Factors That Influence Force Steadiness in Individuals with Upper Limb Spasticity after Stroke

by

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A thesis submitted in conformity with the requirements for the degree of Rehabilitation Sciences
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Abstract

Individuals with post-stroke spasticity are disabled by paresis, soft-tissue shortening and muscle over-activity, which significantly affect functional motor output (FMO). Force steadiness (FS) describes the ability to maintain an isometric contraction, and is associated with functional task performance in healthy individuals. The coupling between FS and FMO suggests that FS may be a sensitive metric of FMO deficits that accompany spasticity that may not be captured using clinical scales. This thesis examined muscle weakness, muscle over-activity, and electromechanical coupling as potential factors influencing FS in upper limb spasticity. The affected limb was significantly less steady than the less-affected limb. Absolute force was negatively correlated with CV of force. However, co-activation indices were not different between limbs. Finally, flexor EMG was temporally correlated with force output. These measures may provide sensitive metrics of functional motor deficits that could be used as a tool to characterize effect of spasticity management interventions.
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List of Abbreviations

AHP: Afterhyperpolarization

CV of Force: Coefficient of variation of force

CMSA: Chedoke-McMaster Stroke Assessment

CNS: Central nervous system

ECM coupling: Electromechanical coupling

EMG: Electromyography

FMO: Functional motor output

FS: Force steadiness

MAS: Modified Ashworth Scale

MVC: Maximal voluntary contraction
Chapter 1
Introduction

1 Overview

1.1 Stroke Prevalence

Stroke is the third-leading cause of death in Canada (Heart and Stroke Foundation of Canada, 2009). Each year, there are approximately 50,000 new cases of stroke, with approximately 70% occurring among individuals over the age of 65. Stroke is also one of the leading causes of neurological disability of the adult population (Adamson, Beswick, & Ebrahim, 2004; Martin, Meltzer, & Elliot, 1988). Seventy-five percent of individuals are left with some level of impairment. Furthermore, given the risk factor of age, the number of strokes is expected to rise concurrently with Canada’s aging population. The annual cost in Canada of direct and informal care and lost productivity is estimated to be $3.6 billion (2000 statistic) (Public Health Agency of Canada, 2009). Despite a decline in mortality rates due in part to early symptom recognition and advances in acute stroke treatment, the prevalence of stroke remains the same and will likely increase.

Common neurological impairments after stroke range from hemiparesis, spasticity, cognitive deficits, decreased vision or blindness, aphasia and sensory deficits (Kelly-Hayes et al., 2003). While all of these deficits deserve attention, this thesis focuses on the motor impairments of the upper limb. In the majority of cases, these impairments affect one’s ability to move in and interact with their environment, significantly impacting quality of life. Even with optimal therapy both as an in-patient and continuing therapy following discharge, most patients remain in a state of incomplete recovery. Approximately two-thirds of individuals who sustain a stroke live with neurological deficits that negatively impact function and participation. Half of these individuals are either partly or significantly dependent on others for activities of daily living (Gresham, Fitzpatrick, & Wolf, 1975; Jette, Pinsky, Branch et al., 1988).

In spite of the profound downstream effects that stroke has on muscle function and control, it is still considered a brain problem. The overwhelming tide of research focuses on longitudinal measures and interventions facilitating brain recovery, but there is surprisingly little focus on measuring concomitant changes in muscle properties aside from at a functional level. This is a
significant issue as the majority of stroke patients do not regain real-world useful function in the affected arm and/or leg (Broeks, Lankhorst, Rumping et al., 1999; Parker, Wade, & Langton Hewer, 1986). Furthermore, the outcomes for efficacy of intervention are determined using objective clinical scales or assessment of one’s ability to perform a task. Yet, as identified recently by Scherbakov & Doehner (2011), studies have emerged over the past decade demonstrating disease-specific changes in muscle properties after stroke. In addition, neurophysiological measures such as electromyography (EMG) have recently shown to be more sensitive than clinical scales in identifying focal changes at the muscle level following treatment (Albani, Bar, Campanelli, & Verbania, 2010; Pandyan et al., 2002). Thus, neurophysiological measures may be the answer in bridging the gap between identifying muscular changes and tailoring treatment modalities accordingly to streamline recovery of the real-world usefulness of the affected limb.

1.2 Defining force steadiness & functional motor output

For the purpose of this thesis, functional motor output is operationally defined as the ability to generate and modulate force optimally to suit task demands. This can include both static and dynamic tasks as they relate to activities of daily living. An important component of functional motor output is force control. The ability to maintain an isometric contraction at a given force level is termed ‘force steadiness’ (FS) and requires an individual to generate and modulate force accordingly. Force unsteadiness presents itself most commonly as a load-dependent deficit in force control. Force unsteadiness is also influenced by visual and proprioceptive feedback that tends to present as a low frequency (<2 Hz) oscillatory and steady-state variability (Tracy, Dinenno, Jorgensen et al., 2007). It is usually quantified as the coefficient of variation (CV of force; standard deviation divided by mean force) during the steady-state portion of a muscle contraction, where less variability is indicative of better force control (Beck, 2011; Brown, Edwards, & Jakobi, 2010; Laidlaw, Bilodeau, & Enoka, 2000; Marmon, Gould, & Enoka, 2011).

A number of other internal factors are known to influence force steadiness in individuals with an intact neuromuscular system and it is important to note that not any single factor alone influences force steadiness. Rather, it is a number of factors that contribute to one’s capacity to maintain optimal force levels. For example, it is well established that force steadiness differs across age and gender (Brown et al., 2010) and that in general, older adults are less steady than their
younger counterparts (Baudry, Maerz, & Enoka, 2010; Tracy et al., 2005; Yoshitake, Masani, & Shinohara, 2008). However, the relationship between age and force steadiness largely depends on the muscle group performing the task, the type of muscle contraction, the intensity of the muscle contraction and the physical activity status of the individual (Enoka et al., 2003). In isometric contractions with the upper limb, older adults have greater force fluctuations (i.e. less steady) compared to younger adults in the first dorsal interosseus muscle but not for the elbow flexor muscles, where CV of force ranges from 2-3% across force levels ranging from 5 to 65% of MVC (Burnett, Laidlaw, & Enoka, 2013; Laidlaw et al., 2000). Furthermore, force steadiness differs between contraction intensities as well as the type of contraction in humans – the upper limb is least steady at lower (≤5% MVC) and highest force levels, and most steady at intermediate force levels (Brown et al., 2010; Slifkin & Newell 1999). The greatest difference in steadiness between older and younger adults occurs in low level isometric contractions (i.e. ≤10% of MVC) (Tracy et al., 2005). This increased motor variability in older adults not only influences motor performance in terms of smoothness and accuracy, but also hampers the ability to learn new tasks (Christou, 2011).

Reduced force steadiness has also been observed in neurological populations. Individuals with essential tremor and Parkinson’s disease (Oliveira et al., 2008; Rose, Løkkegaard, Sonne-holm, & Jensen, 2013) demonstrate increased force variability. This is cause for concern as force steadiness is associated with manual dexterity as well as functional performance in day-to-day life. Force steadiness is associated with a number of daily tasks in healthy individuals ranging from fine motor tasks such as writing and using scissors (Marmon, Gould, et al., 2011) to gross motor tasks such as climbing stairs (Seynnes, Hue, Garrandes et al., 2005). Surprisingly, little attention has been given to force steadiness in stroke until recently (Chang, Francisco, Zhou et al., 2013; Chow & Stokin, 2011; Lodha, Coombes, & Cauraugh, 2012). The issue here is that motor recovery after stroke is a plastic process, where individuals have the capacity to improve functional motor output after stroke (Liepert, Bauder, Miltner et al., 2000; Nelles, Jentzen, Jueptner, et al., 2001; Rijntjes & Weiller, 2002). This process can be optimized by the development of rehabilitation strategies that focus on the specific impairments that hinder or restrict daily activities in order to reduce the current economic and social burden. Accordingly, the investigation of force steadiness is essential to improving functional motor control in the stroke population.
1.3 Physiological determinants of force steadiness

While the above-mentioned factors influencing force steadiness are important to consider, the physiological properties of muscle ultimately contribute to the generation and modulation of muscle force. The motor unit is the final functional unit of force production (Sherrington, 1906). Motor units are organized in pools and recruited by the central nervous system (CNS) to produce force. Although one alpha motor neuron can innervate up to several hundred muscle fibres within a muscle, the muscle fibres can only be innervated by one alpha motor neuron within a motor unit. Motor unit size is dependent on the fibre type and the number of muscle fibres innervated by the alpha motor neuron. Motor units innervating type II fibers are larger than those innervating type I fibers. Muscle fibers are generally classified as either a Type I or Type II fiber, with several sub-types of Type II fibers. Type I fibers are slow twitch fibers that contain many mitochondria and large capillary networks that allow increased blood flow to generate and maintain low tensions without fatigue. Type II fibers are fast twitch fibers that have few mitochondria and smaller capillary networks. Type II fibers are susceptible to fatigue but can produce much larger tensions for brief muscle contractions (Kandel, Schwartz, & Jessell, 2000).

