The Effect of Acute Muscle Tendon Vibration on Motor Unit Activity in the Contralateral, More-Affected Limb in Parkinson's disease

by

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Abstract

Acute tendon vibration is commonly used to activate the Ia afferents though excitation of the muscle spindles; increasing excitation of the alpha motoneurons of the vibrated muscle, enhancing muscle contraction and inducing reciprocal inhibition of the antagonist muscle. Previous reports suggest that the excitatory and inhibitory effects of vibration stimulation on muscle activity can be transferred to the contralateral side of the body and that this occurs via excitation of the polysynaptic crossed-extensor reflex loop. The effect of acute tendon vibration on motor unit (MU) activity in the contralateral more-affected side in Parkinson's disease (PD) has not been studied. Six males and four females with mild to moderate PD severity maintained isometric elbow flexion at 5% maximum (MVC). Vibration was applied to the biceps tendon of the less-affected side and used to quantify the effect of polysynaptic Ia afferent feedback on MU properties in the contralateral biceps muscle during the 5 sec ramp, 5 sec plateau, and 5 sec deramp contraction. Twenty-nine MUs in the biceps brachii were followed. MU recruitment thresholds, derecruitment thresholds, MU discharge rates (MUDR), MU discharge rate variability (MUDRV) and force steadiness, quantified as standard deviation around a mean force, were compared across conditions (no-vibration, biceps-vibration), phases of the contraction (ramp, plateau, deramp) and between sexes. Recruitment thresholds were higher than derecruitment thresholds. MUDR was higher in females during the plateau and higher in males during the deramp phase. MUDR was also higher during the deramp phase of the no-vibration compared to the biceps-vibration condition. MUDRV was higher in males during the plateau phase of both conditions and during the deramp phase of the biceps-vibration condition. Males were steadier and had a higher PD rating score compared with females. Results suggest that

vibration moderately influences MU activity in the contralateral limb in PD and that males and females with PD respond differently to vibration stimulation. These sex differences are likely due to muscle fibre characteristics or level of severity of PD between males and females.

Preface

The University of British Columbia's Clinical Research Ethics Board granted ethics approval for this research on April 22nd 2014. The ethics approval certificate number for the current study is H11-01931. To date, the research included in this thesis has not been published in full.

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List of Abbreviations

ACh: Acetylcholine

AP: Action potential

ATP: Adenosine triphosphate

BR: Brachioradialis muscle

Ca^{2+}: Calcium

CD: Contraction duration

CNS: Central Nervous System

CV: Coefficient of Variation of Force

DR: Derecruitment threshold

EMG: Electromyography

GTO: Golgi tendon organ

Hz: Hertz

HRT: Half-relaxation time

Kcal: Kilocalorie

Kg: Kilogram

LH: Long head of the biceps brachii

MLTPAQ: Minnesota Leisure Time Physical Activity Questionnaire

MN: Motoneuron

ms: Milliseconds

MU: Motor unit

MUDR: Motor unit discharge rate

MUDRV: Motor unit discharge rate variability

MVC: Maximal Voluntary Contraction

Na^+: Sodium

N: Newton

PD: Parkinson's disease

PIC: Persistent inward current

PNS: Peripheral Nervous System

PT: Peak tension

QoL: Quality of life

RT: Recruitment threshold

sec: Seconds

SD: Standard Deviation

SH: short head of the biceps brachii

TPT: Time-to-peak tension

TRI: Triceps muscle

Type I: Slow-oxidative

Type IIA: Fast-fatigue resistant

Type IIB: Fast-fatigable

UPDRS: Unified Parkinson's disease Rating Scale

(+): Facilitation

(-): Inhibition

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Dedication

Dedication of this document is to all those diagnosed with Parkinson's disease, especially to the Parkinson's Society in Kelowna, B.C; a group of truly inspirational individuals who never fail to remind me of why I chose this path and without whom this thesis would never have been achievable.

Chapter 1: Functional organization of the Neuromuscular system:

1.0 Voluntary Control of Movement:

The initiation and control of voluntary movement depends on successful integration between the motor and sensory systems. Motor commands for the initiation of voluntary movements, such as walking or grasping an object, are first integrated in the motor areas of the cerebral cortex. These commands then propagate down through the brain stem, descending systems, spinal cord and finally the skeletal muscle (Kandel, Schwartz, Jessell, 2000). The somatotopically organized primary motor cortex (M1), located in the frontal lobe of the brain, is involved in the voluntary control of movement. It receives information from the posterior parietal and prefrontal association cortices and is responsible for the coordination and planning of complex sequences of movement. The primary motor cortex projects directly to the spinal cord through the lateral corticospinal tract (Ghez & Krakauer, 2000) where fibres descend into the pyramidal tract. The majority of neurons (90%) in the pyramidal tract then cross over to the opposite side of the spinal cord through the midline of the medulla where these axons terminate on alpha motoneurons and interneurons of the spinal cord innervating specific skeletal muscles.

The generation of movement with specific musculature involves excitation of the extrafusal fibres from alpha motoneurons. Electrical input is first received by the dendrites of the motoneurons containing voltage gated ion channels that modify the passive electronic condition of synaptic potentials. These potentials then propagate down and converge upon the axon hillock. If the electrical input is large enough to reach threshold, an action potential (AP) is then generated down the axon of the motoneuron (Beeler & Reuter, 1977). Schwann cells form a protective myelin sheath in a spiralling pattern around the axon. These gap regions, called Nodes of Ranvier, generate rapid salutatory conduction and contain high density voltage gated channels

that allow for regeneration of the AP and propagation along the length of the axon (Landon & Hall, 1976). The motor endplates of the axon terminate in the center of the innervated muscle fibre. Once the AP arrives at the presynaptic terminal, voltage gated Ca^{2+} channels open and Ca^{2+} diffuses into the terminal causing the acetylcholine (ACh) containing synaptic vesicles to move towards the presynaptic membrane. Soluble N-ethylmaleimide sensitive fusion attachment proteins located on the vesicle itself and the presynaptic membrane aid in vesicle docking, allowing the vesicle to fuse with the membrane and Ach to be released into the synaptic cleft (Weber et al. 1998). Once released Ach binds with ligand gated Na^+ channels on the postsynaptic membrane; causing the channels to open and Na^+ to flow in and depolarize the sarcolemma (Torok, 2007).

The AP then depolarizes the transverse tubules and through an interconnection of ryanodine and dihydropyridine receptor activity cause Ca^{2+} to be released from the sarcoplasmic reticulum. Ca^{2+} then binds to the troponin-tropomyosin complex which then allows for actin to bind with myosin-ATP complex producing cross-bridge movement and tension. ATP then binds to the myosin cross-bridge breaking the actin-myosin bond and allowing the cross-bridge to dissociate from actin. This dissociation allows for thick and thin filaments of the sarcomere to slide past each other and contract the muscle fibre (Huxley et al. 1976).

1.1 Reflex Activity and Muscle Receptors:

Peripheral sensory nerve endings serve as specialized receptors that detect sensory information and are highly involved in reflex activity (Liddell & Sherrington, 1925). The two primary muscle receptors are the muscle spindle and golgi tendon organ. The muscle spindle lies in parallel with extrafusal muscle fibres and its primary function is sending proprioceptive input

about changes in the length of skeletal muscle fibres to the spinal cord. The Ia afferent fibres project from primary sensory endings of the intrafusal muscle fibres and are responsive to the rate of stretch of these fibres (Figure 1.0). The Ia afferent fibres are also velocity sensitive and detect the rate of length change; providing information about the speed of movements additional to changes in muscle fibre length (Kandel, Schwartz, Jessell, 2000). The group II afferent fibres also sense the degree of stretch but are responsible for transmission of this input to higher motor centers and are slower than the Ia afferent fibres. The gamma motoneurons innervate the intrafusal muscle fibres, which are responsible for controlling the sensitivity of the muscle spindle itself (Kandel, Schwartz, Jessell, 2000). Activation of the muscle spindles causes input to be relayed to the spinal cord. This input then synapses with an efferent alpha motoneuron and contracts the homonymous muscle fibres, counteracting the detected stretch. The golgi tendon organ (GTO) is located at the junction between muscle fibres and tendon and is innervated by group Ib afferents. The GTO is sensitive to changes in muscle tension, especially when the muscle tension is increased due to contraction (Kandel, Schwartz, Jessell, 2000).
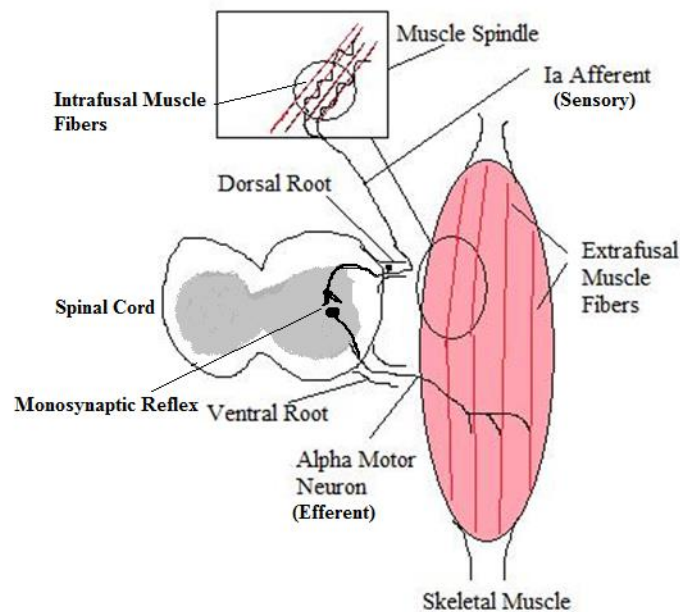
Figure 1.0: Muscle Spindle Reflex Activity. The Ia afferent neuron senses stretch of the intrafusal muscle fibres. It then conveys the information to the spinal cord, entering via the dorsal root, and synapses on the dendrites of the alpha motoneuron cell body located in the ventral horn of the spinal cord- activating the homonymous muscle fibres and contracting the stretched muscle.

Reflexes are involuntarily activated neural circuits, elicited by peripheral stimuli, coordinating patterns of muscle contraction and relaxation (Ghez & Krakauer, 2000). The simplest neural circuit is the monosynaptic reflex which includes the primary sensory neuron, afferent neuron, and the responding efferent neuron. However, most reflexes are mediated by polysynaptic circuits which include a spinal interneuron synapsing between the afferent and efferent neurons (Ghez & Krakauer, 2000) (Figure 1.1). Interneurons receive input from efferent neurons and axons descending from higher centers that modify the reflex response by facilitation or inhibition of these interneurons. Reciprocal inhibition involves excitation of an inhibitory

interneuron and terminates on alpha motoneurons innervating the antagonist muscle (Figure 1.1); this causes inhibition of the antagonist muscle that would otherwise counteract the movement. Recurrent inhibition involves the excitation of a Renshaw cell, an inhibitory interneuron that receives input from an alpha motoneuron, which then inhibits the same alpha motoneuron from which it received the stimulus (Ryall, 1970). Overall, excitation of alpha motoneurons through interneurons and afferent neurons create intricate reflexes through integration of excitatory and inhibitory signals from specific muscle groups that are involved in voluntary movements (Liddell & Sherrington, 1925).
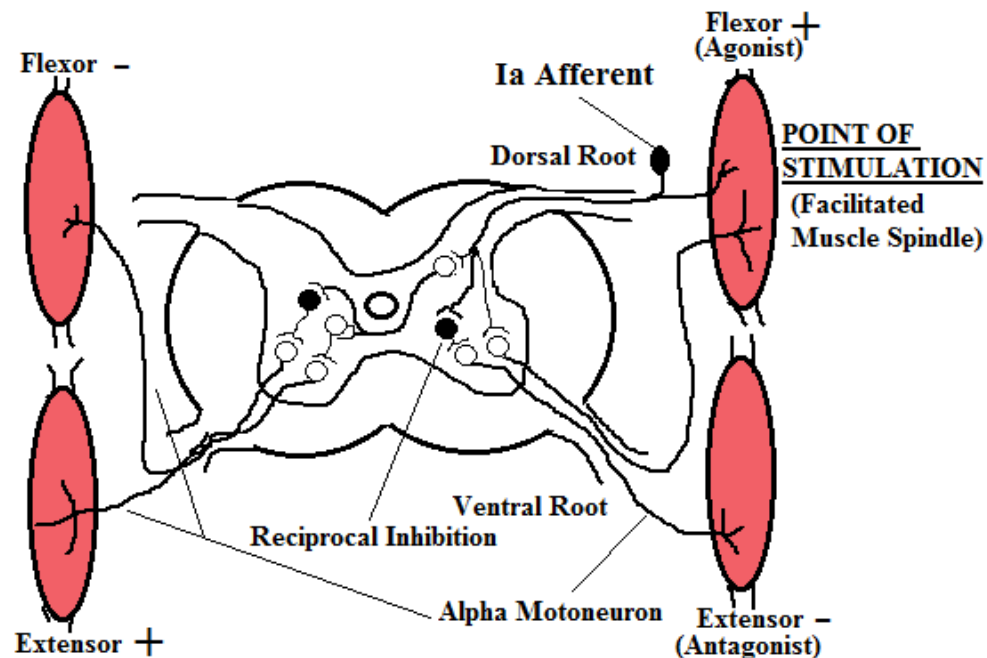
Figure 1.1: *The Polysynaptic Crossed-Extensor Reflex. The polysynaptic crossed-extensor reflex is facilitated by stimulus being applied to the flexor muscle and involves multiple interneurons that excite the flexor muscle (agonist) and inhibit the opposing extensor (antagonist). This is reversed on the contralateral limb and the flexor muscle is inhibited, via reciprocal inhibition, and the extensor muscle is facilitated. Solid filled circles represent inhibitory interneurons non-filled circles represent excitatory interneurons. +, facilitation; - inhibition.*

