg Balance Scale	Voluntary Activation (r^2 = 0.43)
Ten Meter Walk Test	MVC Ratio (r^2 = 0.55)

4.4. DISCUSSION

This study revealed baseline neural measurements of impairment (seen in less paresis, smaller TT response, similar bilateral leg strength and large VA) correlated more with less leg impairment and greater mobility for paretic knee extensors. Individuals with less tendon tap reflex responses (ie less spasticity) and larger neural drive had better balance. Individuals with greater muscle strength symmetry of the paretic and non-paretic knee extensors had less lower leg impairment and walked faster, which was best predicted by the MVC Ratio metric. There was no significant relationship between RT and clinical function in the lower limb, which suggests peripheral sites are not the primary mechanism for poor force regulation post stroke (Knorr et al., 2011; Riley & Bilodeau, 2002). Therefore, clinical function may be predicted by baseline neural measures of impairment post stroke.

Central mechanisms of impairment are likely contributors to impaired force regulation post stroke. One clinical impairment of force regulation is paresis. Paresis may be caused by impaired neural drive (seen in reduced VA and MVC) (Horstman et al., 2008; Knorr et al., 2011; Riley & Bilodeau, 2002). This evidence is comparable to this dissertation result that revealed the less clinically impaired subjects had larger VA values. Likewise, subjects with smaller MVC values (more paresis) and smaller VA were the subjects with the most clinical impairments. These results may suggest that paresis may be caused by a reduced ability to neurally drive the knee extensors post stroke. Furthermore, this paresis may be related to an inability to regulate force post stroke.

More specifically, hyperreflexia may be one neural mechanism of impairment that effects force regulation post stroke. In this study, subjects with larger TT responses had greater clinical function impairments. This relationship is consistant with the positive correlation between VA and MVC with clinical function. Paresis may be affected by amplified stretch reflexes since there were larger TT responses in the most clinicially impaired subjects, which is seen in other stroke literature (Levin et al., 2000). It is reported that increased spasticity causes reduced relaxation, increased co-activation, limited movement in the upper limb elbow muscles (Levin et al., 2000). Therefore, hyperreflexia may explain one contributor of impaired force regulation and thus clinical function post stroke.

Spasticity may affect clinical function, but this point has been debated in the literature (Dietz & Sinkjaer, 2007). It was demonstrated that tonic reflexes were at the same intensity in stroke survivors and healthy controls during gait, which spasticity was assumed to not affect walking (Ada et al., 1998). Likewise, it was suggested spasticity did not affect postural sway during standing because EMG values of the soleus and tibilais anterior did not increase with perturbations in stroke survivors as compared to healthy controls (Nardone et al., 2001). However, there are studies that demonstrate hyperreflexia may impair hip flexor timing (Hyngstrom et al., 2010a), prolong quadricep activity (Lewek et al., 2007) or increase upper limb coupling (Hoffmann, Kamper, Kahn, Rymer, & Schmit, 2009) post stroke. Furthermore, these stroke studies suggest that impaired force regulation is related to impaired walking kinematics (A. Hyngstrom et al., 2010a;

Lewek et al., 2007), which suggests spasticity affects mobility after a stroke. Therefore, the results of this dissertation study are in accordance with previous results that show hyperreflexia is related to impaired clinical mobility post stroke (Hyngstrom et al., 2010; Lewek et al., 2007).

Impaired clinical mobility post stroke did not correlate signficiantly with the resting twtich magnitudes. It is not surprising that this measure of peripheral impairment did not correlate with the clinical metrics of function. First, central mechanisms of impairment such as spasticity are suggested primarily to affect force regulation post stroke (A. Hyngstrom et al., 2010a; Levin et al., 2000; Lewek et al., 2007). Second, the resting twitch measure is a non-voluntary evoked muscle contraction (Gandevia, 2001) and would require less central input, which is different from voluntary muscle contractions need for clinical tests of balance and limb mobility. Limitations of the study are based on the design of the study. First, resting twitches were the only measures completed to probe peripheral mechanisms of impairment. Using measures of M wave amplitudes may have indicated that signal transmission through the NMJ was impaired (Gandevia, 2001). Second, there was a small sample size, which may limit how much of the results can be representative of the stroke population (Green, 1981; Koch et al., 1980; Pastides & Moore-Pastides, 1986). . And lastly, only a few clinical tests were investigated. It is possible the laboratory measures used in this study could correlate with other clinical tests (e.g. Modified Physical Performance Test) that assess frailty in mobility impaired adults (Brown, Sinacore, Binder, & Kohrt, 2000; Tanji et al., 2008). Therefore, this study cannot rule out the