In voluntary muscle contractions, smaller motor units have lower recruitment thresholds and are recruited first (Henneman, 1957). Continued increases in force demands results in the recruitment of larger motor units. A motor neuron that innervates a small number of muscle fibres typically plays a role in precise fine skilled movements. For example, the external eye muscles have about nine muscle fibres per motor unit (Feinstein, Lindegard, Nyman et al., 1955). In contrast, muscles that require larger powerful movements, such as the biceps brachii have a much higher muscle fibre to nerve ratio of approximately 1433 fibres per motor unit (Feinstein et al., 1955; Miller, Macdougall, Tarnopolsky et al., 1993). Accordingly, the way in which force is modulated differs across muscle type – smaller muscles rely primarily on rate coding, while larger muscles rely on recruitment of motor units (De Luca, Lefever, Mccue, & Xenakis, 1982; Kukulka & Clamann, 1981). Therefore, the capacity to produce and maintain force is dependent on the capacity of the central nervous system to adequately recruit and rate code motor units.

Decreased force control, such as in healthy older adults, is associated with a lower motor unit discharge rate and greater variability in discharge rate (Laidlaw et al., 2000; Moritz, Barry, Pascoe et al., 2005).
In addition, fatigue, which is caused by a number of task-depended mechanisms, may also influence motor output (Enoka & Duchateau, 2008). Fatigue can be generally characterized by a decrease in capacity to perform a task and/or the drop-off point of sustained activity represented as a decrease in muscle force. There is no single cause of fatigue; rather, it centers on the mechanisms stressed during the task being performed (Cairns, Knicker, Thompson et al., 2005). These can be divided into both central and peripheral mechanisms. Central fatigue involves the failure of maximal muscle activation at a spinal and supra-spinal level, whereas peripheral fatigue is a reduction in the ability to generate muscle force at or distal to the level of the neuromuscular junction. When a task requires sustained maximal effort from muscles, a substantial increase in peripheral fatigue occurs. In addition, central fatigue may also play a role in the decline of task performance, which is due in part to failure of supraspinal drive to motor neurons in order to protect the muscle from further peripheral fatigue (Gandevia, 2001). However, fatigue may not be functionally limiting, as many tasks of daily living only require submaximal forces, particularly in healthy individuals.

1.4 Factors influencing force steadiness may be impaired in post-stroke spasticity

There are a number of muscle changes that take place after stroke that may impair motor output. The symptoms that accompany an upper motor neuron lesion can be divided into both positive and negative symptoms. The most common manifestation of motor impairment after stroke is paresis, which results in profound weakness that typically affects the contralesional side of the body (Chae, Yang, Park et al., 2002; Chang et al., 2013; Kamper, Fischer, Cruz et al., 2006). Paresis, along with the loss of dexterity, are considered to be negative phenomena of upper motor neuron lesions and results in a weakened motor output. Potentially even more impactful, is spasticity, which is classically defined as a “velocity dependent increase in stretch reflexes with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflexes as one component of the upper motor neuron syndrome (Lance, 1980).” Spasticity is a positive phenomenon that occurs in approximately 38% of individuals within the first year after stroke (Watkins et al., 2002). Direct costs for individuals with spasticity are four times higher than direct costs of individuals with stroke who do not have spasticity (Lundström, Smits, Borg et al., 2010). In addition to spasticity, other positive features also include muscle over-activity and inappropriate muscle activation. Those who develop spasticity bear both the negative symptoms
as well as the additional insults of permanent soft tissue changes, such as muscle shortening and joint retraction, in addition to muscle over-activity (Gracies, 2005a). Thus, the additional effects of spasticity may be a further confound to weakness after stroke. Indeed, individuals with spasticity are significantly more disabled than those who experience a stroke who do not develop spasticity. It has been suggested that spasticity may inhibit motor recovery or that prolonged immobility may result in the development of spasticity in some (Welmer et al., 2006). Addressed later in this section, the physiological consequences of spasticity are directly related to factors the influence FS.

1.4.1Weakness

For the purpose of this thesis, weakness is defined as a lower magnitude of force output relative to the less-affected limb. A relative reduction of force output after stroke is a common consequence of paresis. Paresis is defined as decreased voluntary motor unit recruitment (Gracies, 2005a). That is, individuals with spasticity cannot voluntarily recruit skeletal motor units adequately to generate force or movement. Abnormal patterns of motor unit recruitment are explained, at least in part, by failure of voluntary activation, as demonstrated by studies using the twitch interpolation technique (Harris, Polkey, Bath et al., 2001; Madhavan, Krishnan, Jayaraman et al., 2011). Failure of central voluntary activation is associated with a loss of normally functioning motor units in the spinal cord, which presents as a decrease in discharge rate of voluntarily driven motor units in the paretic muscles (Andreassen & Rosenfalck, 1978; Gemperline, Allen, Walk et al., 1995). Reductions in firing rate affect high-threshold more than low-threshold motor units, and a compression of the range of motor neuron recruitment forces has been found in paretic patients (Frontera, Grimby, & Larsson, 1997; Gemperline et al., 1995). Furthermore, a reduction in the total number of motor units can be observed in as little as 4 hours post cerebral infarct (Arasaki et al., 2006). In addition, Lukács et al. (2008) reported that larger motor units are selectively affected following stroke. It was found that these changes are related to the severity of the symptoms following stroke however, the mechanisms of change remains unclear. Electrophysiological studies have also revealed that there is a selective degeneration of Type II motor units after stroke (Scherbakov & Doehner, 2011), but there is evidence that there is reinnervation of abandoned muscle fibers via collateral sprouting of type I motor units occurs. In contrast to the age-dependent shift from fast-twitch to slow-twitch fibres, an inverse shift towards fast twitch fibres has been reported in stroke (Kallenberg & Hermens, 2011).
Compared to healthy controls, fast twitch motor units in spastic hemiplegic patients are much more susceptible to fatigue (Press, Young, & Mayer, 1982). Increased fatigue contributes to the muscle weakness that is observed in spastic paresis. In addition, the firing rate of spastic motor units is lower than that observed in controls (Andreassen & Rosenfalck, 1978). Recent studies have provided some evidence that motor unit discharge rate variability in spastic muscles of stroke patients is correlated with the increased duration of motor neuron afterhyperpolarization (AHP) (Liang et al., 2010). AHP occurs after the resting membrane potential of an action potential falls below the normal resting potential, thus causing a refractory period. During this time, the neuron cannot initiate another action potential (Fohlmeister & Poppele, 1974). The AHP is caused by a potassium current that is elicited by calcium entry during the action potential. Liang et al. (2010) reported lower firing rates than control subjects in the biceps brachii in individuals with stroke who have spasticity were probably due to longer AHP duration. Furthermore, the patients with spasticity had more irregular firing rates (i.e. less force steadiness). It is suggested that patients have less neuromuscular control, hence their firing rates fluctuate more with larger amplitudes compared to the control subjects. The findings of this study suggest that motor neurons of spastic patients become slower resulting in a decreased rate of force production, and consequently, a lower magnitude of force output. While very few studies have investigated the relationship between weakness and force steadiness in post-stroke spasticity, it is no surprise that greater residual strength in the biceps brachii of the spastic-paretic limb has recently been shown to be strongly associated with force steadiness (Chang et al., 2013).

### 1.4.2 Soft tissue changes

When muscle weakness occurs, a number of changes in soft-tissue properties can occur with continued disuse over time. Contracture is the permanent shortening of muscle and connective tissue that occurs in when a muscle is immobilized, such as in post-stroke paresis and/or chronic spasticity (Gracies, 2005a). Muscle maintained in a shortened position leads to shortening in muscle fibre length caused by a decrease in the total number of sarcomeres (Lieber, Steinman, Barash et al., 2004). This eventually leads to increased joint stiffness in the affected limb. Reduced extensibility of muscle also occurs because of increased volume of connective tissue (Järvinen, Józsa, Kannus et al., 2002). Furthermore, prolonged immobilization of a muscle in a shortened position causes any pulling or stretching to be transmitted more readily to the muscle.
spindles (Gioux & Petit, 1993). This increase in sensitivity of muscle spindles augments the spinal stretch reflexes and contributes to the stretch-sensitive forms of muscle over-activity in spasticity and is a significant contributor to the resistance to passive stretch observed in spasticity. For some patients, spasticity develops later on after stroke because of intrinsic muscle changes (i.e. contracture), rather than reflex mediated spasticity (O’Dwyer, Ada, & Neilson, 1996; Welmer et al., 2006). Although soft-tissue changes were not directly measured for this thesis, the progression of contracture eventually leads to a loss of both passive and active range of motion and is therefore an important factor when considering mechanisms of impaired motor output in post-stroke spasticity.

1.4.3 Muscle over-activity

Paresis and the adaptive changes that take place in the paretic muscle lead to the progressive development of abnormal muscle responses to stretch in the paretic body part. However, it is important to distinguish between the ability to voluntarily recruit motor units and generate force, and the ability to voluntarily relax the muscle when it is not involved in voluntary force production. Both components of motor control are often partially impaired in stroke. Paresis is the impaired ability to voluntarily recruit motor units, while muscle over-activity is the increase in involuntary motor unit recruitment (Gracies, 2005b). In addition to the spinal interneuronal rearrangements that take place, adaptive sprouting emerges from descending pathways that were unaffected by the lesion (rubro-, vestibulo-, reticulo-, and tectospinal) (Dewald, Pope, Given et al., 1995). The consequences of adaptive sprouting can include abnormal regulation with the use of alternative pathways and the innervation of inappropriate motor neuron groups (Farmer, Harrison, & Ingram, 1991). Both mechanisms contribute to muscle over-activity.