1.2 The contribution of motor units to the production of force:

A motor unit (MU) consists of a single motoneuron and all of the muscle fibres that it innervates (Figure 1.2A) and is considered the final common pathway for all motor action (Liddell & Sherrington, 1925). The soma of motoneurons are clustered in motoneuron pools and located in the ventral grey matter of the spinal cord. Each extrafusal muscle fibre is innervated by only one motoneuron but one motoneuron can innervate multiple fibres (Ghez & Krakauer, 2000). MUs and muscle fibres are classified into three main types; slow-oxidative (Type I), fast-fatigable (Type IIB) and fast-fatigue-resistant (Type IIA) (Bellemare et al. 1983; Burke et al. 1971; Frischknecht et al. 1990). Type I MUs consist of small somas that are easily excitable and exhibit slow conduction velocities, contraction durations (CD), and time to peak tension (TPT) but are considerably fatigue resistant (Figure 1.2B). Muscle fibres of Type I MUs have a distinct red-pigmentation due to the high capillary and mitochondrial content suggesting primary utilization of the aerobic energy pathways (Burke et al. 1971). It has been suggested that their slower reaction times are associated with a slower rate of Ca^{2+} uptake by the sarcoplasmic reticulum (Frischknecht et al. 1990). Type IIB and Type IIA MUs consist of large somas that require greater input, rapid contraction duration and exert a large amount of force but tend to fatigue earlier (Zajac & Faden, 1985). Type IIA and Type IIB MUs are characteristically rich in glycolytic enzymes and low in enzymes of aerobic oxidative metabolism (Frischknecht et al. 1990). However, Type IIA MUs are more fatigue resistant than Type IIB, considerably less fatigue resistant than Type I and vary in axon diameter (Burke et al. 1971).
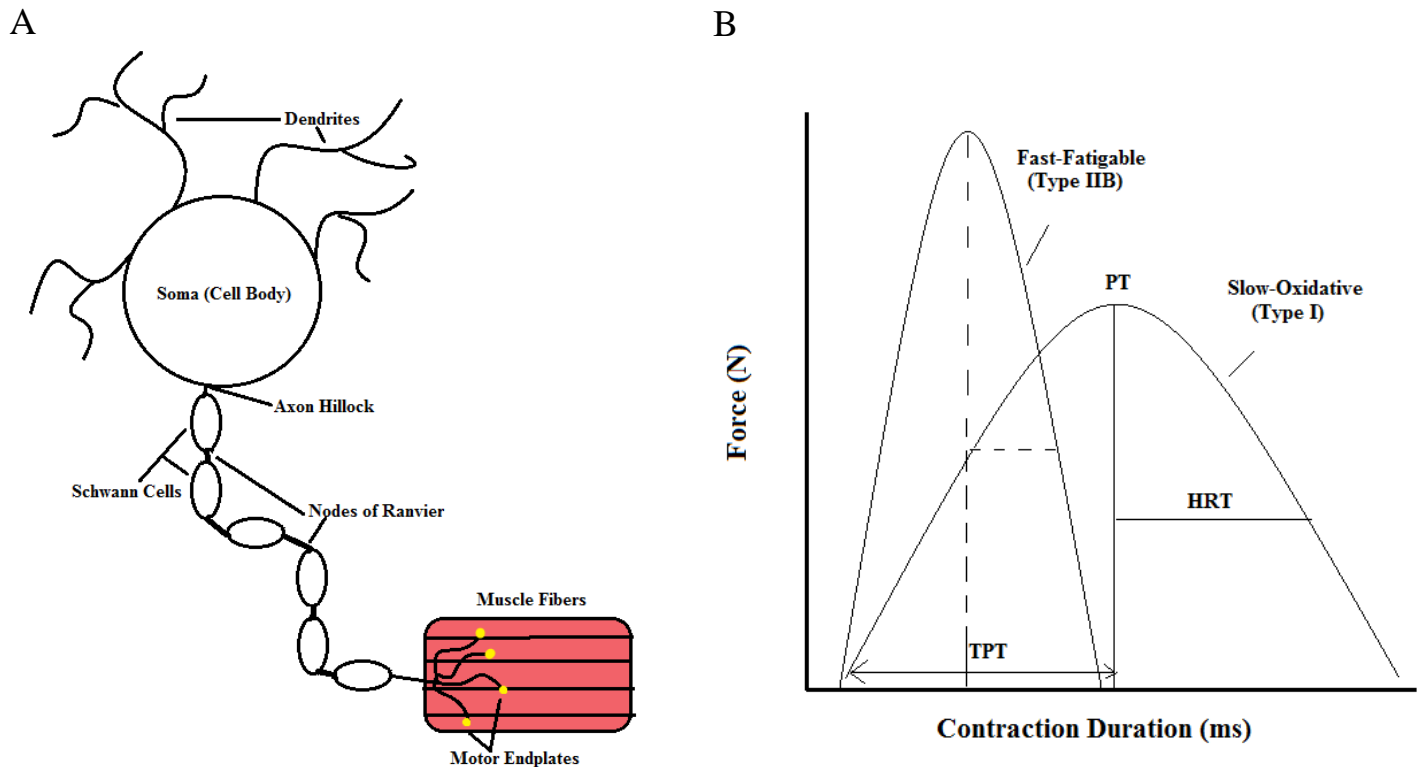
Figure 1.2: *MU Structure (A) and contractile properties (B). Type 1 slow-oxidative low-threshold MUs have a longer CD, HRT and lower PT compared to fast-fatigable, Type II muscle fibres. Type IIA is not represented in this graph but would have contractile properties that fit in-between Type IIB and Type I. N, Newtons; TPT, time to peak tension; HRT, half-relaxation time; PT, peak tension; ms, milliseconds.*

The force that a muscle exerts depends on the activation of MUs through two main modulators; MU recruitment and MU discharge rate (Enoka, 1995). MU recruitment involves adding MUs to increase muscle force and is correlated with a motoneuron's ability to depolarize. Slow-twitch MUs are selectively recruited first during low forces because they are smaller and require less input to fire compared to the larger fast-fatigable MUs. This orderly recruitment is commonly known as the size principle (Henneman, 1957). Therefore, slow isometric ramp contractions usually consist of low-threshold MUs becoming active at lower force levels and as

force increases additional higher-threshold motor units are recruited (Figure 1.3). When force decreases, MUs derecruit in reverse order of their recruitment (Henneman et al.1965).
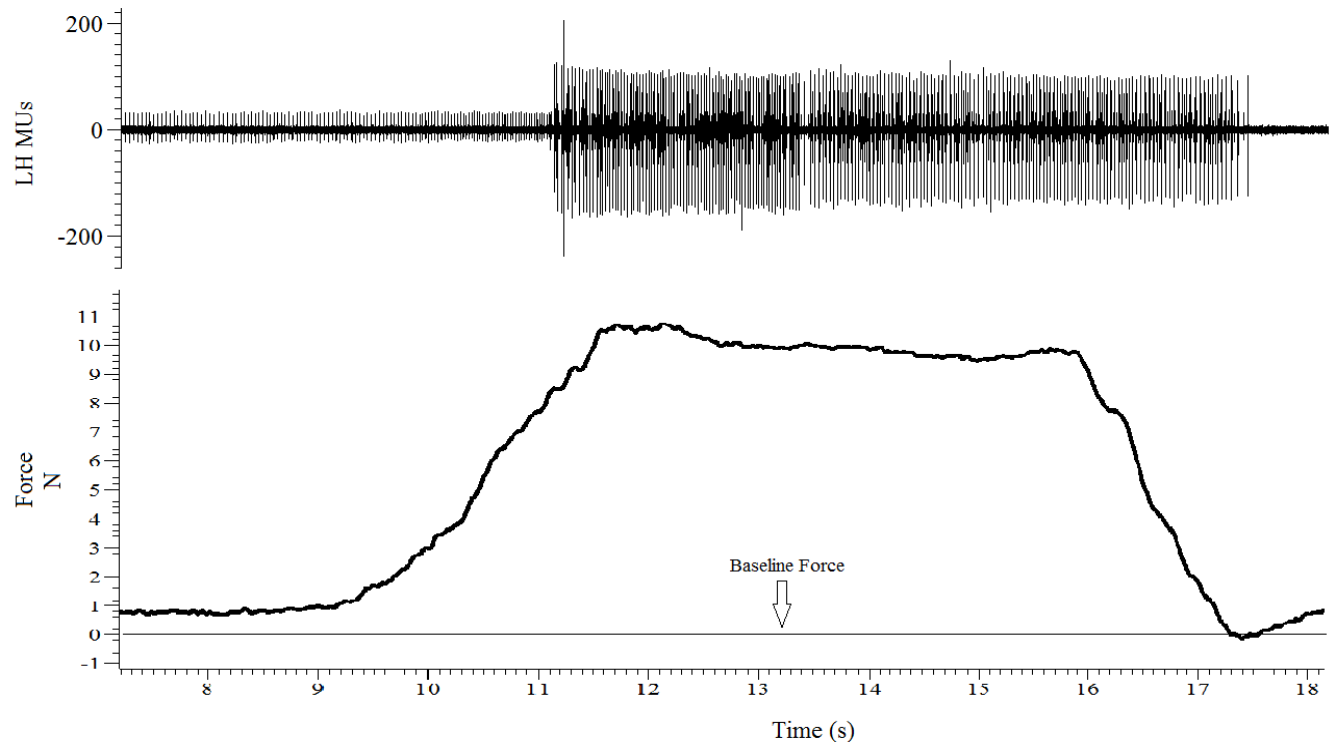
Figure 1.3: *MU recordings taken from intramuscular fine wires inserted into the long head of the biceps brachii muscle during isometric elbow flexion. The lower recording represents force output over time. The top recoding represents the recorded MU data. A small low-threshold MU is first recruited at a very low force level. As force increases, additional higher-threshold MUs become active- represented by the larger spikes. Once force returns to baseline, the muscle becomes completely relaxed and MUs cease firing. N, Newtons; LH, long head biceps brachii; MUs, motor units; s, seconds.*

MU discharge rate (MUDR) is the rate at which a motoneuron discharges action potentials and depends on the pattern and quantity of the synaptic input that it receives (Enoka, 1995). The size of motoneurons determines their susceptibility to discharge (De Luca et al. 1982; Farina et al. 2002; Henneman et al. 1965). Low-threshold MUs are known to discharge more frequently than high-threshold MUs (Deluca, 1985). Erim et al. (1996) found that at any given

time during a contraction, MUs with lower recruitment thresholds have higher firing rates than units with higher recruitment thresholds. Moritz et al. (2005) also reported that the minimum discharge rate and peak discharge rates increased with an increase in recruitment threshold.

MUDRs of active MUs increase with increasing force output (De Luca, 1985; Monster & Chan, 1977) (Figure 1.4). The relation between MUDR and total exerted force depends on the phase of contraction (Denier van der Gon et al. 1984). In isometric contractions, MUDRs increased up to 100% of MVC (Kallio et al. 2013) and during relaxation, decrease slowly and almost linearly with force (Danier van der Gon et al. 1985). For a healthy population, the average discharge rate at lower forces is 8-12 Hz and 30-50Hz at higher forces (Bellemare et al. 1983; Kamen et al. 1995; Monster & Chan. 1977). The variability of MUDR (MUDRV) is a major determinant of the trends in isometric force variability across the working range of muscle (Moritz et al. 2005). An increase in MUDRV is associated with a decrease in force steadiness; with greater MUDRV and fluctuations in force at low force levels and lesser MUDRV and fluctuations in force at higher force levels (Barry et al. 2007; Galganski et al. 1993).
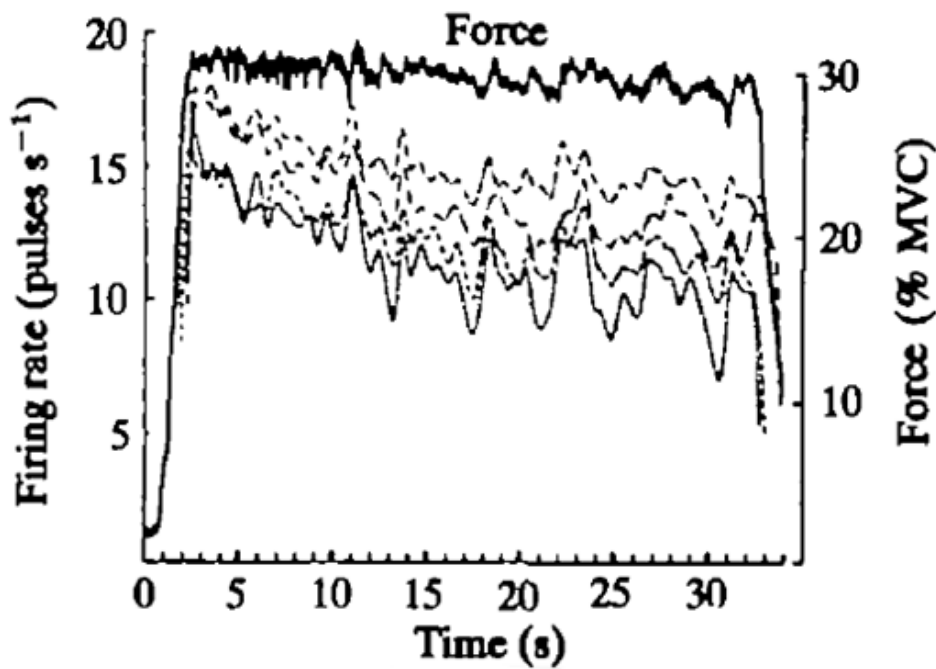
Figure 1.4: Mean firing rates of four motor units during an isometric ramp contraction. Earlier recruited motor units discharge at higher firing rates than later recruited. %MVC, percentage of maximal voluntary contraction; s, seconds, pulses s^{-1}, pulses per second. (Deluca,1985)