possibility of muscle mechanisms or alternative test designs that may have limited force regulation and correlated with clinical function post stroke.

This study gives evidence that baseline central measures of impairments may best predict clinical function post stroke. Increased baseline reflex gain (large TT response) appears to be related to clinical leg function and mobility post stroke. In addition to improve force regulation, neural drive and strength metrics could add to the understanding of clinical function post stroke. Future studies testing TTs and MVC before and after a treatment modaility could reveal the effectiveness of a treament by increasing neural drive to a muscle. Increase neural drive to muscles would assist in improving force regulation post stroke. Therefore, quantitative central measures of impairment could enhance the understanding of stroke survivors' control of function and, thus lead to optimized rehabiliative stroke programs.

CHAPTER 5: DISCUSSION

5.1. SUMMARY OF RESULTS

This dissertation is the first to examine in one study several central and peripheral sites of impairment during a fatiguing task and without a fatigue condition and the effect on force regulation and function post stroke. Neural mechanisms of impairment post stroke may mainly affect force regulation post stroke (Hyngstrom et al., 2012; Knorr et al., 2011; Riley & Bilodeau, 2002) and data from these studies suggest hyperreflexia may be one of those mechanisms. Although, there are studies that have examined fatigue mechanisms in stroke survivors (Horstman et al., 2008; Knorr et al., 2011; Riley & Bilodeau, 2002); few studies have looked at the impact of mechanisms of neuromuscular fatigue being related to changes at the spinal stretch reflex level post stroke (Boudarham et al., 2014). Hyperreflexia manifested as clinical spasticity could affect force regulation and thus walking ability post stroke (Hyngstrom et al., 2010; Lewek et al., 2007). Additionally, fatigue could limit force generation and endurance post stroke (Hyngstrom et al., 2012; Knorr et al., 2011; Riley & Bilodeau, 2002), but fatigue is necessary for muscle strengthening (Folland & Williams, 2007; Gabriel et al., 2006). Furthermore, fatigue may increase EMG responses and reduce MVC torque as is seen in healthy controls (Biro et al., 2007). Therefore, stroke rehabilitation programs may need to inhibit Ia pathways to overcome spasticity, in order to improve force regulation. Moreover, these dissertation studies revealed

how hyperreflexia with and without a fatiguing condition could affect force regulation and may be related to clinical function post stroke.

Each study examined relationship of hyperreflexia on force regulation post stroke. *Study one* investigated how stimulation frequency affected the monosynaptic sensory pathways by use of the H-reflex technique and related the findings to walking speed. Stroke survivors H-reflex responses depressed less than healthy controls and the H-reflex response was inversely related to walking speed. This adds to the larger body of knowledge that the modulation of the H-reflex responses is dependent on stimulation frequency. Additionally, when using high frequency stimulation, the H-reflex response may be predictive of walking speed post stroke. In *study two*, central mechanisms were primarily suggested to cause neuromuscular impairments post stroke as compared to healthy controls after a fatiguing task. For example, the stroke survivors had larger tendon tap responses (indicator of hyperreflexia) and smaller MVC values as compared to healthy controls after fatigue; suggesting hyperreflexia may affect paresis post stroke. Likewise, RT values reduce less in stroke survivors when compared to healthy controls; indicating less peripheral mechanisms contributing force impairment.