The pathophysiology of spasticity is complex; however, the spinal reflexes, under supraspinal control are responsible for a large part of over-activity. In the upper motor neuron syndrome there are three possible routes for the hyperexcitability of spinal reflexes. First, a lesion in the cortex results in disinhibition of the normal reflex pathways (proprioceptive stretch reflex) involved in movements such as walking. In addition, the nociceptive reflexes, which typically act as defense mechanisms from painful stimuli, become disinhibited in stroke and can cause flexor spasms. It is likely that these reflexes become disinhibited because of impaired modulation of afferent input by spinal neuronal circuits (i.e. hyperactivity of gamma motor neurons and alpha
motor neurons due to sudden loss of input from supraspinal centres). Secondly, there is the release of primitive reflexes, such as the Babinski sign, which is the upward extension of the toes. In most cases, the Babinski response does not contribute to disability; however, it can result in a lasting response during standing or walking causing pain and discomfort (Burke, Wissel, & Donnan, 2013). Thirdly, a new reflex develops with the presence of upper motor neuron lesion called the tonic stretch reflex, which is the cause of spasticity. This could result from increased alpha motor neuron excitability or decreased threshold in the stretch receptors (Ivanhoe & Reistetter, 2004; Pandyan et al., 2005). In a healthy person at rest, there should be no detectible reflex activity in response to a muscle stretch, however, in someone with an upper motor neuron lesion, this reflex can be detected by clinicians as a resistance to passive stretch (Sheean, 2002). Thus, it is important to highlight that spasticity is very much a spinal phenomenon – not a peripheral phenomenon. Increased central excitability results in increased spinal reflexes that ultimately have downstream effects on the periphery.

The two most disabling forms of muscle over-activity in spastic paresis are spastic dystonia and spastic co-activation (Gracies, Nance, Elovic et al., 1997). Dystonia refers to an increase in stretch sensitive tonic contraction of the muscle resulting in increased resistance to passive movement, but is not attributable to voluntary command (Gracies, 2005b). This results in an impaired ability to relax the muscle. In individuals with spasticity, dystonia remains relatively constant. The pathophysiology of spastic muscle over-activity is unclear however, there is evidence related to increased stretch-induced stimulation of muscle spindles, and alpha motor neuron excitability. Mottram and colleagues (2010) have addressed this issue in the spontaneous firing rate profiles of motor units in spastic stroke patients. This group observed that the initial increase in firing rate of lower threshold motor units was lower in the spastic-paretic muscle compared to the contralateral limb and the control group. Furthermore, following a contraction the motor units in the spastic-paretic limb continued to fire much longer than in the contralateral limb and that of the control group. It was suggested that a tonic, low-level ionotropic drive to the motor neuron pool keeps a certain proportion of motor units close to firing threshold.

Spastic co-activation on the other hand, refers to the inappropriate recruitment of the antagonist muscle triggered by volitional command to activate the agonist muscle. In wrist flexion for example, the wrist extensors should be inhibited, while in wrist extension, the flexors would be inhibited. This concept is referred to as reciprocal inhibition. There are also occasions where co-
activation is appropriate, such as in tasks that require joint stabilization (i.e. hitting a tennis ball). This is referred to as functional co-activation. The magnitude of co-activation is greater at the stationary joint compared to the dynamic joint. It has been suggested that the magnitude of co-activation is representative of the need for joint stability in the stationary joint in order to minimize the perturbing effects of external loads (Darainy & Ostry, 2008; Gribble, Mullin, Cothros et al., 2003). However, in spasticity, co-activation is uncontrolled and interferes with development and generation of normal movement. Moreover, the presence of co-activation in neurologically intact individuals, specifically under static conditions, complicates the interpretation of pathological co-activation as seen in spasticity. For example, Fellows et al. (1994) reported that co-activation was present during an isometric elbow flexion task in the least impaired and the most impaired subjects with spastic hemiparesis and that no exaggerated antagonist activation was found in that spastic group compared to the healthy control group. A number of other studies using a variety of methodologies including visual inspection, ratios of agonist to antagonist, and normalization techniques have found that co-activation does not differ between limbs in post-stroke spasticity, and does not differ from healthy controls (Davies, Mayston, & Newham, 1996; Gowland, deBruin, Basmajian et al., 1992; Tang & Rymer, 1981; Thomas, Häger-Ross, & Klein, 2010). In contrast, other studies have reported co-activation ratios do differ between affected and unaffected individuals, with post-stroke spasticity of the upper limb (Chae et al., 2002). Review of methodologies assessing co-activation/co-contraction has revealed that the variability across methodologies greatly limits our understanding of this phenomena and that more uniform methodologies are required (Busse, Wiles, & van Deursen, 2005).

1.4.4 Impaired electromechanical coupling

The transmission of muscle activation into force output is termed ‘electromechanical coupling’ (ECM) and is calculated by cross-correlating EMG with force output. It was well demonstrated that motor unit discharge rate and motor unit discharge rate variability are highly cross correlated with force fluctuations around 1-2 Hz (De Luca, 1985; Laidlaw et al., 2000; Moritz, Barry, & Pascoe, 2005). Given the invasiveness of motor unit sampling techniques, recent studies have reported a high correlation between the low-frequency component of rectified surface EMG and force fluctuations (Potvin & Brown, 2004; Yoshitake & Shinohara, 2013). This suggests that fluctuations in force during steady contractions are due to simultaneous fluctuations in motor
unit discharge rate. As described earlier, an upper motor neuron lesion interrupts the transmission of this signal starting from the higher centres of the brain that ultimately impairs neuromuscular control with regard to recruitment and rate coding of motor units. Therefore, rather than measuring EMG and force as separate entities, the relationship between EMG and force (ECM) can be a useful marker of the changes in spinal and/or muscular components of the motor unit during voluntary activation of the muscle in stroke.

In a simulation model, it was demonstrated that with a narrower recruitment range of motor units (such as in stroke), the slope of the EMG-force relation decreased with decreasing recruitment range with a concomitant increase in EMG amplitude at a given force (Zhou, Suresh, & Rymer, 2007). Thus a reduction in motor unit discharge rate results in an increase in the slope of the EMG-force relationship. This relationship was previously reported in the elbow flexors of the affected limb in hemiparetic stroke survivors (Tang & Rymer, 1981). It is suggested that with a reduced motor unit discharge rate, additional larger motor units must be recruited to reach the same level of firing, and that larger motor units generate larger action potentials which results in an increase in surface EMG.

1.5 Evidence that spasticity impairs force steadiness

To date, the investigation of force steadiness in the post-stroke spasticity population remains scarce. However, there is some evidence that force steadiness is diminished both distally and proximally in the upper limb. Two recent studies (Lodha et al., 2012; Lodha, Naik, Coombes et al., 2010) reported that isometric force control is significantly impaired in the affected hand compared to the contralateral hand. Furthermore, a recent study found that FS is significantly impaired in the biceps brachii muscles in individuals with post-stroke spasticity in the affected limb compared to the less affected limb (Chang et al., 2013). One study has investigated the lower limb and found that force steadiness is bilaterally impaired in the quadriceps (Chow & Stokic, 2011), although it is unknown if these results are transferable to the upper limb or across different muscle groups.

As mentioned above, force steadiness is linked with the ability to perform activities of daily living in healthy individuals. Although this link has not been established in the post-stroke spasticity population, activity limitations come hand in hand with spasticity. In part, this link has not been established because the degree of spasticity can change depending on the position of the
joint and the task being performed. Nevertheless, studies using the Barthel index have shown that patients with spasticity experience severe limitations in performing activities of daily living, which includes basic activities such as mobility, dressing, climbing stairs, and grooming (Sommerfeld, Eek, Svensson et al., 2004; Welmer et al., 2006). Furthermore, it has been shown that individuals with spasticity are significantly more disabled 18 months after stroke compared to individuals with stroke who do not have spasticity (Welmer et al., 2006). However, it is also suggested that while spasticity may impede recovery, a lack of recovery combined with immobility actually may cause spasticity due to changes in soft-tissue extensibility.

1.6 Rationale, Purpose, Hypotheses

There are a number of known factors that influence force steadiness in the healthy population (Figure 1). Force steadiness is influenced by age, gender (Brown et al., 2010; Baudry, Maerz, & Enoka, 2010; Tracy, Maluf, Stephenson et al., 2005; Yoshitake, Masani, & Shinohara, 2008), muscle physiology, type of muscle contraction, intensity of muscle contraction, fatigue, and the physical activity status of the individual (Enoka & Duchateau, 2008; Enoka, 2012; Enoka et al., 2003). Interestingly, the motor impairments that characterize post-stroke spasticity - weakness, involuntary muscle co-activation (Gracies, 2005a, 2005b), and poor electromechanical coupling (Potvin & Brown, 2004) - are key elements of functional motor output established in healthy people (i.e. strength, appropriate muscle recruitment, and intact electromechanical coupling between muscle and force output). While it is likely that the above mentioned motor impairments are likely contributors to force unsteadiness in post-stroke spasticity, the extent to which these factors impair force steadiness at specific force levels (i.e. different levels of motor output), remains unknown. This is an important area of study as spasticity significantly impacts upper limb strength and dexterity and ultimately the ability to carry out activities of daily living.