1.3 Force Steadiness:

Force steadiness is the ability to accurately control force around a given force level and is typically represented as a coefficient of variation (CV) of force. Force steadiness is greatest at moderate force levels and lowest at lower force levels (Danion & Gallea, 2004). When compared across force levels, CV appears as a U shape function with increases in force level with maximal steadiness at approximately 22.5% MVC (Danion &Gllea, 2004) (Figure 1.5). Older adults have been found to be less steady than young adults, especially at lower force levels (Carville et al. 2007; Dewhurst et al. 2006; Graves et al. 2000; Sosnoff & Newell, 2006; Tracy et al. 2006). This age associated decline in force steadiness has been attributed to decrease in muscle strength with

age. Higher variability in force output is associated with muscle weakness, but no differences in the variability of force was found when strength is similar between young and old adults (Sosnoff & Newell, 2006). Therefore, variability in force is associated with absolute strength. Furthermore, more variable discharge rates by single motor units have been found to accompany declines in force steadiness (Laidlaw et al. 2000). Males are typically stronger than females and therefore females are less steady than age-matched males (Bazzuchi, et al. 2004; Brown et al. 2010; Clark, et al. 2005). Seynnes et al. (2005) found force steadiness to be an independent predictor of functional performance in older women by determining the level and variance in force steadiness during functional ability tasks such as stair climbing and chair rise time. Therefore, weakness results in a decrease in force steadiness and could potentially lead to an increase in functional limitation and disability, especially in older females (Carville et al. 2007).
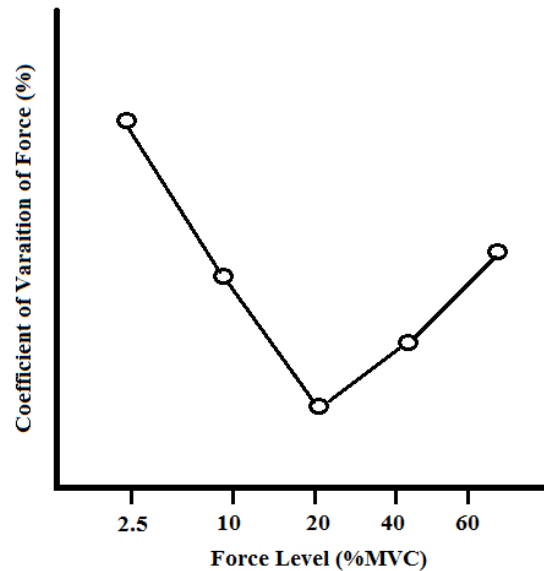
Figure 1.5: *Effects of force magnitude on force steadiness represented as a coefficient of variation of force. Force steadiness is lowest at low forces (>10% MVC) and high forces (>60%) but at moderate force levels (20% MVC) contractions are steadiest. %MVC, percent maximal voluntary contraction; %CV, percentage of coefficient of variation of force. (Data averaged and adapted from: Brown, Edwards, Jakobi, 2010; Danion & Gallea, 2004; Enoka et al, 2003)*

1.4 Altered Neuromuscular Function in Parkinson's disease:

Over a century ago, James Parkinson (1817) found what he called "an unrecognized disorder" in his monograph entitled *An Essay on the Shaking Palsy.* In his monograph he describes patients who had "involuntary tremulous motion with lessened muscular power, in parts not in action even when supported" (Parkinson. J, 1817). This progressive degenerative disease is commonly known as Parkinson's disease (PD). PD severely affects muscle movement and control, in addition to other non-motor dysfunctions (i.e. sleep, mood), leading to limitation in daily activity and quality of life (Canadian Institution for Health Information, 2007; Schrag, 2000). PD is one of the most common neurodegenerative disorders, affecting 1-3% of the population older than 65 years (De Rijk et al. 1999). The prevalence of PD

steeply rises with age and has an average onset of 60 years (Twelves et al. 2003), an average

duration of 15 years (Hoehn & Yahr, 1967), and a mortality ratio of 2 to 1 (Hoehn & Yahr,

1967). It is anticipated that the incidence of PD will only rise with the aging populations (Lees et

al. 2009).

PD is primarily diagnosed in a clinical setting with the appearance of two of the

following four symptoms; rigidity, bradykinesia (slowness of movement), resting tremor and

postural instability, which tends to come later in the disease progression. The two most common

scales used for the assessment of functional deficits and stage of progression are the Hoehn &

Yahr rating scale (1967) (Table 1.0) and the Unified Parkinson's disease Rating Scale (UPDRS)

(Goetz et al. 2005). The UPDRS is divided into scales that are used to assess mental

complications, activities of daily living and motor severity. However, the UPDRS score requires

clinical assessment and is more difficult to administer compared to the Hoehn & Yahr scale

outside of a clinic. Therefore, the Hoehn & Yahr scale is the most useful for defining stage and

severity of PD in a research setting (Roland, 2013).

Table 1.0 : *The Hoehn & Yahr scale (1967)*

Hoehn & Yahr Scale	
Stage	**Symptoms**
I	Unilateral Involvement only, usually with minimal or no functional impairment
II	Bilateral or midline involvement, without impairment of balance
III	First sign of impaired righting reflexes. Unsteadiness as the patient turns or is demonstrated when he is pushed from standing with feet together and eyes closed. Restricted activities. Physically capable of leading independent lives.
IV	Fully developed, severely disabling. Still able to walk and stand unassisted but markedly incapacitated.
V	Confined to bed or wheelchair unless aided.

1.5 Pathophysiology of Parkinson's disease:

Parkinson's disease primarily results from the degeneration of dopaminergic neurons in the substantia nigra pars compacta (Dirnberger & Jahanshahi, 2013) leading to decreased activation of dopamine receptors in the basal ganglia and reduced inhibition of neurons in the cortical pathways responsible for the control of movement (McAuley, 2003). Dopamine is a neurotransmitter within the brain that is involved in motor control and its depletion results in degeneration of descending commands from the basal ganglia to the thalamus and spinal cord. The net result of dopamine's depletion is an excessive activation of basal ganglia output neurons accompanied by excessive inhibition of motor systems leading to Parkinsonian motor features, such as resting tremor and unsteady movement production. The literature on muscular performance in persons with PD is sparse, as evidence for a central origin of PD tremor in the basal ganglia and thalamus is exceedingly strong (Baker et al. 1992; Glendinning & Enoka, 1994) and thus, little attention has been given to the altered functioning of the neuromuscular system that may contribute to the motor dysfunction seen in persons with PD.

1.6 Sidedness

PD symptoms typically first appear unilaterally and slowly progress to the contralateral side. As the disease progresses symptoms become more frequent and more severe on the side in which it first originated (Koller, 1984). Studies have shown that the more-affected PD side is weaker (Corcos et al. 1996; Canode-de-la-duerda, Perez-de-Heredia et al. 2010; Kakinuma, 1998; Nogaki et al. 1999; Roland et al. 2013), has reduced Ia reciprocal inhibition during voluntary movements (Meunier et al. 2000) and more pronounced fatigability compared to the less-affected side (Ziv et al. 1998). Lafargue et al. (2008) also found inter-manual force transfer and in estimation of forces produced by their more-affected hand are impaired in persons with

PD. Furthermore, Roland et al. (2013) reported that there was less muscle activation in the more-affected compared to the less-affected sides in persons with PD.

The asymmetric presentation of PD is common (Uittii et al. 2005) but not well understood. It has been suggested that sidedness could be due to pure chance and not genetically, environmentally, or neurochemically determined (Djaldetti et al. 2006). Others suggest that asymmetry in persons with PD is a result of the asymmetric degeneration of the substantia nigra, with greater neuronal loss contralateral to the initially affected body side (Kempster et al. 1989).

1.7 Sex Differences in Parkinson's disease:

PD is associated with well-reported but poorly understood sex disparities which influence the nature and progression of the disease. The prevalence of PD is higher in males compared to females (Rajput et al. 1984; Gillies et al. 2014; Haaxma, 2011) with twice as many males suffering from PD (Elbaz et al. 2002). It has also been reported that the development of symptomatic PD and the onset of PD is delayed in females by an average of 2 years (Haaxma et al. 2007; Haaxma, 2011; Twelves. et al, 2003). In addition, Luschiel et al. (1999) found decreases in MUDR and increases in MUDRV in PD males and not female subjects. These prominent sex differences could possibly be due to the neuroprotective effect of estrogens on the dopaminergic pathways. Females naturally have higher endogenous-striatal dopamine concentrations prolonging the time to reach thresholds of critical depletion where PD symptoms are known to appear (Haaxma et al. 2007). Sex differences in the metabolism of levodopa, the gold standard treatment for PD, have also been reported (Shulman, 2007). Estrogen protects the dopaminergic neurons by down-regulating the enzyme monamine oxidase catechol-o-methyltransferase, which is known to metabolize levodopa and dopamine within the central

nervous system (CNS) (Shulman, 2007). These higher initial dopamine levels could slow the onset of PD and therefore postpone the development of Parkinsonian symptoms in females.

Regardless of the higher prevalence of PD in males and the delayed onset in females, females still report greater disability and poorer quality of life when compared with males diagnosed with PD (Shulman, 2007). Studies investigating muscle activation patterns indicate that females with PD have more muscle activity, reach lower peak velocities, have a lower magnitude EMG and less muscle quiescence during independent living compared with males with PD (Pfann et al. 2001; Roland et al. 2013). It has also been reported that females with PD are at increased risk for frailty and are known to have greater functional decline.

Based on these current findings, it is evident that the scope of research on sex differences in PD should not solely focus on the effects of hormones on disease progression. Rather is should widen to further understand the neuromuscular components associated with the augmented functional decline in PD females.

1.8 Muscle Activity in Parkinson's disease:

Muscle Weakness and Force Control

The control of force provides quantitative information of motor control and insight into the role of different motor structures and systems during voluntary movement. In persons with PD, slowness of movement is caused by problems generating appropriate muscular force and speed (Allen et al. 2009; Hallett & Khoshbin, 1980; Kunesch et al. 1995). Muscular force is greatly reduced in PD when compared to healthy age-matched controls and this reduction in strength is augmented at faster movement speeds (Kakinuma et al. 1998; Koller & Kase, 1986; Nogaki, et al. 1999). A greater loss of extensor muscle strength compared to flexor

muscle strength has also been reported and is correlated with a reduced ability to generate rapid contractions (Corcos et al. 1996, Kakinuma et al. 1998; Robichaud et al. 2004). It has been suggested that these differences in strength and speed are a result of greater impairment in neural activation and decreased tonic activation of the extensor muscles in persons with PD (Corcos et al. 1996). It has been found that in healthy individuals, flexor muscles are more facilitated and less inhibited by corticospinal neurons than extensor muscles; suggesting a higher level of brain activation is required to activate the extensor muscles (Palmer & Ashby, 1992). In PD there is a lower level of activation of the supplementary motor cortex (Berardelli et al. 2001) and because extension movements generally require more brain activity, persons with PD move more slowly during extension movements (Robichaud et al. 2004).

During isometric contractions, persons with PD have slower muscle relaxation (force release) times and the ability to maintain a constant force over time has been found to be impaired even when medicated (Kunesch et al. 1995). Sheridan, Flowers & Hurrell (1987) also reported an increased variability in maintaining steady force. Impaired rate of force release in PD (Corcos et al. 1996; Jordan et al. 1992) is coupled with longer reaction times (Grasso et al. 1996; Wierzbicka, et al. 1991) and an increase in background muscular activity when relaxed (Berardelli et al. 1983).

Motoneuron drop-out and altered motor unit activity:

Alterations in muscle properties contribute to the decline in strength and force control in PD. Persons with PD have significantly lower MU number estimates than age-matched controls (Caviness et al. 2002) suggesting a disease associated greater motoneuron drop-out with reinnervation occurs (Caviness et al. 2000). This increase in motoneuron drop-out, reinnervation

and decline in the total number of active motor units, results in a reduction of force production and control. Furthermore, increased MUDRV (Das Gupta, 1963; Dietz et al. 1974; Luschiel et al. 1999; Rosenflack & Andreasson, 1980), increase MU recruitment at low forces (Milner-Brown et al. 1979, Dietz et al. 1974), abnormalities in the firing pattern between small and large MUs (Dietz et al. 1974), and firing at abnormally low frequencies contribute to the loss of force control in PD (Milner-Brown et al. 1979).

Tremor and motor unit synchronization

Tremor in PD is strongly influenced by the force of voluntary contraction and it is strongest at rest or during weak muscular effort. As force increases, tremor becomes continuously more frequent and of smaller amplitude (Dietz et al. 1974). Tremor amplitudes in PD can be partially explained by synchronization of unfused twitches of MUs, which summate more powerfully than the partially fused contractions during physiological tremor (Dietz et al. 1974; Dengler et al. 1986). Smaller MUs discharge once per tremor beat in weak contractions but change into bursts of two or three spikes at stronger forces (Dietz et al. 1974). Additionally, synchronous MU activity during PD tremor represents rhythmical sequences of spike doublets and triplets resulting in in-phase rhythms that enhance tremor force (Christakos et al. 2009) and is associated with a periodic synchrony of 10 Hz (Baker et al. 1992). However, these higher incidences of synchrony in PD have been found to be unrelated to the lower discharge rates of MUs (Baker et al. 1992) and are more so indicative of altered recurrent inhibition (Das Gupta, 1963).

Proprioception and Spinal Reflexes in Parkinson's disease:

The changes in MU activity, muscle characteristics and altered force control in PD are thought to be caused by disinhibition of groups of neurons in the basal ganglia that affect the excitability and sensory responses of areas in the cerebral cortex involved in voluntary movement (Djaldetti & Melamed, 2006). Furthermore, it has been suggested that the disruption in constant force production could be due to a dysfunction of the integration of proprioceptive inputs and impaired proprioceptive delivery to the brain (Cano-de-la-Duerda et al. 2010).