In *study three*, hyperreflexia was implicated as a cause for impaired force regulation because stroke survivors with larger tendon tap torque responses had the most leg impairments and mobility dysfunctions. These dissertation results show that hyperreflexia may limit functional mobility post stroke, which is similar to other stroke research (Hoffmann et al., 2009; Hyngstrom et al., 2010; Lewek et

al., 2007). In *study one*, stroke survivors with less H-reflex depression (presumably caused by hyperreflexia) were slowest walkers. In *study three*, the stroke survivors with the largest tendon tap responses were the most clinical impaired. This is similar to finding showing that spasticity may cause impaired hip flexor timing (Hyngstrom et al., 2010), prolonged quadriceps activity (Lewek et al., 2007) and impaired upper limb coupling (Hoffmann et al., 2009) that can affect that may be related to impaired clinical function (Hyngstrom et al., 2010; Lewek et al., 2007). Although, there are stroke survivor studies that report hyperreflexia does not affect function (Ada et al., 1998; Dietz & Sinkjaer, 2007). However, the results from this dissertation give evidence that hyperreflexia may affect force regulation and thus impair clinical function and mobility post stroke.

Another novel finding of this dissertation is central mechanisms of impairment may be predictive of clinical function post stroke as compared to muscle property impairments as was seen in *study three*. Measures of neural drive, paresis and hyperreflexia correlated best with the clinical metrics of function when compared to muscle property integrity measure. Other stroke studies have shown similar findings of central mechanisms of impairment correlating with clinical impairment and function. For instance, stroke researchers found that H-reflex responses (indicator of stretch reflex gain) depress less in the subjects who have spasticity (Bhagchandani & Schindler-Ivens, 2012; Roche et al., 2012) and those subjects are the slowest walkers (Bhagchandani & Schindler-Ivens, 2012). This dissertation study is unique because it is of the few studies that show central and peripheral mechanisms of impairment relationship to clinical function. This

dissertation gives evidence that central mechanisms may primarily affect force regulation and thus clinical function post stroke.

Another interesting finding is that instrumented tendon taps may be a more quantitative way in examining stretch reflex responses in the clinic. Manual tendon taps are used routinely in clinics. On the other hand, use of a dynamometer has been reported to be the gold standard in research investigations for collecting data about the stretch reflex response (Perell, Scremin, Scremin, & Kunkel, 1996). Likewise, other stroke studies have used this method and related spasticity to impaired force regulation (Hoffmann et al., 2009; Hyngstrom et al., 2010; Lewek et al., 2007). However, the use of instrumented tendon taps in this dissertation has shown to have a strong relationship with clinical functional tests. The peak TT response and the 10 meter walk test (r^2 = 0.44, $P < 0.05$) correlated better (i.e. larger r^2) than the H-reflex response and 10 meter walk test (r^2 = 0.41, $P < 0.05$) for the stroke survivors in this dissertation. Both measures are assumed to be measuring stretch reflex responses (Knikou, 2008; Toft, 1995). However, two different stroke survivor groups participated in each study, where one group may have been more impaired. Additionally, the difference may be that instrumented TT latency is similar to manual TT for the stretch reflex. Whereas, the H-reflex response is an electrical, mechanical and man-made product that may have other ogliosynaptic inputs that affect its response (Knikou, 2008; Misiaszek, 2003) and has a faster latency than TT (Burke et al., 1983). A shorter latency may reduce the input of the normal fusimotor input needed to regulate the stretch reflex response (Burke et al.,

1983). Therefore, instrumented TTs may better predict walking speed post stroke and may be better applicable to manual TTs performed in the clinical setting.

In conclusion, neural mechanisms of impairment may best predict force regulation and clinical leg impairment and function post stroke. Evidence from these studies show neural measures of impairment correlated with clinical leg function. Study one suggests high stimulation frequency of the H-reflex response may predict walking speed post stroke. In study two, the stroke survivors had less RT reduction, higher post-TT responses, less change of TT output and less MVC difference as compared to healthy controls. Furthermore, study three demonstrated that baseline measures of neural drive and stretch reflex correlated better with the clinical function test as opposed to peripheral measures of muscle property integrity. Therefore, neural mechanisms may be the primary contributors to limited force regulation post stroke and those central impairments may need to be treated to improve clinical function post stroke.