Therefore, this thesis asks the question: how do factors influencing force steadiness impact motor output in individuals with spasticity? The purpose of this thesis was to determine the extent to which post-stroke spasticity influences force steadiness during volitional motor activities of the upper limb. This thesis examined three potential determinants for impaired force steadiness: weakness, co-activation and electromechanical coupling between EMG and force. It was hypothesized that (1) force steadiness is significantly impaired in the affected limb compared to the less-affected limb, (2) weakness is negatively correlated with force steadiness (3) higher co-
activation is negatively correlated with force steadiness (4) flexor EMG is temporally correlated with force output.

This thesis studied three potential factors that influence force steadiness in individuals with post-stroke spasticity of the elbow flexors: muscle weakness, muscle co-activation, and electromechanical coupling. In Chapter 2 we present data to support the general study hypothesis that the aforementioned factors are contributors to impairments in force steadiness. Overall, the results of this study showed that the affected limb is less steady and significantly weaker than the less-affected limb across all force levels, that flexor EMG is temporally correlated with force fluctuations (high EMC coupling), and that the magnitude of EMG in the agonist muscle was not significantly correlated with force steadiness. The results of this study contribute to a greater understanding of the neuromuscular factors that impair motor output in post-stroke spasticity and thus potentially offering new routes toward measuring the efficacy of treatment modalities. We also provided single subject data comparing individuals with and without spasticity to demonstrate how spasticity may be a greater confound to impairment than not having spasticity after stroke. In Chapter 3 we present the overall discussion of the strengths and limitations, as well as the clinical significance, and future directions related to this research study.

**Figure 1:** Conceptual model identifying factors that contribute to force steadiness specific to individuals with post-stroke spasticity. While there are a number of determinants for force steadiness in neurologically intact individuals, the unique neuromotor consequences of spasticity ultimately contribute to a decrease in functional motor output.
Chapter 2

Factors influencing steadiness in post-stroke spasticity of the upper limb

2.1 Introduction

When force is produced, it does not remain constant but fluctuates around an intended level. The ability to control one’s force is often referred to as force steadiness (FS), which reflects the ability to maintain an isometric contraction around a given force level. Force steadiness has been examined in a variety of contexts and is associated with the performance of functional tasks. For example, Carville et al. (2007) found that young and older adults who did not have a history of falling were similar in strength and steadiness of the quadriceps. However, older adults who did have a history of falling were both weaker and less steady compared to healthy young adults. Seynnes et al. (2005) measured force steadiness in the quadriceps of older women and found that force steadiness is an independent predictor of some functional tasks, such as chair rise time and stair-climbing power in women. Force steadiness is also associated with hand function in young, middle-aged and healthy adults (Marmon, Pascoe, Schwartz et al., 2011). Marmon et al. (2011) reported that fluctuations in force during steady contractions with hand muscles were associated with performance on functional tests that involved pinching, writing and scissor use.

Force steadiness has also been investigated in the stroke population. This is an important area of study as many tasks of daily living require sustained submaximal force such as carrying groceries, personal hygiene and grooming, as well as eating and drinking. Lodha et al. (2012) recently reported that bimanual isometric force control is significantly impaired in the affected hand compared to the contralateral hand. This study suggested that bimanual asymmetry was likely due to impaired recruitment and rate coding of motor units as this is a common characteristic of hemiparesis in stroke (Frontera et al., 1997; Gemperline et al., 1995). In a study of the lower limb, Chou et al. (2013) recently reported that significant impairments in motor unit rate coding accompanied the pronounced weakness in the paretic limb during forceful and fast contractions of the ankle. While one would suspect that the link between force steadiness and weakness would be linked to the hemiparesis associated with stroke (Kamper et al., 2006), it is
also possible that spasticity may be an even greater confound to the ability to maintain stable levels of force.

Spasticity is classically defined as a velocity dependent increase in muscle tone resulting from hyper-excitability of the stretch reflex (Lance, 1980), and is thought to impact motor control because of the resulting motor impairments, which includes, in addition to paresis, muscle over-activity, and soft-tissue changes (Gracies, 2005a, 2005b). Spasticity is also characterized by spontaneous motor unit activity (Mottram et al., 2010). And, while motor unit discharge rate and motor unit discharge rate variability are key mechanisms contributing to force steadiness in healthy adults (Laidlaw et al., 2000; Moritz et al., 2005; Tracy et al., 2005), spontaneous motor unit discharge rate in spastic paretic muscles is not related to spasticity or force steadiness (Chang et al., 2013). This dissociation indicates that factors other than motor unit properties may contribute to the decrease in force steadiness in individuals with post-stroke spasticity.

Potential alternative indicators include residual strength, co-activation of antagonist muscle pairs and electromechanical coupling. Greater residual strength in the biceps brachii of the spastic-paretic limb has been shown to be strongly associated with force steadiness (Chang et al., 2013). However, strength was not shown to be associated with force steadiness in the quadriceps of the spastic-paretic leg, but rather only in the non-paretic limb (Chow & Stokic, 2011). Given these mixed results, further investigation on the link between recovery of strength and force steadiness is needed. Specific to the upper-limb, studies investigating co-activation of spastic antagonist muscles have yielded conflicting results. One study has reported that co-activation of antagonist muscles differ between affected and unaffected limb, (Chae et al., 2002). In addition, Fellows et al. (1993) reported that co-activation was present during an isometric elbow flexion task in spastic hemiparesis but that no exaggerated antagonist activation was found in that spastic group compared to the healthy control group. A number of other studies using a variety of methodologies including visual inspection, ratios of agonist to antagonist, and normalization techniques have found that co-activation does not differ between limbs in post-stroke spasticity, and does not differ from healthy controls (Davies et al., 1996; Gowland et al., 1992; Tang & Rymer, 1981; Thomas et al., 2010). As such, these findings warrant further investigation on the effects, if any, of co-activation on force steadiness. Finally, electromechanical coupling between EMG and force provides insight not only into the neural component of force steadiness (i.e. motor unit discharge rate variability) but also the mechanical oscillations of muscle (Yoshitake
& Shinohara, 2013). A simulation study revealed that a reduction in motor unit discharge rate results in an increase in the slope of the EMG-force relationship (Zhou et al., 2007). This relationship was previously reported in the elbow flexors of the affected limb in hemiparetic stroke survivors (Tang & Rymer, 1981).

Given the number of potential contributors to impaired force steadiness in post-stroke spasticity, the purpose of this study was to characterize impairments in FS and to determine the role of possible components of spasticity on force steadiness. This study investigated three potential determinants for impaired force steadiness: muscle weakness, co-activation and electromechanical coupling. It was hypothesized that (1) force steadiness is significantly impaired in the affected limb compared to the less affected limb, (2) weakness is negatively correlated with force steadiness (3) higher co-activation is negatively correlated with force steadiness, and (4) Flexor EMG is temporally correlated with force output.

2.2 Methods

Fourteen individuals with upper limb post-stroke spasticity participated in this study. Subjects were recruited from the Spasticity Clinic at Sunnybrook Hospital as well as through an electronic database tracking longitudinal recovery after stroke (Heart and Stroke Foundation Canadian Partnership for Stroke Recovery Rehabilitation Affiliates Database). Inclusion criteria were: (1) greater than 180 days post-stroke, (2) residual voluntary elbow flexion force; (3) spasticity in the elbow flexors or extensors of the stroke-affected arm as measured by the Modified Ashworth Scale score and (3) ability to communicate in English. Exclusion criteria were: (1) bilateral stroke, (2) contracture. All subjects gave informed consent prior to participation. This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and the University of Toronto.

2.2.1 Data collection

All subjects were asked to maintain their usual medication schedules on the day of assessments. Two subjects (Subjects 13 & 14) were taking dantrolene sodium capsules for spasticity management. Thirteen subjects were receiving Botulinum toxin injections. With the exception of two participants, all participants were assessed outside of the three month period during which botulinum toxin is most active. The other two participants were assessed after the peak period of
Botulinum toxin efficacy (i.e. > 4 weeks post-injection). Clinical assessments were performed by a physiotherapist on the same day prior to the experimental protocol. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIH). Arm motor impairment was assessed using the Chedoke McMaster Stroke Assessment (CMSA) and muscle tone in the elbow was evaluated using the Modified Ashworth Scale (MAS). Subjects were seated on a height adjustable chair. The elbow was secured firmly at 90 degrees with the wrist in neutral position in a customized apparatus designed to measure elbow flexion forces (8524-6001, Burster Praezisionsmesstechnik GmbH, Gernsback, Germany) (Figure 2). For EMG collection, the skin was first abraded using an exfoliant and then cleaned using a 70% isopropyl alcohol swab. Bipolar surface electrodes were placed over the belly of the long head of the biceps brachii and the lateral head of the triceps brachii muscles with an interelectrode distance of 2 cm (8mm Ag/AgCl Covidien Kendall™). Palpation, visual inspection, and functional movements such as elbow flexion and extension were used to determine appropriate placement. A ground electrode was placed on the metacarpophalangeal joint of the index finger.