A number of studies have found a disruption of proprioceptive information in PD (Khudados et al. 1999; Schrader et al. 2008) represented by an enhanced long-latency stretch reflex (Cody et al. 1986; Diener et al. 1987; McLeod & Walsh, 1972; Mortimer & Webster, 1989; Rothwell et al. 1983). This altered polysynaptic reflex could be an expression of disturbed neuronal excitability (Valls-Sole & Valldeoriola, 2002). In fact, increased alpha motoneurone excitability has been recorded in PD (McLeod & Walsh, 1972). This heightened excitability could be due to the reduced reciprocal inhibition in PD (Bathien & Rondot, 1977; Delwaide et al. 2004; Lelli et al. 1991) indicating abnormal supraspinal influence on spinal reflex mechanisms, such as an increase in intracortical inhibition (Lewis & Byblow, 2002). Increased intracortical inhibition would cause elevated activity of efferent tracts that inhibit both the Ib interneurons and activate Ia interneurons (Delwaide et al. 1991), resulting in hyperactivity of the Ia inhibitory interneuron (Delwaide et al. 1991; Delwaide et al. 2004) and contributing to the mismatch of sensory and motor information.

1.9 Vibration

When a tendon is vibrated, a transference of energy occurs from the vibration source to the body part, creating reactive forces that have the potential to excite the Ia afferent reflex loop (Cochrane, 2011). Studies have found that vibration elicits an alteration in neuromuscular recruitment patterns that enhance neuromuscular excitability (Rittweger et al. 2003). There are two common types of vibration: indirect whole-body-vibration and direct tendon vibration. Whole-body-vibration is usually administered via a vibrating platform that produces sinusoidal oscillations (Cochrane, 2011). Direct tendon vibration involves vibration to a tendon that induces activation of a single muscle in which the response to this vibration does not extend to the muscles that are synergistic to the vibrated tendon (Kouzaki et al. 2000). Vibration in a variety of different modalities has been used to excite the muscle spindles, test proprioceptive feedback, and cause increased gains within the neuromuscular system (Cochrane, 2011).

A variety of factors determine the effect vibration will have upon the excitation of the muscle, cortical excitability (Kossev et al. 2001), force production (Griffen, et al. 2001)**,** and co-contraction (Eklund & Hagbarth, 1966)**.** It is well known that tendon vibration of 100-150 Hz (Cochrane, 2011; Eklund & Hagbarth, 1966) applied to the tendon of either a flexor or extensor muscle in the upper or lower extremities elicits a reflex contraction and reciprocal inhibition of the antagonist muscles (Eklund & Hagbarth, 1966). This reflex depends solely on the excitation of the primary spindle endings. Muscle spindles detect the vibration and excite the Ia afferents. There is a general acceptance that Ia afferent fibres within the muscle spindle are the principle receptors in the muscle for signaling relative changes in proprioception with vibratory stimulation (Hagbarth &Valbo, 1968, Goodwin et al. 1972). This modulation in Ia afferent drive results in an increase in the excitation of the alpha motoneurons, which facilitate the extrafusal

muscle fibres of the homonymous muscle; ultimately leading to increased activity and contraction of the homonymous muscle. The reflex resulting from vibratory stimuli is known as the tonic vibration reflex.

Crossed-Effects of Vibration:

Exercise adaptations that occur in one limb can produce beneficial effects in the contralateral limb. This transference of neural activation between limbs is known as cross-education. Significant improvements in strength have been reported in the contralateral untrained limb following resistance exercise (Fimland et al. 2009; Lee et al. 2009; Sariyildiz et al. 2011). This increase in strength is not accompanied with an increase in hypertrophy in the untrained limb suggesting this strength transfer is attributed solely to neural adaptations: however, the underlying mechanisms to cross-education are still not well known. Furthermore, improvement in strength as a result of cross-education has been suggested as a potential means of neuromuscular rehabilitation for individuals who have conditions that prevent them from exercising a limb (Zhou, 2000). Some have found that spinal mechanisms are responsible for the adaptations in the untrained limb (Hortobagi et al. 1999), whereas others claim supraspinal mechanisms are more likely the cause of these neural adaptations (Shima et al. 2002).

There is strong evidence that acute indirect vibration acts on muscle to enhance force, power, flexibility, balance and proprioception suggesting neural enhancement (Cochrane, 2011). The crossed-effects of vibration have been studied in a healthy population and it has been found that prolonged vibration on the contralateral leg causes fatigue in the non-vibrated leg: this suggests that vibration excites heteronymous motoneuron pools acting on central descending drive and spinal reflex pathways (Jackson & Turner, 2003). Furthermore, vibration augments

motor evoked potentials in the non-vibrated limb indicating an increase in excitability of the cortex, motoneurons and muscle fibres to the contralateral non-vibrated muscle (Kossev et al. 2001). It has also been suggested that these crossed-effects of vibration could occur through the crossed-extensor reflex pathway by which vibration of an extensor muscle on the ipsilateral limb could cause excitation of a flexor muscle in the contralateral limb (Rothwell, 1987).

Vibratory Effects in Parkinson's disease:

Studies suggest that vibration in persons with PD could be used as a positive influence on motor symptoms and as a potential therapy for the disease (Christova, et al. 2010; King et al. 2009). Interestingly, the tonic excitatory vibration reflexes are unaffected by PD (Cody et al. 1986, Burke et al. 1972) and in persons with PD the tonic vibration reflex has been found to affect resting tremor by abolishing tremor or reducing the frequency of tremor (Jobges et al. 2002). In addition, it could also contribute to a better understanding of how proprioceptive information can influence PD resting tremor (Jobges et al. 2002) by identifying the underlying mechanism of the interaction between proprioceptive inflow from muscle spindles and tremor driven outflow. Furthermore, King et al. (2009) reported that whole body vibration therapy led to significant decreases in rigidity, tremor and gait abnormalities in PD. However, the crossed-effects of acute tendon vibration on the upper body in PD have not been studied. The positive effects of acute direct tendon vibration on the less-affected PD side could potentially be transferred to the more-affected PD side resulting in neural adaptations and a reduction in PD symptoms of the more-affected limb. Due to the distinct varied differences in MU activity, augmented reflex loops, altered proprioception and modulation in descending drive in PD, the effects of vibration in a healthy population cannot be used as a valid comparison to the outcome of vibration in persons with PD. Therefore the purpose of this study was to determine the

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crossed-effects of acute tendon vibration on MU activity and force steadiness of the contralateral

limb in PD. Furthermore, these responses to vibration in persons with PD were evaluated

between males and females.

1.9.3 Purpose and Hypotheses

Purpose:

a) To study the effects of acute direct tendon vibration applied to the biceps brachii of the less-affected limb on MU activity in the biceps brachii and elbow flexor force steadiness of the contralateral more-affected limb in males and females with PD.

Hypothesis:

Acute direct vibration applied to the biceps brachii tendon of the less-affected limb will facilitate the polysynaptic crossed-extensor reflex via Ia afferent reflex loop causing the following to occur in the contralateral biceps brachii of the more-affected limb during a sustained submaximal voluntary isometric contraction:

a) A reduction in total active MUs

b) A decrease in MUDRs and increase in MUDRV

c) An increase in recruitment thresholds and reduction in derecruitment thresholds

d) Vibration will cause greater fluctuations in force

e) Vibration will cause a greater change in MU activity in males compared to females

f) Males will be less steady than females

Chapter 2: Methods

2.1 Participants

Six males (66.1 ± 6.8 yrs) and four females (69.7 ± 1.8 yrs) with mild to moderate PD severity (stages I-III; Hoehn & Yahr, 1967) living independently in the community were recruited through newsletter advertisement, public presentations and word-of-mouth for this study. The Clinical Research Ethics Board (University of British Columbia) approved the experimental procedures and subjects provided written informed consent prior to participation. Individuals who scored greater than 4 on the Hoehn & Yahr scale, had severe cognitive impairments, cardiorespiratory complications or neurological disorders other than PD were excluded from the study. A health history questionnaire was administered and subjects self-reported disease duration, carbidopa-levodopa regime, and more-affected body side. Carbidopa and levodopa were administered simultaneously to prevent the metabolism of levodopa in the gastrointestinal tract. The experiment was conducted within one-hour of taking medication. The Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ) was administered to gauge average levels of physical activity in kilocalories (kcal). Subjects self-reported what type of activities they performed within the last two-weeks prior to the testing session and total kcal were calculated based on the intensity, duration, and frequency of the activity. All subjects were independently mobile (with or without gait-aids), able to read and speak English fluently and considered to be in a steady clinical state (i.e., controlled by medication).

2.2 Study Design

All physiological and mechanical force recordings were obtained from the upper limb of the self-identified more-affected side in the neutral forearm position. Force and muscle activity were recorded from the long head (LH) and short head (SH) of the bicep brachii, lateral triceps (TRI), and brachioradialis (BR) muscles. MU activity was also recorded from the LH and SH of the biceps brachii. Subjects were seated in custom-design force dynamometer chair grounded through a Coulbourn Instruments Unit (Coulbourn Electronics, Allentown, PA, USA). The chair was adjusted so that each subject's target arm rested with the elbow on a plate with the joint positioned at 90º. The shoulder was abducted 20º with 0º flexion while the target hand grasped a manipulandum with a MLP-150 linear calibrated force transducer fastened underneath (68kg sensitivity 32.5 N) (Transducer Techniques, Temecula CA. USA) to measure application of upward elbow flexion force. Chest and waist constraints were used to ensure consistent subject positioning and vibration placement throughout the experiment (Figure 2.0). The wrist and hand of the vibrated less-affected arm rested on the thigh with the elbow abducted away from the body for ease of access to the biceps brachii for tendon vibration.

Visual feedback of force output was provided with a 20.5 inch monitor screen located 1-m away from eye level. The visual feedback was scaled relative to the target force of each subject's maximal voluntary contraction (MVC) for consistent feedback (Figure 2.2).

Surface Electromyography:

Four pairs of bipolar surface electrodes (4mm Ag/AgCl) were placed longitudinally on the more-affected side with an interelectrode distance of 2 cm over the muscle belly of the LH, SH, TRI and BR muscles. Ground electrodes were placed over the bony processes of the lateral epicondyle, clavicle and acromion process. The placement of the surface electrodes were

prepared by gently abrading the area with a coarse, dry sponge and swabbing the area of the skin with 70% isopropyl pads. Palpations and functional contractions were performed to ensure proper placement of electrodes, which were followed by verification of the EMG signal isolated from the desired muscle. Electromyography signals were amplified ($\times$ 1,000) and band pass filtered (13-500 Hz) (Coulbourn Instruments, Allentown, PA, USA) and analog-to-digital converted at a rate of 1,024 Hz (CED, Cambridge, UK).

Intramuscular Fine-Wires

Two pairs of hooked tip custom made fine wires (15-30 cm), specifically designed for selectivity and stability, were inserted into the LH and SH of the target arm to record single MU action potential trains. The tips of each of these stainless steel fine wires were threaded through a sterilized 25-gauge hypodermic needle for insertion into the muscle. Insertion of the needles involved penetration of the fascia and subcutaneous tissue approximately 1.0 cm into the muscle. The insulation was removed from the fine wire ends not inserted into the muscle by briefly exposing the tips to a flame to remove the coating. The wires were then abraded with sandpaper to ensure contact between the wire and amplifier input. Once inserted, the fine wires were secured to the skin with surgical tape. The common ground electrode was placed over the bony process of the carpometacarpal joint head of the wrist. Intramuscular fine wires were pre-amplified (100-1000$\times$, Neurolog, Welwyn City, England), filtered (500- 1000 Hz) at a sampling rate of 10,000 Hz.
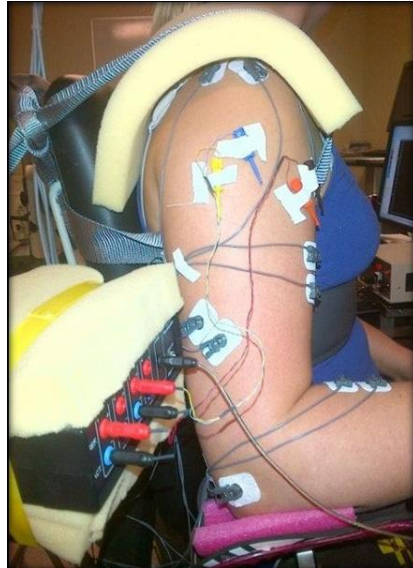
Figure 2.0: *Experimental Set-Up. Subjects were seated in a custom-designed force dynamometer chair with surface EMG electrodes placed on the LH, SH of the biceps, the triceps, and brachioradialis muscles. Intramuscular fine wires were inserted into the SH and LH of the biceps muscle.*

Twitch Contractile Properties:

Twitch contractile properties of the elbow flexors were evoked through two custom-made stimulation pads coated in electrode gel firmly secured over the biceps brachii. Using a constant voltage stimulator (DS7AH: Digitimer. LTD. Welwyn Garden City. Hertfordshire. UK) current intensity (80-260 mA) was increased until twitch force plateaued then the intensity was increased an additional 10%.

Vibration

Vibration was applied to the center of the biceps tendon of the less-affected arm with a custom-made vibration apparatus (Don Clarke, University of Windsor, ON, Canada) (Figure 2.1). To landmark the position, subjects were instructed to perform brief elbow flexion of the less-affected arm while the center of the biceps tendon was palpated and marked to ensure consistent positioning of vibration. The frequency and amplitude range of the vibration apparatus

was 100Hz and 3.5-4.0mm, respectively. The vibration occurred throughout the entire duration of the isometric ramp contraction.