5.2. IMPLICATIONS FOR REHABILITATION

One important finding from this dissertation is that central mechanisms of impairment such as hyperreflexia may affect stroke survivors force regulation. With this evidence, stroke treatments may need to be refocused at impacting the central nervous system. Possible interventions to affect the central nervous system are as follows: brain stimulation, drug therapy, rehabilitation sensory techniques. Each of these techniques could impact the central nervous through various pathways and could possibly improve force regulation and clinical function post stroke.

Stimulation to the brain could possibly alleviate some impairments post stroke when combined with traditional physical therapy treatments (Page, Cunningham, Plow, & Blazak, 2015). Non-invasive procedures such as TMS and transcranial direct current stimulation (tDCS) can create electric currents in the brain to change cortical excitability (Hummel et al., 2005). Use of anodal tDCS applied to the primary motor cortex of the affected hemisphere was suggested to improve paretic hand pinching force and reaction times post stroke (Hummel et al., 2006). Likewise, a 1 Hz - repetitive TMS (rTMS) applied to the contralesional hemisphere was suggested to assist stroke patients with dexterity in affected hand (Liepert, Zittel, & Weiller, 2007). Therefore, it is possible that central mechanisms of impairment could be impacted by brain stimulation to improve force regulation post stroke.

Subcortical pathways can be impacted by drug therapy. For instance, increases in brainstem monoamines could increase motoneuron outputs

(Heckman, Hyngstrom, & Johnson, 2008; Heckman, Lee, & Brownstone, 2003; Heckman, Mottram, Quinlan, Theiss, & Schuster, 2009). After stroke, these monoamines may be increased because of cortical disinhibition to brainstem centers. In stroke survivors, regulated neuromodulators appear to improve function with the use of serotonin antagonist medication (Chollet, Acket, et al., 2013; Chollet, Cramer, et al., 2013). Additionally, spinal cord injured studies suggest serotonin antagonist medications can improve force generation (D'Amico et al., 2013; Gorassini, Knash, Harvey, Bennett, & Yang, 2004; Thompson & Hornby, 2013; Thompson, Jayaraman, Kinnaird, & Hornby, 2011). Therefore, to improve paretic muscle force control, treatments may need to regulate brainstem neuromodulators post stroke.

Other drugs such as baclofen and tetrazepam have been used to treat spasticity at the spinal cord level post stroke, which could improve force regulation (Milanov, 1992b; Milanov, 1992). Baclofen is suggested to normalize interneuron activity and decrease MN activity by activating the $GABA_B$ receptor (Milanov, 1992). Baclofen blocks reflexes by acting as an inhibitory neurotransmitter (Milanov, 1992). Baclofen is suggested to depress the central nervous system to cause spastic muscles to relax, but this increase relaxation may make it difficult for paretic muscles to control walking (Kofler, Quirbach, Schauer, Singer, & Saltuari, 2009). Tetrazepam acts by increasing PSI and decreasing MN excitability by activating the $GABA_A$ receptor, which increases the conductance of these inhibitory channels (Milanov, 1992b) and could assist with

paretic muscle relaxation, but determining the effective dosage of these drugs is needed to assist in force regulation.

Conventional rehabilitation programs of Neuro-Developmental Treatment NDT and Proprioceptive Neuromuscular Facilitation (PNF) may affect sensory afferent pathways. These techniques combine movement therapy with repetitive tasks to excite the sensory feedback system. The effectiveness of these types of treatments have shown to be moderately effective in improving force regulation post stroke (Bowen, Knapp, Gillespie, Nicolson, & Vail, 2011; Pollock et al., 2014).

A combination of using drug therapy, sensory treatments and brain stimulation to affect the central nervous system's output may be needed to improve force regulation and clinical function (Page et al., 2015; Pollock et al., 2014)

5.3. FUTURE STUDIES

Hyperreflexia may be predictive of stroke survivors' clinical function and could be useful in optimizing treatment plans. In Aim 1, it was revealed that high levels of stimulation frequencies might produce similar muscle behaviors in stroke survivors and healthy controls, which could be tested clinically. This finding is important because clinicians may be able to replicate this frequency stimulation response in the clinic in order that have paretic muscle force mimics healthy control muscle behavior. In Aim 2, it was shown that neuromuscular impairments in stroke survivors may be predicted by measuring neuromuscular function of TT torque. In Aim 3, the results demonstrate that clinical function and impairment in stroke survivors may be predictable by measuring neuromuscular function of TT torque (spinal), VA (neural/cortical), MVC (muscle/neural) and task endurance. Metrics of central mechanisms of impairment such as hyperreflexia may give insight into the effectiveness of stroke rehabilitation.