Figure 2: The subject is seated with the arm at 90° with the wrist locked in neutral position in a custom torque device.
Participants were asked to perform 3 maximal voluntary isometric contractions (MVCs) of elbow flexion with 30-60 seconds rest between each trial. A computer screen placed approximately 50cm from the participant provided visual feedback of both force and EMG signals (Figure 3). The maximum force of the 3 trials was used to determine sub-maximal target force levels of 5, 10, 25 and 50% MVC. Each participant performed 2 trials at the target force levels in a randomized order. Participants were asked to increase their force using their elbow flexors to match the target line displayed on the computer screen as accurately as possible for 20 seconds. A 30-60 second rest period was given between each trial. The same protocol was repeated in the opposite limb. The signal from the surface EMG was sampled at 1000 Hz and converted from analog to digital format (Power 1401 mkII; Cambridge Electronic Design, Cambridge, England). The signal was rectified and low-pass filtered at 30Hz (Spike 2 version 7, Cambridge Electronic Design, Cambridge, England).

Figure 3: Representative raw data figure of a 50% MVC force steadiness trial for one subject. Panel A is the steady phase force trace where CV of Force was calculated for the constant 50% force. Panel B is the raw EMG for the triceps brachii. Panel C is the raw EMG for the biceps brachii.
2.2.2 Data analysis

Force steadiness was measured by calculating the coefficient of variation of force (CV of Force) during the most stable 10-second steady phase portion of each contraction. To ensure the steadiest phase of the contraction was used, the first 5 seconds of force output was discarded. The CV of force was calculated as the mean force divided by the standard deviation of force and multiplied by 100%. Weakness was measured by identifying the absolute force measured in Newtons (N) during the 10-second steady-phase of each contraction at a given submaximal relative force level. For co-activation analysis, the raw EMG data was full-wave rectified and low pass filtered at 30 Hz, yielding the linear envelopes of each muscle EMG. The biceps brachii EMG was then normalized to the max point of biceps brachii EMG achieved during the MVC task. The triceps EMG was normalized to the max point of triceps brachii EMG achieved during the MVC task.

The co-activation index was calculated using a method developed by Kellis et al. (2003) using the following equation:

\[
I_{\text{agonist}} = \frac{iEMG_{\text{agonist}}}{iEMG_{\text{agonist}} + iEMG_{\text{antagonist}}} \times 100\%
\]

This value yields the percentage of target muscle EMG activity relative to the total level of limb EMG.

Electromechanical coupling was measured by calculating the cross-correlation between biceps brachii EMG and real time-time force output for each contraction. A sustained 20 second contraction was required to be included for analysis. EMG was rectified and low-pass filtered at 5 Hz. Force was also low-pass filtered at 5 Hz. The rectified and filtered flexor EMG was cross-correlated in 5 second windows with a 2.5 second offset using Spike2 software (version 7, Cambridge Electronic Design, Cambridge, England). Briefly, this process involved multiplying both waveforms together on a point-by-point basis, and summing the products, producing a single result. The reference waveform (i.e. the flexor EMG waveform) moved one point to the right and the process was repeated, producing the next result. This procedure was repeated for all points in the window.
2.2.3 Statistical Analysis

All statistical analyses were conducted with Statistical Package for Social Sciences (SPSS) Version 20.0. Descriptive statistics were used to characterize study participants. To test the hypothesis that spasticity affects the ability to control force output across force levels as measured by the coefficient of variation of force, absolute force output and electromechanical coupling, a 2 (limb) x 4 (force level) repeated measures analysis of variance (ANOVA) was used. Bonferroni-corrected paired t-tests were performed when there was a significant effect (p≤ 0.008). Probability for significance was set at p≤ 0.05. Variables were log transformed if they did not meet assumptions of normality. To probe the hypotheses that weakness, co-activation and ECM coupling are associated with force steadiness, bivariate correlations between force steadiness (CV of force) and factors that influence force steadiness (absolute force, co-contraction, and electromechanical coupling) as well as the degree of spasticity (MAS) and the degree of impairment (CMSA) were performed. We correlated each individual factor with CV of force in both limbs and across each force level.

2.3 Results

All subject demographics are presented in Table 1. Subject demographics. Fourteen individuals (10 males, 4 females) aged 55.67 ± 14.58 participated in this study. The average maximal strength (MVC) for the affected limb was 73.55 ± 15.22 N and 168.05 ± 19.70 N for the less-affected limb.

Table 1. Subject demographics.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Age</th>
<th>Gender</th>
<th>Lesion Type</th>
<th>Years Post-Stroke</th>
<th>Affected Body Side</th>
<th>MAS Elbow</th>
<th>Tardieu Elbow</th>
<th>NIH</th>
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2.3.1 CV of force

CV of force data was log transformed to meet the assumption of normality. The repeated measures ANOVA revealed a significant effect for limb \( [F(1, 13) = 22.995, p<0.001] \). Force variability (CV of Force) was greater on the impaired side than on the non-impaired side (impaired: 5.51 ± 0.78; non-impaired 2.42 ± 0.22, p<0.001). There was also a main effect of force level \( [F(3, 39) = 6.718, p=0.004] \) (Figure 4). Bonferroni-corrected follow-up paired-samples t-tests \( (p=0.008) \) revealed that the 25% MVC force level showed significantly less force variability than 5%, 10% and 50% MVC \( (t_{(13)} = 4.60; p=0.001; t_{(13)} = 5.06; p<0.001; t_{(13)} = -3.38, p=0.005) \). However, there were no interactions between limb and force level.

![Figure 4: Coefficient of Variation of Force (representing force steadiness) at each level of relative force output, for the affected limb (red) and the less-affected limb (black). The affected limb exhibited significantly higher CV values than the less-affected limb across all force levels combined (p<0.001). The 25% MVC force level exhibited significantly lower values than all other force levels (*, p≤0.005). There were no other significant differences between force levels. The affected limb of one subject with stroke with no spasticity (blue) provides context for the effect of spasticity on FS.](image)
2.3.2 Force output at relative force levels (Weakness)

Absolute force was log transformed to meet normality assumptions. Mauchly’s test indicated that that assumption of sphericity had been violated; therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. There was a statistically significant main effect of limb \( [F(1,13) = 54.19, (p<0.001)] \), as the affected limb had lower absolute force across all force levels compared to the less-affected limb (impaired: 15.64 ± 2.44; non-impaired: 36.57 ± 4.52). There was also a main effect of force level \( [F (3, 39) = 838.86, (p<0.001)] \) (Figure 6).

Absolute force at the 5% MVC force level was significantly lower than 10%, 25% and 50% MVC \( (t_{(13)} = -11.66, p<0.001; t_{(13)} = -38.84, p<0.001; t_{(13)} = -87.50, p<0.001) \). The 10% MVC force level was significantly lower than 25% and 50% MVC \( (t_{(13)} = -12.58, p<0.001; t_{(13)} = -30.40, p<0.01) \). The 25% MVC force level was significantly lower than 50% MVC \( (t_{(13)} = -21.73, p<0.001) \). There was no interaction between limb and force.

**Figure 5:** Coefficient of variation of force (CV of Force) for each subject in the affected limb (left panel) and the less-affected limb (right panel).
Figure 6: Absolute force output (measured in N) at each relative force level in the affected limb (red) and the less-affected limb (black). Absolute force increased in accordance to with increases in relative force demands, however, the affected limb had lower absolute force output across all force levels combined (p<0.001). There was also a main effect of force where all force levels were significantly different from each other (p≤0.01).

Figure 7: Absolute force output (measured in N) for the affected limb (left panel) and the less-affected limb (right panel) across each relative force level.
2.3.3 Co-activation

Regardless of force level, there were no differences in flexor activation between the affected limb and the less-affected limb (impaired: 51.88±2.12; non-impaired:56.42±2.39). There was also no main effect of limb, force level or interaction between limb and force level.

Figure 8: Co-activation index (% of total limb EMG) for the affected limb (red) and the less-affected limb (black). There were no significant differences in co-activation index values between limbs or across force levels.
Figure 9: Co-activation index (CI) (% of total limb EMG) for each subject at each relative force level for the affected (left panel) and the less-affected limb (right panel).

Figure 10: Flexor Force/EMG relationship between the affected limb (red) and the less-affected limb (black). The slope of the relationship is lower in the affected limb (0.5; dashed line) compared to the less-affected limb (0.8; solid line).
2.3.4 Electromechanical coupling (EMG/Force Cross-Correlation)

There was a main effect of limb for the analysis of ECM coupling \[ F(1, 11) = 7.00, p=0.023 \], whereby the affected limb had lower ECM than the less-affected limb (impaired: 0.531±0.029; non-impaired:0.651±0.041). There was also a main effect for force level \[ F(3, 33) = 27.55, (p<0.001) \] (Figure 11). Bonferroni-corrected follow-up repeated measures t-tests revealed that ECM coupling at 5% MVC was significantly less than ECM coupling at both 25% and 50% MVC \( (t_{13}= -3.72, p=0.003; t_{13}= -7.24, p<0.001) \). The 10% MVC force level was significantly less than 25% and 50% MVC \( (t_{13} = -3.15, p=0.008; t_{13} = -4.503, p=0.001) \). The 25% MVC force level was significantly less than 50% MVC \( (t_{13} = -3.20, p=0.007) \). There was also an interaction between limb and force \[ F(3, 33) = 3.29, p=0.033 \]. Follow-up Bonferroni-corrected paired samples t-tests performed between limbs at each force level only revealed a difference between limbs at 5% MVC \( (t_{13}= -3.148, p=0.008) \).