Figure 2.1: Custom-made vibration apparatus. Vibration was applied to the biceps tendon of the less-affected arm. The frequency and amplitude range of the vibration apparatus was 100Hz and 3.5-4.0mm. Vibration was applied throughout the isometric ramp contractions.

2.3 Experimental Procedure

Maximal Voluntary contraction (MVC) and Twitch Interpolation

To assess maximal strength, participants performed three isometric elbow flexion MVCs that were held at a steady state for 3-5 sec in the neutral position. Participants also performed an isometric elbow extension MVC in the neural position to assess maximal strength in the triceps muscle. Subjects were verbally encouraged to flex the forearm upward as hard and as fast as possible. Twitch stimuli were delivered immediately preceding (resting twitch), during the plateau in MVC force (interpolated twitch) and immediately following a return to baseline force (post MVC twitch) to determine percent voluntary activation with the twitch interpolation technique (Figure 2.2). Estimates for the degree of voluntary activation were obtained by taking

the ratio of superimposed twitch (Tw_s) to the potentiated (post-MVC) twitch (Tw_p) and expressing it as a percentage: $[(1- Tw_s/Tw_p) \times 100 = \%\text{activation}]$. Each contraction was maintained for 5 sec and separated by 2-3 min of rest. The highest MVC value was used to establish isometric target forces and to determine the load for all subsequent contractions. Following completion of the targeted ramp isometric contractions, a final MVC attempt was performed to assess whether a reduction in maximal force generating capacity occurred as a result of the protocol.
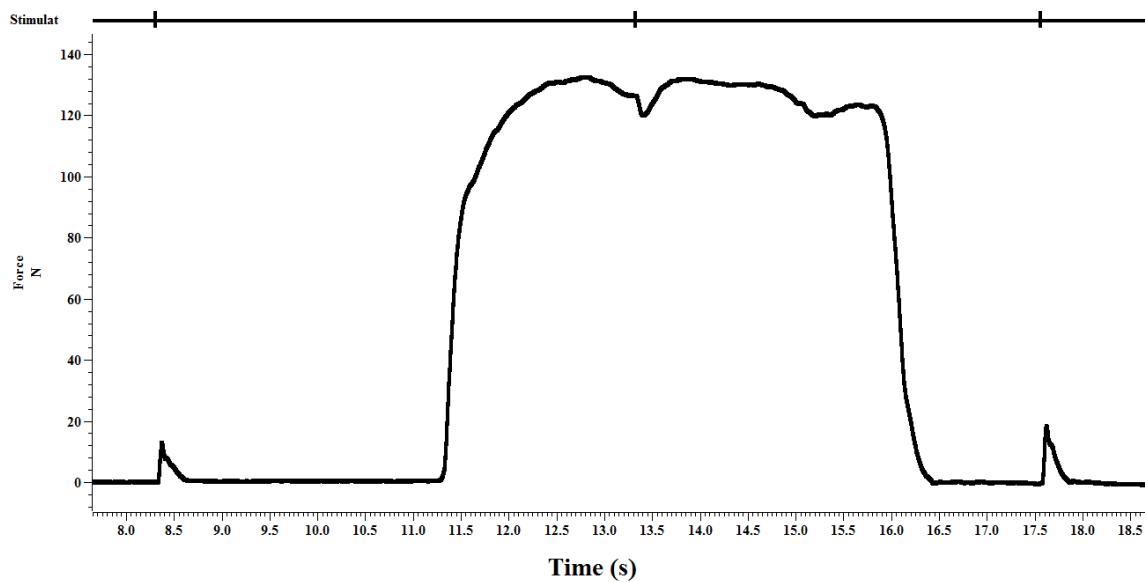
Figure 2.2: *Maximal voluntary contraction (MVC) with twitch stimuli administered before, during and after MVC. Stimulation was used to determine contractile properties (twitch before MVC) and voluntary activation (interpolated twitch and post twitch).*

Submaximal Voluntary Contractions:

Subsequent to assessment of MVC, submaximal force levels of 5% MVC were calculated. Submaximal force levels of 5% of MVC were used as this force level exhibits a high level of variability and MUs are readily recorded and tracked between conditions. Elbow flexor MVC data were used to determine the target force for the tracking task (Figure 2.3). The tracking

task involved elbow flexion force initiated in a ramp fashion ending at the targeted force level of 5%. Following a steady plateau, a descending ramp contraction was initiated until a zero force level was evident. The total length of the isometric tracking task was 15 sec in duration which was comprised of 1) a 5 sec ramp increase in force to 5% MVC, 2) a 5 sec isometric hold phase and 3) a 5 sec ramp decrease in force to rest. Subjects performed the tracking task three to four times for each of the three conditions (no-vibration, biceps-vibration, post-no-vibration) with 2-3 min rest between trials.
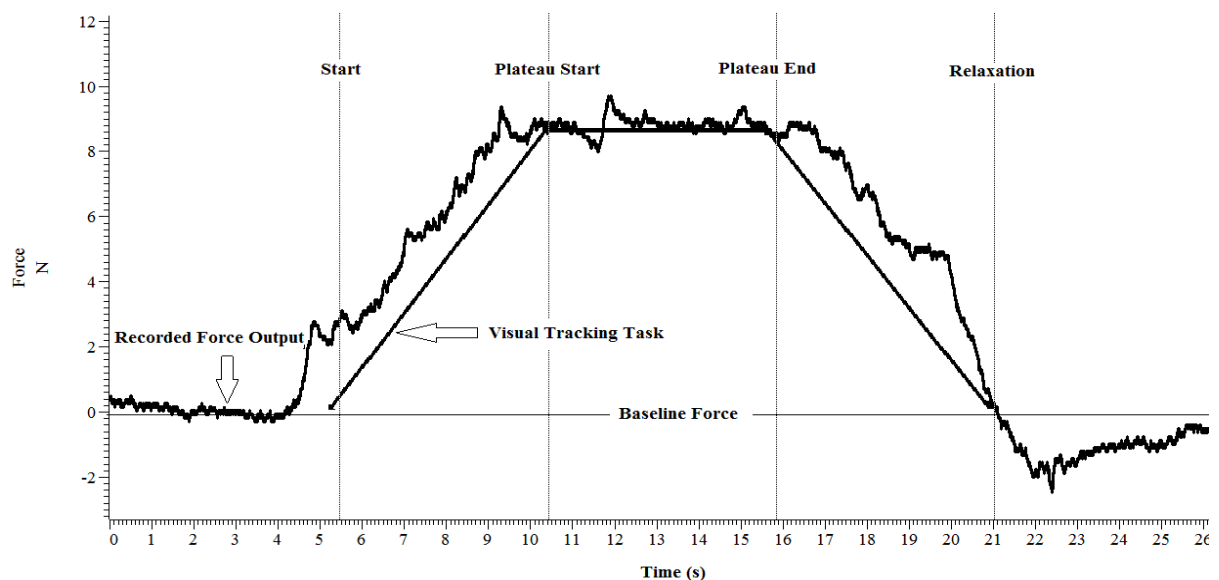
Figure 2.3: Example of the submaximal voluntary contraction tracking task at 5% of MVC. Visual feedback of force output was scaled relative to the target force. The solid line represents the output of the graphical sequence editor that plateaus at 5% MVC. The variable line represent the subject's actual force output.

Data Analysis

Off-line data analysis was performed using a custom software package (Spike 2 version 7,0, CED, Cambridge, UK). Intramuscular recordings were high-pass filtered and sloped to reduce noise and enhance the signal for clear MU analysis. Determination if a MU action potential belonged to a single MU was done by visual inspection. Single MUs were identified
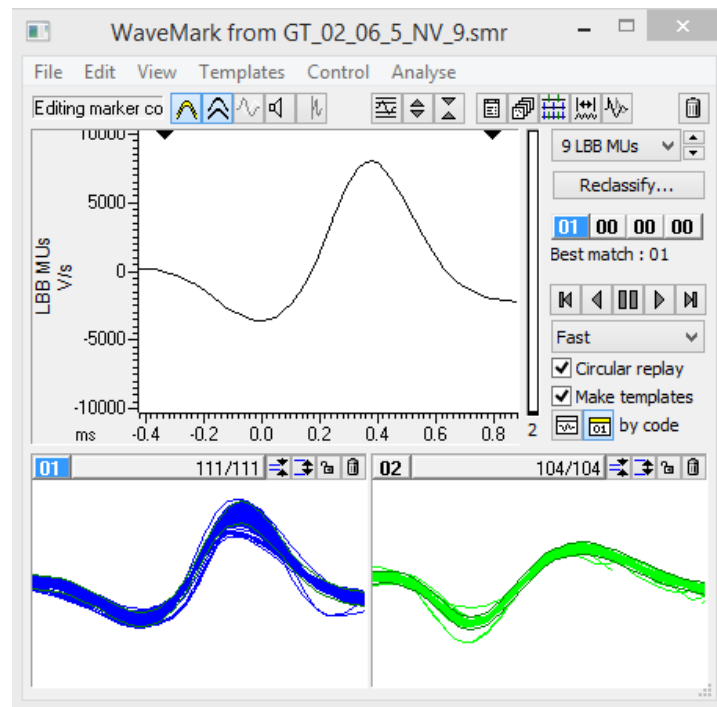
using a template-matching algorithm (Spike 2 version 7.0 waveform discrimination, CED, Cambridge, England) where individual MU action potentials were identified by waveform shape, and firing behavior by comparing action potentials with respect to temporal and spatial characteristics (Figure 2.4). MU trains had to have a continuous discharge of at least five consecutive MU action potentials to be included. MU trains were included provided that they discharged continuously throughout the entire contraction with no interspike intervals of less than 10 msec or greater than 150 msec during consecutive discharge. All trains were tracked through each phase of the isometric ramp contractions (ramp, plateau, deramp) and between vibration conditions (no-vibration, biceps-vibration, post-no-vibration). For each MU train, the average MUDR (Hz) and MUDRV (SD of discharge rates) were calculated using customized software (Spike 2 version 7.0) based upon the absolute MU discharge times (Figure 2.5). Both average MUDR and MUDRV were calculated for the entire contraction for all conditions to assess changes in MUDR and MUDRV between the vibration and no-vibration conditions, across all phases of the contraction and between sexes. Recruitment thresholds (%MVC) were calculated as the level of force at which a MU train discharged its first action potential. Derecruitment thresholds (%MVC) were calculated as the level of force at which a MU train ceased firing. All MUs recorded were assigned a number based on their specific waveform characteristics and shape. All recorded MUs were counted and the absolute numbers were separated into those continuously tracked for each of the 3 conditions (no-vibration, biceps-vibration, post-no-vibration), each of the 3 phases (ramp, plateau, deramp) as well as those MUs that were not tracked across all phases and conditions.

Surface EMG, indicated by the integral of the rectified EMG signal (iEMG), was averaged for each muscle separately (SH, LH, BR, TRI) over the 5 sec plateau phase of the

isometric ramp contractions across all conditions (no- vibration, biceps-vibration, post-no-

vibration). Relative iEMG values were determined for each submaximal contraction and an

average iEMG (AEMG) were calculated for the three contractions performed in each condition.

Measures were expressed as a relative percentage of iEMG recorded during 3 sec plateau of the

highest MVC in the corresponding muscle for each subject (%MVC).

Force steadiness was evaluated for 5 sec during the plateau phase of each contraction and

was assessed offline (Spike 2 Version 7.0; CED, Cambridge, UK) as the inverse of the

coefficient of variation (CV) of force (standard deviation of force $\times$ average force-1$\times$ 100%).

Figure 2.4: Template matching algorithm used to discriminate between individual MU spikes by overlaying and comparing temporal and spatial characteristics taken from the LH of the biceps brachii of a male participant. Each shape represents a different active MU. The top box is one MU and the bottom boxes represent the overlay of two unique MU trains.
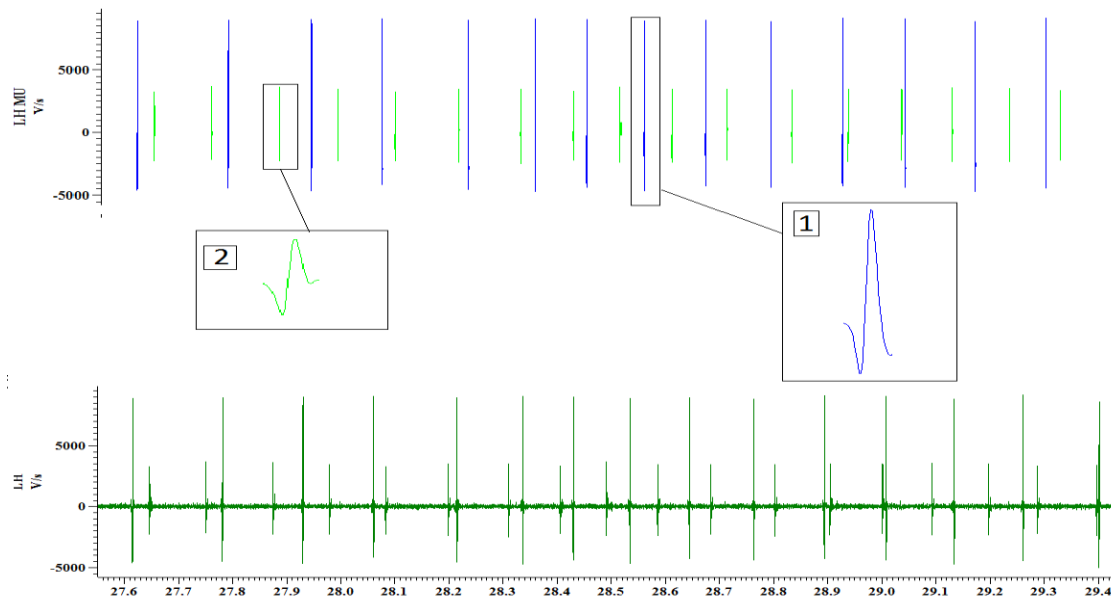
Figure 2.5: *Sample waveform output from a MU recording from two distinct MU trains. The top recording represents the waveform output and the bottom recording represents the raw data signal collected during testing. The larger amplitude MU (1;blue) represents an individual MU train firing less frequently than the smaller amplitude MU (2;green). In this 1.8-s window, the smaller amplitude MU has a total of 17 discharges, whereas the larger amplitude MU has 15 discharges.*

Statistical Analysis:

Data were analyzed using SPSS version 22 (SPSS, Chicago, IL, USA) and Microsoft Excel XP version. The dependent variables measures were average MUDR (Hz), MUDRV (SD of MUDR), recruitment thresholds (%MVC), derecruitment thresholds (%MVC), surface EMG (AEMG), and force steadiness (CV of force) (SD/mean force). MUs were tracked across each phase of the contraction (ramp, plateau, deramp) and MUDR and MUDRV were analyzed for each individual MU at each phase. Inferential statistics were conducted on all tracked MUs, surface EMG and force steadiness. MU recruitment thresholds were analysed for the ramp phase while derecruitment thresholds were analyzed for the deramp phase of all tracked units. Student's t-tests were conducted to evaluate differences in subject characteristics and twitch

contractile properties (PT, TPT, HRT, CD), rates of contraction and relaxation and twitch potentiation between males and females with PD.