Several studies can be created from these projects to enhance stroke rehabilitation. One study is to quantify the effects of high frequency stimuli with therapeutic exercise post stroke. This study could verify if high frequency stimulation improves motor output and/or functional mobility. A second study could use TT and/or RT outputs as a predictor or prognosis of performance in stroke rehabilitation. Tendon taps or resting twitch magnitudes could be measured prior and after a therapeutic intervention. The motor output could reveal treatment effectiveness and the need for the treatments continued use. For instance, if using ice increases TT output and limits functional mobility post

stroke, clinicians may consider not using ice as a treatment. A third project could be to use TT torque (spinal), VA (neural/cortical), MVC (muscle/neural) and task endurance to predict or provide a prognosis of performance in stroke rehabilitation programs. These neuromuscular function outputs could be measured pre/post-therapeutic interventions to predict function. In addition, these studies mentioned above could be combined with drug therapy or brain stimulation to improve central impairments. Further studies could demonstrate treatment benefits if the modality improves clinical function post stroke.

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APPENDIX A: DIAGRAMS OF EACH AIM

Figure 5.1. H-reflex Spinal Synapse Diagram

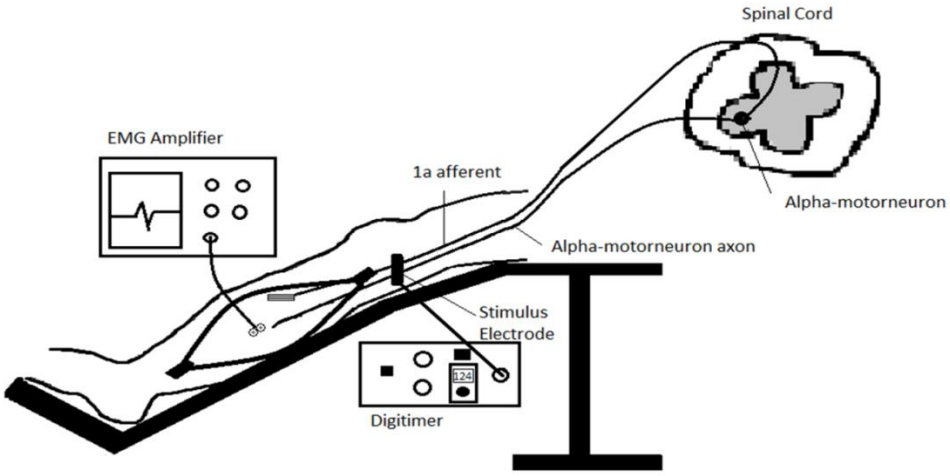


Figure 5.2. Aim 1 Study Set-up: Eliciting H-reflex in Stroke Survivor

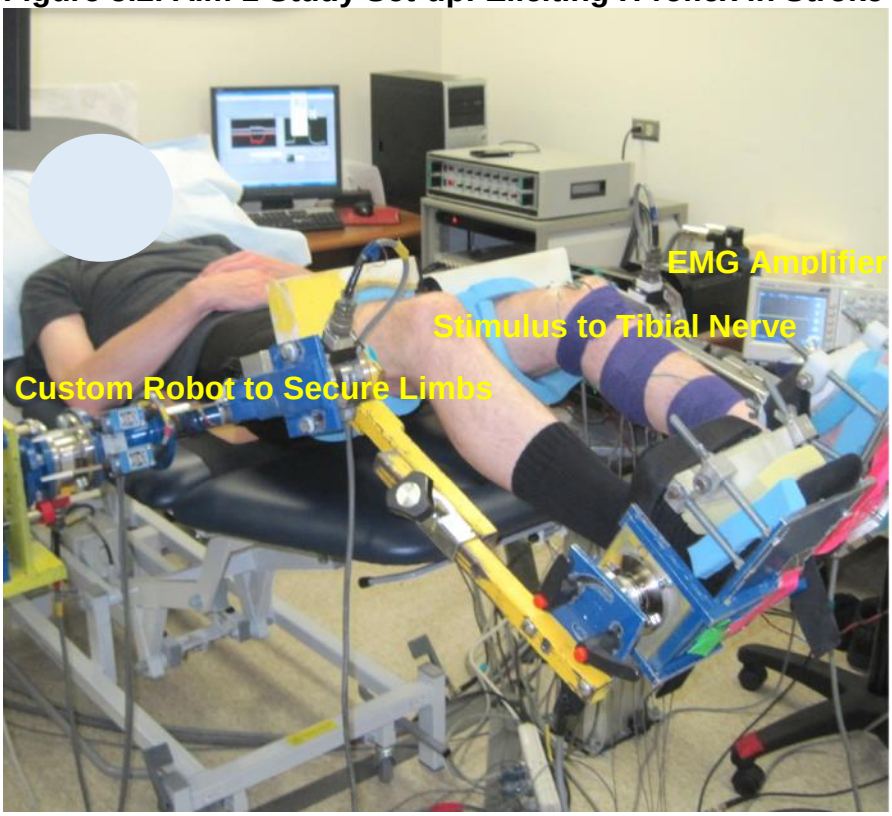
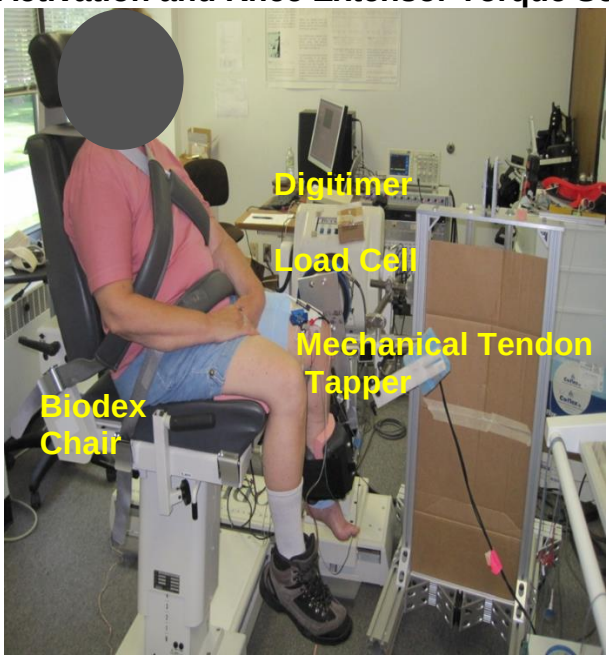


Figure 5.3. Aim 2 and Aim 3 Study Set-up: Tendon Tap, Voluntary Activation and Knee Extensor Torque Set-up for Stroke Survivor



APPENDIX B: ABBREVIATIONS

CMEPs	cervicomedullary motor evoked potentials
CNS	central nervous system
CVA	cerebrovascular accident
Berg	Berg Balance Scale
DGI	Dynamic Gait Index
FM	Fugl Meyer
F	female
EEG	electroencephalogram
EMG	electromyography
EPSP	excitatory postsynaptic potentials
Hz	hertz
H-reflex	Hoffmann reflex
Hmax	maximal H-reflex EMG response
M	male
MEPs	motor evoked potentials
Mmax	maximal motor response wave
MN	motoneuron
MVC	maximal voluntary contraction
Nm	Newton meter
NMJ	neuromuscular junction
PICs	persistent inward currents
PSI	presynaptic inhibition

RI	reciprocal inhibition
RT	resting twitch
SD	standard deviation
SPs	silent periods
STD	standard deviation
TT	tendon tap
TVR	tonic vibratory reflex
10 m Walk	self –selected 10 m walk test
VA	voluntary activation
yrs	years