![Figure 11: ECM coupling (Rxy (Peak)) function between EMG and real-time force output at each relative force level for the affected limb (red) and the less-affected limb (black). The affected limb had lower ECM coupling across all relative force levels combined (p= 0.041). There was a main effect of force – all force levels were significantly different from each other except the 5% and 10% MVC force level (p<0.008). The 5% MVC force level exhibited lower ECM coupling values than the 25% and 50% MVC force levels (*) p≤0.003). The 10% MVC force level exhibited lower ECM coupling than the 25% and 50% MVC force levels (**) (p≤0.008). The 25% MVC force level exhibited significantly lower ECM coupling than the 50% MVC force level (***) (p=0.007). The affected limb exhibited significantly lower ECM coupling than the less-affected limb at the 5% MVC force level (+) (p= 0.008).]
Figure 12: Electromechanical coupling (ECM) (Rxy (Peak) EMG/Force) for each subject in the affected limb (left panel) and the less-affected limb (right panel).

2.3.5 Case Comparison

To highlight the effect of spasticity on factors that influence force steadiness, we compared two individuals who were matched for level of impairment (i.e. CMSA score) but who had different MAS scores, on measures of weakness, co-activation and ECM coupling (Figure 13). We also compared one individual with spasticity with one control subject with stroke who does not have spasticity (Figure 14).
Table 2. Subject demographics for subject 8 and subject 12 for case comparison.

<table>
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<tr>
<th>Subject #</th>
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<th>MAS Extensors</th>
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<td>R</td>
<td>1</td>
<td>1+</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 13: Comparisons of force steadiness outcomes in impairment matched stroke survivors. Subject 12 (black – low spasticity) and Subject 8 (red – moderate spasticity). Subject 8 has lower CV of force (more steady) across all force levels in both the affected limb (Panel A) and the less-affected limb (Panel B) compared to subject 8 with the biggest differences at 5% MVC. Subject 8 produces lower absolute force at relative force outputs in the affected (Panel C) and the less-affected limb (Panel D). Both subjects exhibit a similar CI at 5% MVC in the affected limb, but subject 8 has a lower CI at 10, 25 and 50% MVC (higher co-activation) (Panel E), while in the less affected limb, (Panel F) the biggest differences in CI between subjects are at 5% MVC and are more comparable at 10, 25 and 50% MVC. In the affected limb (Panel G). Subject 8 has lower ECM coupling in the affected limb (Panel G), however, both subjects show an increase in ECM coupling in accordance with increases in force. In the less-affected limb (Panel H), subject 8 has lower ECM coupling at 5 and 10% MVC, but is comparable to subject 12 at 25 and 50% MVC.
Table 3. Subject demographics for subject 7 and a control subject for case comparison.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Age</th>
<th>Gender</th>
<th>Affected Side</th>
<th>MAS Flexors</th>
<th>Extensors</th>
<th>NIH</th>
<th>CMSA Arm</th>
</tr>
</thead>
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<tr>
<td>7</td>
<td>71</td>
<td>M</td>
<td>L</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Control</td>
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<td>M</td>
<td>R</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

**Figure 14:** Coefficient of Variation of Force (representing force steadiness) of the affected limb (Panel A) for the control subject (black) and subject 7 (red) at each level of relative force output. Subject 7 has greater force variability (less steady) than the control subject across all force levels. In the less affected limb (Panel B), both subjects exhibit the same pattern of force variability across force levels. However, subject 7 is more variable (less steady) at 5 and 50% MVC compared to the control subject, whereas both subjects exhibit similar variability at 10 and 25% MVC. Subject 7 has lower overall force output (weaker) than the control subject in both the affected limb (Panel C) and the less-affected limb (Panel D). Subject 7 also has lower ECM coupling (lower Rxy (Peak)) in the affected limb (Panel E) except at 25% MVC where both subjects exhibit similar ECM coupling and 50% where subject 7 had slightly higher ECM coupling. In the less-affected limb (Panel F) subject 7 displayed lower ECM coupling across all force levels compared to the control subject.
2.3.6 Bivariate Correlation Analysis

To determine which factors influence force steadiness, bivariate correlations were performed between CV of force and each of the dependent variables (weakness, co-activation, and ECM coupling) and our clinical measures (MAS and CMSA). Spearman’s rank correlations were performed for variables that were not normally distributed. Overall, CV of force was negatively correlated with absolute force in the affected limb ($\rho = -0.74$, $p < 0.001$) (Figure 15), but not significantly correlated in the less-affected limb ($r = -0.07$, $p = 0.82$). Furthermore, maximal strength in the affected limb (MVC) was negatively correlated with CV of Force, but was not statistically significant ($\rho = -0.52$, $p = 0.059$). However, this relationship was not seen in the less-affected limb ($r = 0.02$, $p = 0.94$). At specific force levels, CV of force was not significantly correlated with absolute strength at 5% MVC ($\rho = -0.51$, $p = 0.06$), or at 50% MVC ($\rho = -0.46$, $p = 0.10$). However, CV of force was negatively correlated with absolute strength at 10% MVC ($r = -0.55$, $p = 0.04$), and 25% MVC ($\rho = -0.62$, $p = 0.02$). For the less-affected limb, CV of Force was not significantly correlated with absolute force at 5% MVC ($r = -0.16$, $p = 0.60$), 10% MVC ($r = 0.29$, $p = 0.31$), 25% MVC ($\rho = -0.02$, $p = 0.95$) or 50% MVC ($r = 0.18$, $p = 0.54$).

**Figure 15:** Coefficient of variation of force (CV of Force) is negatively associated with absolute force (more steady) in the affected limb (left panel) but is not significantly associated with absolute force in the less-affected limb (right panel).

Overall, there was no significant correlation between CV of Force and co-activation (CI) in the affected limb ($r = -0.37$, $p = 0.27$) or the less-affected limb ($r = 0.480$, $p = 0.14$). However, when
we looked at specific force levels in the affected limb, CV of force was negatively correlated with co-activation at 5% MVC ($r= -0.63$, $p=0.04$) (Figure 16), while there was no significant correlation at 10% MVC ($r= -0.45$, $p=0.17$), 25% MVC ($r= -0.11$, $p=0.75$), or 50% MVC ($r= -0.20$, $p=0.56$). For the less affected limb, CV of force was not significantly correlated with co-activation at 5% MVC ($r= -0.06$, $p= 0.86$), 10% MVC ($r= 0.59$, $p=0.054$) 25% MVC ($r=0.14$, $p= 0.70$) or at 50% MVC ($r= 0.07$, $p=0.84$).

**Figure 16:** Co-activation index (measured as % of total EMG) is negatively associated (lower co-activation) with CV of force (better FS) at 5% MVC in the affected limb.

There was no significant correlation between CV of Force and ECM coupling in the affected limb ($r= 0.12$, $p=0.69$) or the less-affected limb ($r= 0.13$, $p= 0.67$). For the affected limb, CV of force was not significantly correlated with ECM coupling at 5% MVC ($r= 0.174$, $p=0.57$), 10% MVC ($r= 0.11$, $p=0.71$), 25% MVC ($r= -0.01$, $p= 0.98$) or 50% MVC ($r= 0.27$, $p= 0.36$). Similarly in the less-affected limb, CV of force was not significantly correlated with ECM.
coupling at 5% MVC (r = -0.157, p = 0.59), 10% MVC (r = -0.3, p = 0.31), 25% MVC (ρ = -0.22, p = 0.45), or 50% MVC (r = 0.34, p = 0.23).

There was no significant overall correlation between CV of force in the affected limb and MAS (ρ = 0.39, p = 0.17). In the affected limb, CV of Force was not significantly correlated with MAS at 5% MVC (ρ = 0.21, p = 0.48), 10% MVC (ρ = 0.34, p = 0.24), 25% MVC (ρ = 0.33, p = 0.24) or 50% (ρ = 0.28, p = 0.34). However, there was a significant negative correlation between CV of Force and CMSA in the affected limb (ρ = -0.82, p < 0.001) (Figure 17). Furthermore, there was a significant correlation between CV of Force and CMSA at 5% MVC, (ρ = -0.80, p = 0.001), 10% MVC (ρ = -0.79, p = 0.001), 25% MVC (ρ = -0.82, p < 0.001) and 50% MVC (ρ = -0.77, p = 0.001).

![Figure 17](image.png)

**Figure 17:** CV of force (representing force steadiness) is negatively associated with CMSA.
2.4 Discussion

This study examined three potential factors that influence force steadiness at four submaximal force levels between the affected and less-affected elbow flexors in individuals with post-stroke spasticity. Our primary findings confirmed that weakness and abnormal electromechanical coupling in the affected limb are key factors that influence force steadiness. However, in contrast to our hypothesis, muscle co-activation was not significantly different from the less-affected limb. The novel findings of this study include: (1) force level specific factors that may influence force steadiness in spasticity, and (2) higher absolute force output is correlated with force steadiness in spasticity.

2.4.1 CV of Force

The results of this study confirmed our first hypothesis that force steadiness is significantly reduced (high CV of force) in the affected limb compared to the less-affected limb across all force levels. This finding is consistent with the literature that the spastic-paretic limb tends to exhibit greater force variability than the contralateral limb. Furthermore, the degree of impairment (CMSA) was negatively correlated with CV of force, meaning that the more impaired a subject was, the less steady they were. This could have functional implications with regard to independent activities of daily living such as household chores, bathing and dressing. Furthermore, this finding supports the literature that the magnitude of disability is related to the degree of body impairment (Roth et al., 1998).