All primary dependent variables were initially analysed and compared between the no-vibration and post-no-vibration conditions using Student's t-test which yielded no significant effect in MUDR (p=0.50), MUDRV (p=0.78), recruitment thresholds (p=0.70) or derecruitment thresholds (p=0.61). Based on an absence of differences between the no-vibration conditions applied before (pre) and after (-post), the data from the no-vibration condition was utilized as the control condition.

A 2 (condition; no-vibration, vibration) $\times$ 2 (sex; male, female) $\times$ 3 (contraction phase; ramp, plateau, deramp) repeated measures analysis of variance (ANOVA) was used to examine MUDR and MUDRV and a 2 (condition; no-vibration, vibration) $\times$ 2 (sex; male, female) repeated measures ANOVA was used to examine MU recruitment thresholds (%MVC), derecruitment thresholds (% MVC) and force steadiness (CV of force). Surface EMG was analyzed using a 4 muscle (LH, SH, TRI, BR) $\times$ 2 (sex; male, female) $\times$ 2 (condition; no-vibration, vibration) repeated measures ANOVA.

Additional MUs detected but not present across all three phases of the task (ramp, plateau, deramp) were analyzed using a three-way (condition $\times$ sex $\times$ phase) repeated measures ANOVA. Partial eta-squared (n^2) effect sizes were determined for all significant interactions and main effects revealed by repeated measures ANOVAs of MUDR, MUDRV, MU recruitment thresholds and MU derecruitment thresholds. For dependent measures evaluated using repeated-measures ANOVA, the Greenhouse-Geisser corrected n^2 was reported when the assumption of sphericity was not satisfied. The critical value for statistical significance was set at $p < 0.05$. Student's t-tests were used to examine significant interactions. All data presented within the text

are expressed as means $\pm$ standard deviation (SD), whereas all figures are displayed as values $\pm$ standard error of the mean.

Chapter 3.0 Results:

Subject Characteristics:

Of the ten subjects recruited (n=4 female), eight were right hand dominant and two were left hand dominant. The majority of subjects were more-affected on the non-dominant side (n=7) compared to those more-affected on the dominant side (n=3). Disease duration ranged from one-nine years (2.8 ± 2.5 yrs) and did not differ between sexes (p=0.73). Average disease severity assessed from the Hoehn & Yahr Scale (1967) was 2 ± 0.6 and was significantly greater in males compared with females (p=0.04). Males were significantly taller (p=0.03) with greater body mass (p=0.04) compared with females (Table: 3.0).

Table 3.0: Subject characteristics

	Males (n= 6)	Females (n=4)	Overall (N=10)
Age (yrs)	66.1 ± 6.8	69.7 ± 1.8	67.6 ± 5.5
Height (cm)	173.0 ± 9.0*	161.1 ± 3.1	168.8 ± 9.6
Weight (kg)	79.5 ± 9.1*	58.6 ±8.6	71.7 ± 13.7
BMI (kg/m^2)	26.4 ± 1.4*	22.6 ± 3.3	24.9 ± 2.9
HY	2.3 ± 0.5*	1.5 ± 0.5	2.0 ± 0.6
PD Diagnosis Duration (yrs)	2.6 ± 3.1	3.2 ± 1.5	2.8 ± 2.5
R dominant, R PD	0	1	1
R dominant, L PD	5	2	7
L dominant, L PD	1	1	2
Laterality Quotient (%)	80.4 ± 17.6*	49.4 ± 18.1	68.1 ± 23.2
MLTPAQ (Kcal)	6255.6 ± 3607.3	3874.6 ± 3951.5	4993.5 ± 3524.5

Values are means ± SD. * significantly different from females; cm, centimeter; kg, kilogram; yrs, years; HY, Hoehn Yahr Rating; BMI, Body Mass Index; %, percent of right hand dominance; R, right hand; L, left hand; PD, Parkinson's disease more-affected body side; MLTPAQ, Minnesota Leisure Time Physical Activity Questionnaire; Kcal, kilocalorie.

Contractile Activity:

Twitch contractile properties, voluntary activation and post-activation potentiation were recorded across all subjects and compared between males and females with PD. All subjects were highly activated (98.2% ± 1.3). Contraction times did not differ between sexes (p=0.06) but peak tensions (PT) were higher in males compared to females (p=0.01) (~47%). Males had 45% higher elbow flexion force (p>0.001). Maximal triceps extension force did not differ between sexes (p=0.58). The relative forces exerted for the tracking task were similar between males (5.6

± 0.7 % MVC) and females (5.5 ± 1.4 %MVC) (p=0.68) (Table 3.1) and did not differ between

tracking with vibration and without (p=0.24).

Table 3.1: Contractile Properties.

	Males (N=6)	Females (N= 4)	Overall (N=10)
Average Rise (n/ms)	0.6 ± 0.4	0.4 ± 0.3	0.5 ± 0.4
Average Fall (n/ms)	-0.4 ± 0.4	-0.1 ± 0.0	-0.2 ± 0.3
TPT (ms)	51.7 ± 16.0	43.5 ± 16.4	48.43 ± 15.8
HRT (ms)	51.9 ± 28.2	75.4 ± 32.6	61.3 ± 30.7
CD (ms)	103.6 ± 41.5	118.9 ± 39.9	109.8 ± 39.4
PT (N)	23.8 ± 7.09*	12.6 ± 2.7	19.3 ± 8.02
PAP (%)	27.1 ± 6.3	33.2 ± 7.4	30.7 ± 7.3
Voluntary Activation (%)	98.5 ± 1.2	97.8 ± 1.6	98.21 ± 1.34
Elbow Flexor MVC (N)	196.0 ± 40.4*	107.1 ± 27.4	160.9 ± 57.4
Triceps Extension MVC (N)	108.3 ± 15.2	97.7 ± 41.8	104.0 ± 27.2

Values are means ± SD. *significantly different; ms, milliseconds; %, percent of
activation compared to MVC; N, Newton; TPT, time to peak tension; HRT, half
relaxation time; CD, contraction duration; PT, peak tension; PAP, post-activation
potentiation.

Muscle Activity:

Surface EMG was analyzed during the plateau phase of the isometric contraction tracking

task in both males and females during the no-vibration and biceps-vibration conditions. No three-

way interaction for vibration condition × muscle × sex was found (F= 1.0, p=0.39, n^2=0.1) and

there were no two-way interactions or main effects for sex (F=1.9, p=0.18, n^2=0.06), vibration

condition (F=0.03, p=0.87, n^2= 0.00) or muscle (F=0.61, p=0.61, n^2=0.06).

Motor Unit Activity:

A total of 32 recruitment and derecruitment thresholds were compared between males

(n=18; 3.5 ± 0.8) and females (n=14; 4.4 ± 1.0) in the no-vibration and biceps-vibration

conditions. There was no significant interaction for condition $\times$ sex (F=1.5, p=0.23, n^2=0.05) and no main effects for sex (F=0.77, p=0.39, n^2=0.03) or condition (F=0.09, p=0.76, n^2= 0.00) in recruitment thresholds. There was no significant two-way interaction for condition $\times$ sex (F=1.2, p=0.28, n^2=0.04) or a main effect for sex (F=0.5, p=0.47, n^2=0.02) or condition (F= 2.1, p=0.16, n^2=0.07) for derecruitment thresholds (Table 3.2).

Table 3.2: Average recruitment and derecruitment thresholds.

	Recruitment Thresholds (%MVC)	Derecruitment Thresholds (%MVC)
No-vibration	1.6 ± 1.5	0.02 ± 0.017
Biceps-vibration	1.7 ± 1.8	0.01 ± 0.013
Males	1.9 ± 0.3	0.01 ± 0.003
Females	1.5 ± 0.4	0.02 ± 0.003
Overall	1.7 ± 0.2*	$0.01 \pm .002$

Values are means $\pm$ SD. %MVC, percentage of maximal voluntary contraction.

Recruitment thresholds and derecruitment thresholds were compared to each other and between no-vibration and biceps-vibration conditions. There was no significant two-way interaction for condition $\times$ sex (F= 1.49, p=0.23, n^2=0.05) or main effect for sex (F=0.75, p=0.40, n^2=0.02) or condition (F=0.09, p=0.76, n^2=0.00) in either recruitment threshold or derecruitment thresholds. When recruitment thresholds and derecruitment thresholds were compared to each other there was however, a main effect between recruitment thresholds and derecruitment thresholds (F=49.4, p>0.001, n^2=0.62), with recruitment thresholds being significantly higher than derecruitment thresholds.

A total of 29 motor units were tracked across all phases of the isometric ramp contractions (ramp, plateau, de-ramp) and compared between sexes (males n=17; females n=12) in the no-vibration and biceps-vibration conditions. Three motor units were excluded from these analyses because they were not active in all three phases of the contraction. No three-way interaction for MUDR between contraction phase, condition and sex was found (F= 2.3, p= 0.64, n^{2}= 0.32). There was a significant two-way interaction for phase $\times$ sex (F=6.697, p>0.001, n^{2}=0.34). Post hoc tests indicated that females (12.5Hz $\pm$ 0.8) had higher MU discharge rates (~18%) during the plateau phase of the contraction when compared to males (10.2Hz $\pm$ 0.7) (p=0.02) and males had higher MU discharge rates during the deramp phase (11.5Hz $\pm$ 0.6) of the contraction compared with females (9.9Hz $\pm$ 0.7) (p=0.05). Females also had higher MUDR during the plateau phase (12.5Hz $\pm$ 0.8) compared to the deramp phase (9.9Hz $\pm$ 0.7) of the contraction (p=0.01) (Figure 3.0). There was also a significant two-way interaction between phase and condition (F=4.58, p=0.01, n^{2}=0.261). Post hoc tests revealed that the no-vibration condition (11.6Hz $\pm$ 0.6) had a higher MUDR compared to the biceps-vibration condition (9.8Hz $\pm$ 0.6) during the deramp phase (p=0.02) (Figure 3.1). No significant differences between the no-vibration and biceps-vibration conditions during the ramp (p=0.65) or plateau phases (p=0.81) were observed. No significant main effects for phase (F= 91.3, p=0.27, n^{2}=0.88), sex (F= 0.34, p=0.69, n^{2}=0.02) or condition (p=0.36) were found.
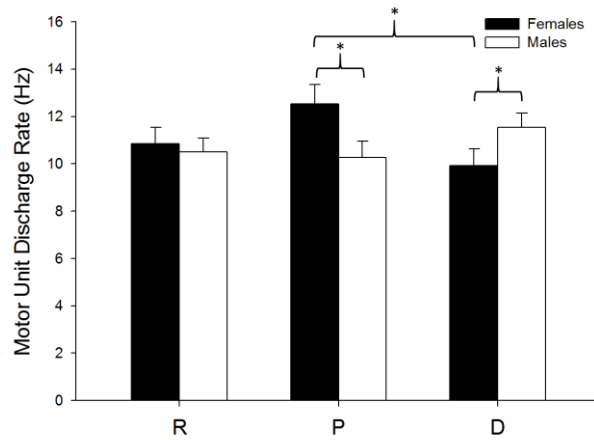
Figure 3.0 : *Average MUDRs compared between males (open bars) and females (filled bars) across the three separate phases of the isometric ramp contractions and pooled across conditions. R, ramp phase; P, plateau phase; D, deramp phase. Hertz, Hz. Data are shown as means ± SE. *p<0.05.*
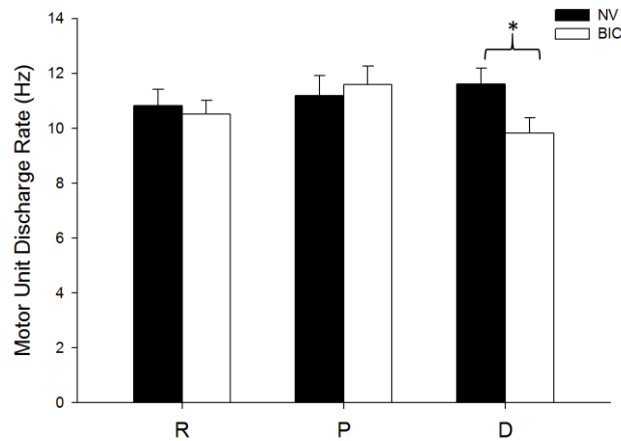
Figure 3.1: *Average MUDRs compared between the no-vibration condition (filled bars) and biceps-vibration condition (open bars) across all three separate isometric ramp contraction phases. R, ramp phase; P, plateau phase; D, deramp phase. Hertz, Hz. Data are shown as means ± SE. *p<0.05.*