In addition, our CV of force values were comparable to the 5, 25 and 50% MVC investigated in a recent study involving force steadiness of the hand in individuals with spasticity of the wrist after stroke (Lodha, Misra, Coombes et al., 2013). Irrespective of limb, individuals were the steadiest at 25% MVC. This finding is consistent with previous literature that intermediate force levels (i.e. 25% MVC) tend to be steadier than low submaximal force levels (i.e. 5% MVC) (Brown et al., 2010; Lodha et al., 2013). Force variability between 5% and 50% MVC depicts a U-shape function where force output is least variable in the mid-range of relative force output (Slifkin & Newell, 1999). It has been suggested that intermediate force levels are more steady because they are likely controlled by both recruitment and rate coding of motor units (Slifkin & Newell, 1999). In contrast, it has been suggested that force is predominantly mediated by motor unit recruitment at low force levels (Kukulka & Clamann, 1981; Milner-Brown, Stein, & Yemm,
1973), potentially resulting in increased force variability. In addition, given the shift in muscle phenotype to predominantly fast-twitch fibers after stroke (Hafer-Macko, 2008), it is possible that muscle contractile properties are not aligned with the force requirement of the task or force-generating capacity of the muscle at low force levels, thus resulting in increased force variability. At higher force levels, individuals with post-stroke spasticity have fewer total motor units that can be activated and are less capable of increasing motor unit discharge rate with increases in force demands (Gemperline et al., 1995; Zhou et al., 2007), which may contribute to the higher force variability in the affected limb at higher force levels (i.e. 50% MVC). In addition to varying motor unit activity, there are other task dependent factors that are associated with force steadiness in post-stroke spasticity. The present study found a strong linear correlation between absolute strength and force steadiness in the affected limb, but not in the less-affected limb. This is in agreement with Chang et al. (2013) who also reported a strong correlation between maximum residual strength (i.e. MVC) and force steadiness of the elbow flexors. Previous work has shown that elbow flexor force is strongly correlated with the ability to bring the stroke-affected hand to the mouth, whereas the degree of spasticity (as measured by the MAS) was not significantly correlated with the task performance (Bohannon, Warren, & Cogman, 1991). Indeed, weakness has also been shown to be the primary contributor to finger impairment after stroke rather than spasticity (Kamper et al., 2006). Therefore, muscle weakness may be one of the most important targets for rehabilitation strategies after stroke. Muscle weakness, altered muscle activation properties and impaired electromechanical coupling are discussed in detail below.

2.4.2 Absolute Force (Weakness)

Our second hypothesis that greater absolute force output is associated with better force steadiness was supported in the affected limb. Furthermore, when we looked at individual force levels, greater absolute force output was associated with better force steadiness at 10 and 25% MVC. While all individuals in this study have retained some capacity to voluntarily generate force, the affected limb was significantly weaker than the less-affected limb. It has been shown that motor unit rate coding is reduced and compressed in stroke (Chou et al., 2013), which is likely why the affected arm is significantly weaker and less steady than the less-affected arm. Furthermore, Liang et al., (2010) reported that individuals with post-stroke spasticity have longer afterhyperpolarization potentials (i.e. motor neuron slowness), which contribute to a decreased
magnitude in absolute force output. It has also been demonstrated that a decrease in motor unit numbers occurs in as little as four hours after stroke onset (Arasaki et al., 2006). This may be functionally significant as it has been shown that force steadiness is related to the number of motor units that are activated at a given force level (Hamilton, Jones, & Wolpert, 2004). Therefore, those that produce greater absolute force output at a given force level, are more likely to also maintain the capacity to recruit a greater number of motor units thereby increasing steadiness.

One of the novel findings of this study was that strength was significantly correlated with 10 and 25% MVC. This is an important finding as many independent activities of daily living require submaximal force output such as pouring, buttoning, zipping and opening jars (Harris & Eng, 2007). It has been shown that upper limb strength is the greatest contributor to activity performance after stroke (Bohannon et al., 1991; Harris & Eng, 2007), whereas spasticity (as measured by the MAS) has been shown to have little to no influence on activity performance (Harris & Eng, 2007). Therefore, the results of this study suggest that upper limb rehabilitation strategies should be more focused on strength training and task-specific functional training.

2.4.3 Co-activation

Our third hypothesis that co-activation influences FS in the spastic limb was for the most part, not supported. There were no significant differences between limbs in the amount of agonist contribution at each relative force output. Co-activation of antagonist muscle is often seen when a task requires precision or joint stability (Gribble et al., 2003). However, in spasticity, co-activation of antagonist muscles is involuntary and is caused by impaired descending commands or by the stretch reflexes that occur during movement (Gracies, 2005b). In this study, co-activation index was negatively correlated with FS at 5% MVC, meaning that higher flexor EMG activation is associated with less force variability (more steady). This is an important finding as functional tasks that require precision are likely to be impaired in spasticity. Therefore, therapeutic interventions could focus on improving task performance by emphasizing training the initiation and termination of muscle contractions at low force levels.

On the other hand, levels of co-activation were not associated with FS at the 10, 25, and 50% MVC levels in the affected limb or at any force level in the less-affected limb. These findings are supported by a recent study using intramuscular EMG that did not observe any incidences of co-
activation at submaximal force levels of 20, 40 and 60% MVC except at very high force levels (80% MVC) (Chang et al., 2013). The majority of previous studies have also reported that co-activation patterns in the elbow do not differ between limbs or from co-activation patterns of healthy controls (Dewald et al., 1995; Fellows et al., 1994; Gowland et al., 1992; Tang & Rymer, 1981). Furthermore, it has been shown that co-activation of the antagonist muscle does not co-vary with force steadiness in healthy older adults (Burnett et al., 2013). However, Dewald et al. (1995) identified novel patterns of co-activation of elbow flexor/shoulder abductors and elbow extensors/shoulder adductors muscles in spastic patients that was attributable to task specificity and complexity. Co-activation is commonly observed in isometric tasks as a strategy for joint stability (Franklin & Milner, 2003; Gomi & Osu, 1998; Perreault, Kirsch, & Crago, 2002). In this study, co-activation was seen in both limbs and there were no differences in the amount of co-activation that occurred. As such it cannot be concluded that co-activation of antagonist muscles results in force dyscontrol. Therefore, the results of this study suggest that co-activation may be task-dependent and that there are factors other than co-activation that may impair force steadiness in post-stroke spasticity.

2.4.4 Electromechanical Coupling

Finally, our fourth hypothesis that flexor EMG is temporally correlated with force output was partially supported. The temporal correlation between flexor EMG and force was significantly lower in the affected limb compared to the less-affected limb across all force levels. This is an important area of study because it reflects the capacity of the neuromuscular system to control movement. Bilodeau et al. (1992) reported that the EMG/force relationships are similar between limbs in healthy individuals, which suggests that this methodology is valid for detecting differences in a neurological population. However, it was also suggested that the results of such studies should be interpreted with caution as weakness after stroke may ultimately account for the largest differences in EMG/force comparisons. This may be the case in the present study. While there were differences between limbs, ECM coupling was not correlated with force steadiness in either the effected or the less-affected limb. This suggests that ECM coupling may not directly influence FS. Furthermore, the slope of the EMG amplitude in the affected limb was higher than it was in the less affected limb at the same relative force levels, which suggests that the EMG-Force relationship may explain the weakness component in stroke (Figure 10). Greater EMG amplitude has been shown in the hand of hemiparetic stroke patients regardless of force
level (Suresh, Zhou, & Rymer, 2008). However, there is also evidence that the EMG-force relationship is not altered in the elbow flexors and extensors in spastic hemiparesis (Fellows et al., 1994).

Nevertheless, a recent study has shown that the strong relationship between low-frequency component of rectified EMG and force are likely reflective of the underlying motor unit properties that control force output (Yoshitake & Shinohara, 2013). This is in agreement with De Luca and colleagues (1985) who originally reported that motor units were highly cross-correlated with force fluctuations around 1-2Hz. Therefore, fluctuations in force at low frequency are likely due to simultaneous fluctuations in motor unit discharge properties. In the present study, the lower cross-correlation between EMG and force taken together with the lower EMG/Force slope in the affected limb suggests that motor unit properties are impaired and that greater effort is required to recruit more motor units to maintain any given level of force. Overall, ECM coupling may be a sensitive measure to characterize the impairments in the neural factors that influence force steadiness.

### 2.4.5 Single-Subject Comparison

We matched two subjects for impairment based on their CMSA arm scores but with different MAS scores to highlight the potential effects of spasticity on force steadiness. Surprisingly, subject 8, who had a higher degree of flexor spasticity (MAS = 2) compared to subject 12 (MAS = 1), was also more steady (lower force variability) (See figure 2.11). However, both subjects exhibited comparable patterns of variability across force levels similar to the overall participant group pattern. Interestingly, subject 8 had a lower CI, which implies a higher level of co-activation. Greater levels of co-activation may be beneficial to force steadiness because it allows for joint stability. However, this may not be a function of spasticity as this subject was also steadier in the less-affected limb. Subject 8 was also weaker than subject 12 and exhibited lower electromechanical coupling in the affected limb. Thus, while subject 8 may have better force control, the transmission from muscle to mechanical output is slower and the overall magnitude of force output is smaller.

We also compared one subject with spasticity with one subject who had a stroke who did not have spasticity (See figure 2.12). Similarly to the above case-comparison subject 7 was less steady in the affected limb compared to the control subject. As expected, subject 7 also had
lower absolute force output and lower ECM coupling compared to the control subject at lower force levels. However ECM coupling was similar in both limbs at 25% MVC and subject 7 actually exhibited slightly greater electromechanical coupling at 50% MVC. This is in line with the overall group results where deficits in the affected limb are most pronounced at lower force levels (5 and 10%) MVC.
Chapter 3
General Discussion

3 Summary and conclusions

3.1 Conclusions about Objectives and Hypotheses

The objective of this thesis was to examine factors influencing force steadiness in post-stroke spasticity of the upper limb. To probe this, we identified three factors: weakness, co-activation and electromechanical coupling as being potentially important contributors to impaired force steadiness in spasticity. The first hypothesis that force steadiness is significantly impaired in the affected limb compared to the less affected limb was confirmed. FS was significantly worse in the affected limb between 5 and 50% MVC. The hypothesis that flexor EMG is temporally correlated with force steadiness was confirmed. The hypothesis that weakness is negatively correlated with force steadiness was also confirmed. The hypothesis that higher co-activation is negatively correlated with force steadiness was refuted.

3.2 Implications

This study, in agreement with other recent studies, showed that individuals with post-stroke spasticity are less steady in their affected limb as compared to their unaffected limb. Since force steadiness has functional implications, particularly with age (Seynnes, Hue, Garrandes et al., 2005), these abilities are likely confounded by spasticity. It has been suggested that individuals who do have spasticity are much more disabled than individuals who do not have spasticity (Watkins et al., 2002). The ability to generate and maintain different levels of force are easily measured and could be used in clinical practice in combination with clinical scales to corroborate or better inform the results. More specifically, measurement of force steadiness may be a useful outcome to determine the efficacy of interventions that are geared toward improving motor control. A reduced CV of force would indicate improvement in force steadiness. Furthermore, the difference in CV between the affected and less-affected limb would also provide a quantitative indicator of improvements in force steadiness. A reduction in the difference in CV between limbs could be representative of a decrease of the control deficits in the affected limb. In addition, our measure of ECM coupling in individuals with spasticity allows for the quantification of the relationship between the underlying physiological processes and the
subsequent motor output. Dissociations between these factors that are specific to spasticity may be sufficiently sensitive to accompany traditional measures of spasticity to enhance characterization of alterations motor control. This is especially appropriate if one considers newer definitions of spasticity which characterize it as “disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as an intermittent involuntary activation of muscles” (Pandyan et al., 2005).

The two most common clinical assessments for spasticity are the Modified Ashworth Scale (MAS) and the Modified Tardieu Scale (MTS). The MAS is a six point scale that scores the location and extent of resistance to passive stretch when the muscle is in its most relaxed state (R. W. Bohannon, Larkin, Smith, & Horton, 1987). The MTS has a similar six point scale that is performed at three different speeds (Gracies et al., 2000). While these scales have been used broadly to assess spasticity, they do not necessarily reflect the impact that spasticity has on function. This presents a significant problem because the clinical scales that are routinely used to investigate the clinical efficacy of spasticity treatment modalities may underestimate the effect. For example, Pandyan and colleagues (2002) reported a lack of correspondence between MAS scores and EMG. They found that reductions in spasticity following botulinum toxin injections were reflected in surface EMG but not in the MAS. An additional issue is that the clinical measures of spasticity are not indicators of the underlying physiological contributors to changes in motor control. Even clinical measures of function (i.e. Box and Blocks (Mathiowetz, Volland, Kashman, & Weber, 1985)), Motor Activity Log (Taub et al., 1993), Nine Hole Peg Test (Mathiowetz, Weber, Kashman, & Volland, 1985) are limited in that they do not inform about changes in the quality of control. Measures of force steadiness and ECM coupling may be more sensitive of the changes at the muscle level that occur with spasticity treatment modalities and may provide information of changes in the quality of control and improved function that are essential to advancing the practice of neurorehabilitation.

While we did not find any significant differences in the level of co-activation across all force levels, we did find a significant correlation between co-activation and FS at 5% and between strength and force steadiness at 10 and 25% MVC. This is an important finding as the greatest impairments were observed at lower force levels. Furthermore, recovery submaximal force production and modulation as well as position-holding during early recovery after stroke are
correlated with improvements clinical arm impairment scores (Turner, Tang, Winterbotham, & Kmetova, 2012). This is functionally significant, as many tasks of daily living require only submaximal levels of force (Harris & Eng, 2007). Furthermore, weakness and disuse result in biomechanical changes within the muscle, which can further disable an individual (i.e. via contracture) (Parker et al., 1986). Therefore, the goal of treating those with spasticity should be to treat the impairments of the spastic muscle rather than treating the exaggerated reflexes that classically define spasticity. Studies in healthy individuals have shown that strength training improves force steadiness (Gault & Willems, 2013). Furthermore, practicing functional tasks also improves force steadiness (Marmon, Gould, et al., 2011). Therefore, practicing goal directed movements may improve neuronal coupling and facilitate re-learning.

### 3.3 Strengths and Limitations

One limitation of this study is the absence of a control group in which to demonstrate how a group of individuals with spasticity deviate from the healthy control group. Due to the variable nature of stroke, it is often difficult to match individuals based on age, sex, and general physical status. However, this study used each subject as their own control by comparing the affected limb to the less-affected limb which helps reduce sources of variability. In addition, our sample group of stroke patients were only included if they had residual strength in the affected limb. Therefore, our clinical implications on improving strength may only apply to those who have shown some recovery in strength. Positioning the elbow at 90° may also be a limitation as other potential synergist and/or antagonist muscles may have been activated during the elbow flexion protocol. While positioning the elbow at 90° in the horizontal plane would eliminate this issue, many individuals are not able to raise their affected arm to this height due to any or a combination of paresis, soft-tissue changes (i.e. muscle/joint stiffness), and pain.

Using MAS is a limitation to classify spasticity as it may not be sensitive enough to accurately measure the severity of muscle impairment. This study, in agreement with a similar upper limb study (Chang et al., 2013) did not demonstrate any significant association between spasticity and force steadiness. While the present study used a static task that did not involve a protocol that evokes the exaggerated stretch reflexes that classically define spasticity, other studies that have examined dynamic tasks of daily living have also shown no such relationship (Harris & Eng, 2007). It is possible that no relationship was observed in the present study as all subjects had
only low to moderate levels of spasticity, thus we cannot eliminate the possibility that those with higher levels of spasticity (i.e. MAS ≥ 3) may exhibit a stronger relationship to impaired force steadiness. On the other hand, the effect of spasticity on motor control may be underestimated as the MAS has been widely deemed as an invalid measure of spasticity.

A lack of uniformity in the literature with respect to calculating levels of co-activation is another limiting factor in this study. Fellows et al. (1994) reported that co-activation was present during an isometric elbow flexion task was present in the least impaired and the most impaired subjects with spastic hemiparesis and that there were no differences spastic group compared to the healthy control group. Furthermore, other studies using a variety of methodologies including visual inspection, ratios of agonist to antagonist, and normalization techniques have also reported that co-activation does not differ between limbs in post-stroke spasticity, and does not differ from healthy controls (Davies, Mayston, & Newham, 1996; Gowland, deBruin, Basmajian et al., 1992; Tang & Rymer, 1981; Thomas, Häger-Ross, & Klein, 2010). Yet, others have reported co-activation does indeed differ between limbs in individuals with post-stroke spasticity (Chae et al., 2002). The present study did not find any differences in co-activation levels between limbs however, the variability across methodologies greatly limits our understanding of co-activation and that more uniform methodologies are required (Busse et al., 2005).

### 3.4 Future Directions

This study has identified three variables of interest for determinants of force steadiness – strength, co-activation and electromechanical coupling. With the addition of more participants, future analysis should use a regression model to identify these variables as true determinants of force steadiness. Future analysis should include more sensitive measures of neuromuscular control, particularly motor unit properties and their influence on upper limb force steadiness in post-stroke spasticity. Furthermore, measures of force steadiness may be useful tool in characterizing the longitudinal effects of various treatment modalities after stroke. In addition to characterizing improvements in force steadiness, studies could also examine the relationship between force steadiness with the performance of functional tasks.
3.5 Conclusion

This study examined three factors that may influence impaired force steadiness in individuals with post-stroke spasticity of the upper limb. The results of this study confirmed that the affected limb exhibits significantly greater force variability (less steady) than the less-affected limb, across a range of submaximal force levels. Overall, greater absolute force output was the most strongly correlated factor influencing force steadiness particularly at low to moderate force levels. Electromechanical coupling was lower in the affected limb, indicating impaired neuromuscular and mechanical control. Finally, co-activation levels were not significantly different between limbs. Furthermore, we did not find any relationship between spasticity (MAS) and force steadiness. Therefore, given the results of this study, strength training in addition to task specific training at submaximal force levels may be the most beneficial to improving functional motor output after stroke.
References