A three-way interaction was observed for MUDRV between contraction phase, condition and sex (F=5.185, p>0.001, n^2=0.285). Post hoc analysis determined that males had significantly higher MURDV during the ramp phase in the biceps-vibration condition (0.04Hz ± 0.01) when

compared with females (0.02Hz ± 0.01) (p=0.04). Males also had a significantly higher MUDRV in the plateau phase (0.02Hz ± 0.0) of both the no-vibration condition (p=0.04) and the biceps-vibration condition (p>0.001) compared with females (0.01 Hz ± 0.0) (Figure 3.2). There were no differences between males (0.03Hz ± 0.01) and females (0.03Hz ± 0.01) during the ramp phase in the no-vibration condition (p=0.90) and there were no differences between sexes in the deramp during either the no-vibration (p=0.22) or the biceps-vibration (p=0.34) conditions. There were no two-way interactions with phase × sex (F= 0.12, p=0.84, n^2=0.01), condition × sex (F= 1.4, p=0.61, n^2= 0.12), or phase × condition (F= 0.63, p=0.53, n^2=0.12). There were no significant main effects for sex (F=3.8, p=0.17, n^2=0.15) or condition (F= 0.38, p=0.69, n^2=0.04) but there was a main effect for phase (F=15.339, p>0.001, n^2=0.63). MUDRV was the lowest during the plateau phase (0.02Hz ± 0.0) of the contraction compared to the ramp (0.03Hz ± 0.0) (p=0.00) and deramp (0.05Hz ± 0.01) (p=0.00) phases. The deramp phase had the highest MUDRV when compared to the ramp (p=0.00) and plateau phases (p=0.00) (Figure 3.3).
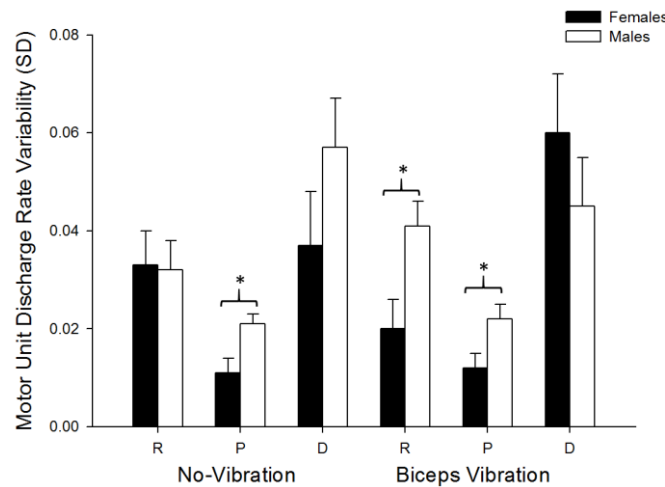

Figure 3.2: *Average MUDRV between males (open bars) and females (filled bars) across all three separate isometric contraction phases in both no-vibration and biceps-vibration conditions. R, ramp phase; P, plateau phase; D, deramp phase. SD, standard deviations about the mean. Data are shown as means ± SE. *p<0.05.*
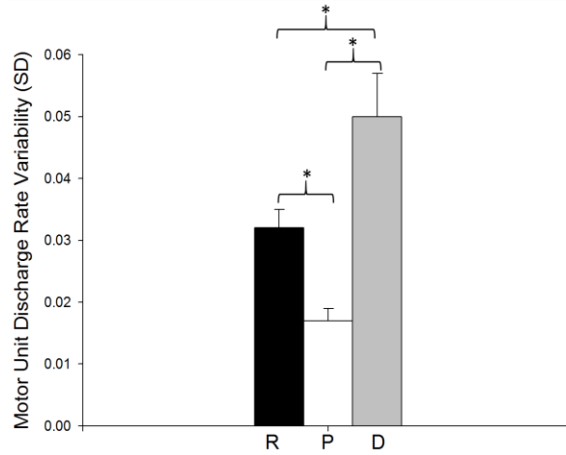
Figure 3.3: *MUDRV compared across all three separate isometric contraction phases pooled across conditions. R, ramp phase; P, plateau phase; D, deramp phase. Data are shown as means ± SE. *p<0.05.*

Additional to those units that were followed through both conditions and across all phases (N=29), there were 79 non-tracked active MUs (males n=46; females n=33). No three way interaction for phase × condition × sex (F= 0.3, p=0.73, n^2=0.05) was found for the number of active MUs. There were no two-way interactions for phase × condition (F=2.5, p=0.12, n^2= 0.17), sex × phase (F= 2.6, p=0.19, n^2=0.30), or sex × condition (F=1.8, p=0.19, n^2=0.12). There was no main effect for sex (F=0.39, p=0.55, n^2=0.03), phase or condition for the number of active MUs that were evident but not tracked.

Force Steadiness

Force steadiness was calculated as the coefficient of variation of force (CV) for 5 sec of the plateau phase for each isometric contraction then compared between conditions and sex. There was no two-way interaction for condition × sex (F= 0.00, p=0.96, n^2=0.00) or main effect for condition (F= 0.22, p=0.66, n^2=0.03) (vibration; 6.7% ± 1.0, no-vibration; 6.5% ± 0.9).

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There was a main effect for sex (F= 13.37, p= 0.006, n^2=0.626) as females (9.9%CV ± 1.4) were

less steady than males (3.2% ± 1.1) (Figure 3.4).
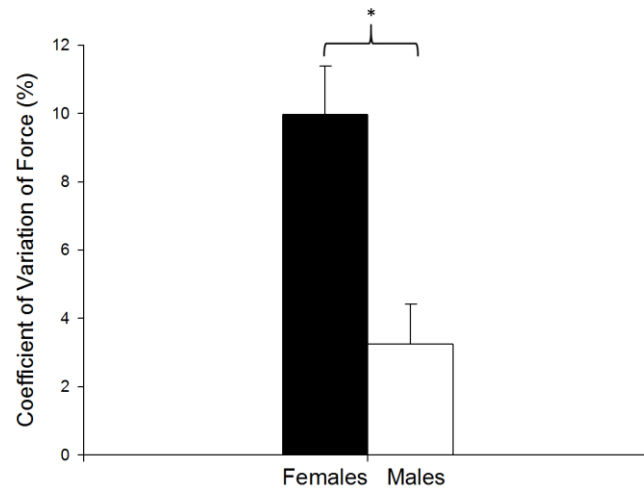
*Figure 3.4: Force steadiness measured during the 5 sec plateau phase of the isometric ramp contractions, compared between males and females pooled across conditions. Data are shown as means ± SE. *p<0.05.*

Chapter 4.0 Discussion:

To date, no study has measured the crossed-effects of tendon vibration on MU activity and force steadiness in males and females with PD. The current study is the first to assess MU activity in the biceps brachii during low-intensity isometric elbow flexion of the more-affected PD side in response to acute tendon vibration applied to the contralateral less-affected biceps tendon. Results indicate that vibration (pooled for sex) elicited a lower MUDR during the deramp phase (~16%). Males had increased MUDRV during the ramp phase (~22%) during the vibration conditions compared to females. MUDRV was higher in males compared to females in the plateau phase of both the no-vibration (~48%) and biceps-vibration conditions (~45%). Males had a greater stage of PD severity score, greater twitch peak tensions (~47%), and greater elbow flexion force (~ 45%) and were steadier than females (~ 67%). Irrespective of vibration condition, females had higher MUDRs in the plateau phase (~18%) compared with males and males had higher MUDRs during the deramp phase (~14%). Recruitment thresholds were higher than derecruitment thresholds and MUDRV was greatest in the deramp phase and lowest during the plateau phase.

Sex Differences:

In this study males have significantly lower MUDRs during the plateau phase (~18%) and albeit non-significant, lower MUDRs during the ramp phase coupled with higher MUDRs in the deramp phase (~14%). These sex-differences found in MUDR could be due to differences in MU composition between males and females. There is speculation within the literature that fibre type distribution is different between sexes (Hicks et al. 2001). A higher number of average MUs as well as a larger number of Type II MUs have been found in healthy male compared to female

rats (Celichowski & Drzymala, 2006). The higher peak tensions (~47%) found in males in this study supports this, as higher peak tensions are associated with more Type II muscle fibres (Zajac & Faden, 1985). Additionally, lower MUDRs, a higher number of muscle fibres and a larger innervation ratio have been found in male compared to female rats (Mierzejewska-Krzyowska et al. 2011). In healthy individuals, females have more Type I muscle fibres and less cross-sectional area than males in the biceps brachii muscle (Kanehisa, et al. 1993; Miller et al. 1993; Nonaka et al. 2006) as well as a longer time to reach fatigue compared to males (Clark et al. 2005; Hunter & Enoka, 2001). Although not statistically significant, it should be noted that males in this study also had higher recruitment thresholds (~22%) compared to females. Type II MUs tend to have lower steady state firing rates than their lower force-threshold, Type I counterparts (Deluca, 1985; Moritz, et al. 2005) and the rate in which MUDRs change are correlated to recruitment thresholds. Higher recruitment thresholds are associated with Type II MUs (Erim et al. 1996) and lower recruitment thresholds are associated with Type I MUs (Adam et al.1998; Zajac & Faden, 1985). However, at 5% of MVC the pool of total MUs active is few and constitute low-threshold MUs in both males and females. Therefore, it is difficult to determine differences in MU type at such small force levels. These sex differences could also be due to greater absolute muscle mass in males compared to females. Greater muscle mass results in higher peak tensions and greater force development. These results coupled with previous findings suggest that females likely have more Type I MUs compared to males and this coupled with greater muscle mass in males can be extend to persons with PD.

Males with PD had higher MUDRV compared to females during the ramp phase of the biceps vibration condition (~25%) as well as the plateau phase in both the no-vibration (~48%) and biceps-vibration (~45%) conditions. The augmented MUDRV found in males could be due

to the greater PD severity and an elevated loss of cortical and spinal motoneurons. Augmented neuronal loss in PD contributes to increased synaptic noise and alters the synaptic input of neurons; increasing interspike variability. For example, synaptic noise has been found to account for interval variability in the cat lumbrosacral motoneurons (Calvin & Stevens, 1967). MUDRV is the result of summing synaptic noise with the afterhyperpolarization of the motoneuron membrane voltage after an action potential (Matthews, 1966). In cat and rat models synaptic noise reduces the efficacy of any one input and this reduction in efficacy is related to firing frequency. Furthermore, this reduction in efficacy was more pronounced in MUs firing at low rates (Poliakov et al. 1992). Similarly, older adults tend to have higher MUDRV compared to young adults (Laidlaw et al. 1999) and there is evidence that this change in MUDRV is due to a reduction in Ia synaptic transmission efficacy (Boxer et al. 1988) and reorganization of the spinal cord resulting in altered synaptic drive to motoneurons (Laidlaw et al. 1999; Morales et al. 1987). Alterations which occur to the neuromuscular system with age that contribute to the increased synaptic noise and reduced transmission efficacy include a reduction in myelinated and unmyelinated fibre density (Jacobs & Love, 1985), a reduction in nerve conduction velocity by 8-18% (Verdu et al. 2010), an overall deterioration of peripheral nerve function, greater cortical activation and greater cortical disinhibition (Papegaaij et al. 2014). Thus, results from this study further highlight statements of PD being referred to as accelerated aging. Natural changes in neuronal function that occur with age could be accelerated in PD; augmenting synaptic noise and MUDRV. Excessive loss of neurons and lewy body inclusions in cortical and spinal neurons have been found in mice overexpressing human A53T mutant alpha-synuclein, which is dominant in familial PD, and are a result of apoptotic-like death of neocortical, brainstem and spinal motoneurons (Martin et al.2006). Martin et al. (2006) also found a reduction in spinal cord

activity and a depletion of motoneurons by 75% in PD mice. Critical regulators in neurodegeneration such as mutations in mitochondrial DNA and oxidative stress have been reported in early PD and progressively increase with the disease (Lin & Beal, 2006). Excessive loss and damage to neurons in PD would change signal transmission efficacy along the corticospinal and reflex pathways which could contribute to increased synaptic noise and MUDRV in persons with PD.

In the present study, males with PD were observed to be ~67% steadier and ~45% stronger in elbow flexion force than females with PD. Despite these differences in maximal voluntary strength, there was no difference in voluntary activation (98.5%-97.8%). Our finding that females with PD were less steady and weaker than males with PD is in agreement with previous investigations on sex differences in force steadiness in healthy young and old individuals where males are steadier than females (Brown et al, 2010; Harwood et al. 2014). It is well known that in healthy individuals the fluctuations in force during constant force contractions are a manifestation of the low-frequency oscillations inherent in MUDRs (Deluca, 1985). Modeling work on force steadiness also suggests that a decline in force steadiness is associated with an increase in MUDRV (Moritz et al. 2005). This relationship between lower MUDRs and MUDRV relative to force steadiness was not evident in the males and females with PD. In this study, females were less steady but had higher MUDR and lower MUDRV compared with males. Thus, it seems that MUDRV is not a primary factor contributing to the sex-related differences in force steadiness in PD contradictory to what is typically seen in healthy populations.

Males in this study were also more active than females as indicated by MLTAPQ results (Table 3.0). Irrespective of the fact females had a lower PD rating score than males, females

were still weaker, less steady and less active than males. Although the ~38% greater caloric expenditure in males did not differ statistically between the sexes, the literature is clear in that PD females report greater levels of fatigue compared to PD males (Fried et al. 2001) and increased levels of fatigue are associated with decreased levels of leisure physical activity (Garber & Friedman, 2003). These findings are in accordance with prior reports which suggest more active PD individuals are stronger and experience less fatigue than less active PD persons (Garber & Friedman, 2003). Physical activity level is also tightly coupled to muscle strength and musculoskeletal weakness has been attributed to functional decline in PD (Falvo et al. 2008). Furthermore, caloric expenditure is a strong predictor of frailty status in PD with non-frail individuals reporting higher physical activity levels compared to frail (Ahmed et al. 2008; Roland et al. 2012). Frailty, defined as a presence of three or more of five clinical criteria of weakness, weight loss, slow walking speed, fatigue and low level of activity (Fried, et al. 2001) is more prevalent in females with PD than males (Roland et al. 2012; Shulman, 2007) and is predictive of incident of falls, worsening mobility, disability, hospitalization and death (Fried et al. 2001). Considering males in this study were significantly more progressed in PD but stronger, steadier and more active compared to females suggests that absolute strength and physical activity level are likely better indicators of steadiness, and thereby frailty, than MU activity and disease stage.

Dibble et al. (2009) reported that resistance training interventions increase muscle force, reverse bradykinesia and increase quality of life in persons with PD and that these adaptations occurred in the absence of significant changes in PD rating score. The greater muscle strength, physical activity level and enhanced force control observed in PD males in this study, combined with the findings from previous reports, highlight the benefits of resistance training in PD and its

potential to reduce symptoms. Simultaneously, resistance training could enhance force steadiness and strength; thereby reducing the incidence of frailty especially in PD females.

This study demonstrates that males and females with PD respond differentially to afferent inputs from the contralateral limb. The findings that males with PD increase MUDRV in response to vibration suggest that there could potentially be a subtle difference between sexes in persons with PD in how the neuromuscular system responds to stressors such as vibration. MUDRV in males increased during the ramp phase during the biceps-vibration condition when compared to females. The different responses between sexes to vibration stimulation could also be due sex-differences in muscle characteristics. Females are predisposed to Type I MUs which have been found to be less responsive to vibration. Both recruitment and firing behaviour show a size dependent orderly pattern and it has been reported that the firing rates of the smallest (earlier recruited) MUs are least responsive to changes in motoneuron pool excitability (Monster &Chan, 1977). Kiehn & Eken (1997) reported low-threshold MUs tend to jump quickly to a very narrow frequency range during voluntary movement and remain unchanged during vibration. In healthy individuals the effects of vibration on the reflex threshold of single MUs is concordant with their rank order of activation with the last recruited MUs most susceptible to the effects of vibration (Desmedt & Godaux, 1978). Therefore, males who predominantly have more Type II MUs and higher recruitment thresholds, would be more sensitive to vibratory changes in firing rates than female Type I MUs.

Crossed-Effects of Vibration:

It appears that tendon vibration on the less-affected side modestly reduces MU activity on the more-affected side in persons with PD. In this study excitation of Ia afferents with tendon

vibration resulted in a significant decrease in MUDR (~16%) of the contralateral side during the

deramp phase. Additionally, there were many modest changes as a consequence of tendon

vibration that might offer physiological insight albeit not statistically significant. For example,

the significant decrease in MUDR during the deramp phase of the isometric contraction was

accompanied by an increase in MUDRV (~7.5%) and a decrease in the total number of MUs

active but not tracked across phases (~23%). In healthy individuals, MUDRs are typically lower

during the relaxation (ramp-down) phase compared with the force generation (ramp-up) phase of

the contraction (Denier van der Gon et al. 1985) which is in part attributed to the reduction of

input to pyramidal neurons that are mediated by intracortical inhibitory neurons (Rothwell et al.

1998). However in persons with PD a compromised rate of force release (ramp-down phase) is

evident (Corcos et al. 1992) and this has been associated with slowed relaxation times due to the

impaired inhibitory activity of the motor cortical circuits and corticospinal outflow (Kleine et al.

2001). The addition of vibration to the contralateral limb during voluntary movement at low

forces likely exacerbated this impairment in force release through activation of polysynaptic

proprioceptive pathways inhibiting alpha motoneurons in the contralateral biceps and decreasing

MUDR. There was also an increase in recruitment threshold (~5.8%) coupled with a decrease in

derecruitment threshold (~31%). Robichaud et al. (2005) reported that the ability to recruit motor

units to initiate movement (ramp-up) is not related to the severity of the disease, rather the

relaxation time (ramp-down) was correlated with the severity of motor impairment. Longer

relaxation times were also associated with greater agonist EMG signal, suggesting individuals

with PD have more difficulty in derecruiting motor units (Robichaud et al. 2005). In order to

compensate for this reduction in MUDR and total number of MUs active the remaining MUs

contributing would have to become more synchronous and remain active for longer to control

force release in the deramp phase thereby lowering derecuritment threshold. Furthermore, in healthy individuals prolonged MUDR (later derecruitment) has been observed in response to short lasting vibratory excitation (Kiehn & Eken, 1997) and in the cat this prolonged MUDR causes a bistable discharge shifting between high and low frequencies (Eken & Kiehn, 1989; Eken & Lomo, 1993) which could also contribute to our findings of lower derecruitment thresholds and increase in MUDRV with vibration in persons with PD.

Although vibration appeared to inhibit activity in the contralateral biceps muscle subjects in this study were able to maintain the same relative force level during the isometric contractions. MUDRs tend to synchronize with vibratory frequency (Martin & Park, 1997) and tendon vibration in persons with PD augments MU synchrony with the frequency pattern of tremor becoming more time-locked to the onset and offset of vibration (Jobges et al. 2002). The functional role of MU synchronization is to increase the rate of force development during contractions as a mechanism to coordinate the activity of multiple muscles in synergy (Semmler et al. 2004) and it has been found that enhanced force production with resistance training in healthy individuals is due to augmented MU synchrony (Fling et al. 2008; Semmler & Nordstrom, 1998; Milner-Brown & Lee, 1975). The maintenance of the submaximal force level during vibration coupled with a reduction in MU activity indicates that vibration likely enhances MU synchrony in the contralateral limb in persons with PD, allowing them to maintain the same level of force with fewer MUs active.

In this study, the rate of force development was controlled in the tracking task and vibration was not used during the MVC, thus if synchronization was enhanced it would not be evident from the measures undertaken. Moreover, to quantify MU synchronization a tracking task of >15s would be necessary and for this duration prolonged vibration would not have the

same effect as acute tendon vibration. Prolonged vibration results in impaired sensorimotor and motor performance and depression of spinal reflexes (Lance et al. 1966). It has been suggested that this decline in spinal reflex activity is due to oversaturation of the muscle spindles and increased pre-synaptic inhibition of the Ia spindle afferents (Desmedt & Godaux, 1978). Furthermore, prolonged vibration forces the driving of MUs and impairs excitation contraction coupling thereby decreasing contraction efficiency (Martin & Park, 1997). Thus, if applied chronically overtime, the effects of vibration could potentially become detrimental to the muscle and natural MU functioning.

In healthy individuals, muscle vibration progressively recruits MUs according to Henneman's size principle through polysynaptic reflex pathways in the homonymous vibrated muscle (Desmedt & Godaux ,1978, Grande & Caferelli). Some studies report a reduction in MUDR with vibration (Grande & Caferelli, 2003; Harwood et al. 2014), an increase in the total amount of MUs active (Grande & Cafarelli, 2003; Harwood et al. 2014) and decrease in recruitment thresholds on the vibrated muscle (Grande & Caferelli, 2003; Romaiguere et al. 1993). The present study suggests that tendon vibration influences the contralateral homonymous muscle through excitation of a pathway likely similar to the crossed-extensor reflex, causing reciprocal inhibition of the contralateral agonist muscle (Cardinale & Bosco, 2003; Rothwell, 1987; Matthews, 1966) and ultimately leading to an increase in recruitment thresholds and decrease of total MU's active. However, the crossed-effects on MUDR do not correspond with the crossed-extensor reflex activity suggesting that other mechanisms could be responsible for this decrease in MUDR with vibration during the deramp phase in persons with PD.

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Similarities between PD persons and healthy populations:

It is well known that during an isometric contraction, MUDR is related to the total amount of force produced (Denier van der Gon, 1985) where an increase in the level of force is accompanied by an increase in MUDR and decrease in MUDRV (Moritz et al. 2005). Irrespective of vibration or sex, differences in MUDRV were found between all phases of the isometric ramp contractions. The plateau phase exhibited the least amount of MU variability with the largest amount of variability being produced in the deramp phase. Albeit non-significant, MUDR was highest during the plateau phase and lowest during the ramp phase. These findings are consistent with previous observations in healthy populations that indicate MUDRV is highest when controlling the release of force (Moritz et al. 2005; Person & Kudina, 1972) and this holds true for persons with PD. Furthermore, when MU recruitment and derecruitment thresholds were compared, derecruitment thresholds were significantly lower than recruitment thresholds with no effect for sex or vibration condition. This finding is consistent with previous reports that recruitment thresholds are naturally higher than derecruitment thresholds in healthy individuals (Deluca, 1985; Denier van der Gon et al. 1985). This suggest that the onion skin phenomenon could extend to persons with PD. However, in order to truly determine whether the onion skin phenomenon extends to persons with PD, studies of recruitment threshold and derecruitment thresholds would have to extend to forces higher than 5%, as undertaken in this study.

Contradictory to the onion skin phenomenon, some studies have found that dendritic persistent inward currents (PIC), self-sustained firing of motoneurons mediated by voltage-dependent channels, are responsible for lower derecruitment thresholds compared to recruitment thresholds (Grimby et al. 1979; Oya et al. 2009). However, these studies have been conducted in the lower body, whereas the onion skin phenomenon holds true for most studies investigating

upper body motoneurons (Deluca et al. 1981; Freund et al. 1975; Mendell, 2005). Furthermore, in persons with PD it is unlikely that PICs are responsible for the difference in recruitment compared to derecruitment thresholds. The amplitude of the PIC is directly proportional to the input from the brainstem mediated by monoamines serotonin and norepinephrine (Heckman et al. 2005) and in PD there is a substantial reduction of serotonin within the brainstem and frontal cortex (Halliday et al.1989). Reduction in serotonin would result in a decrease in the amplitude of PICs as well as total reduction in the potential of PICs occurring. However, no study to date has investigated PICs in persons with PD and further investigation is warranted.

Conclusion:

It was hypothesized that acute direct tendon vibration applied to the biceps brachii tendon of the less-affected side in persons with PD would reduce the total amount of MUs active, decrease MUDR and increase in MUDRV in the contralateral biceps brachii muscle No differences were seen in the total number of MUs active in either the no-vibration or biceps vibration conditions. MUDR decreased during the deramp phase of the biceps vibration condition and MUDRV increased during the ramp phase but only in males. Furthermore, it was hypothesized that the biceps vibration condition would increase recruitment threshold, decrease derecruitment thresholds and cause greater fluctuations in force. No differences in recruitment thresholds or derecruitment thresholds were observed between either the no-vibration or biceps-vibration condition. Because males are more affected by PD (Haaxma et al. 2007) and tend to have higher MUDRV when compared to females (Luschiel et al. 1999) it was hypothesized that the biceps vibration condition would cause a greater change in MU activity in males compared to females and that males would also be less steady when compared to females. There were no changes in force steadiness between the no-vibration condition and the biceps vibration

condition. However, males were steadier than females when pooled across phase and condition, thus the hypothesis was rejected.

In summary, acute tendon vibration of the less-affected limb moderately influences MU activity in the contralateral more-affected limb during relaxation (force release), suggesting that neural stimuli can be modestly transferred to the contralateral side of the body in persons with PD. This vibratory response was also found to be stronger in males than females with PD during the ramp phase and is likely due to sex differences in muscle fibre characteristics, muscle mass, or PD severity. Sex differences in force steadiness were unlikely to arise from MUDR or MUDRV, rather reductions in force steadiness were better correlated with muscle strength and lower physical activity levels in females relative to males with PD. Furthermore, vibration decreased MUDR during the deramp phase and could potentially augment MU synchrony in PD when performing voluntary movement on the contralateral side. The reduction in MUDRV during steady state isometric contractions and increase in MUDRV during the deramp phase in healthy individuals can be extended to persons with PD.

Future Research Directions and Limitations:

This study is the first to evaluate and quantify MUs during contralateral vibration in persons with PD. The literature on PD and the cross over effect of polysynaptic reflex loops to contralateral limbs is scarce. Further research is needed to better understand the effect of PD progression on polysynaptic reflex loops between the less and more-affected sides of the body. In addition, the concept of cross-education albeit not evaluated in the traditional manner in this thesis, has also not been explored in persons with PD and could be a potential mechanism to lessen the impairment on the more-affected side. In the very least an increase in strength would

enhance force steadiness. Thorough investigations of the alterations in polysynaptic reflex loops in persons with PD could strengthen our understanding of how fluctuations in afferent feedback affect motor performance and impact functional ability.

The difference in MU properties with respect to sex or level of disease severity have not been investigated in persons with PD. The sample of males and female subjects with PD in this study were representative of the PD population with the prevalence being higher in males than females. Considering there are known sex-disparities with PD in functional decline and physical activity level the difference in MU properties between males and females with PD should be further studied.

Some limitations include that the present study consisted of a relatively small sample size consisting of ten subjects and a total of 29 tracked MUs. Future studies should include a greater number of subjects and tracked MUs to further strengthen the findings on MU activity in response to contralateral stimuli in persons with PD. Also, this study expanded on MU activity conducted at low force levels in persons with PD but no investigation has been conducted on higher force levels. More detailed investigations should be conducted at higher force levels to determine if the vibratory response in persons with PD is similar across all forces and if the onion skin phenomenon can be extended to persons with PD. This research also highlights that it is necessary to consider the disease scale and questionnaires used. The Hoehn & Yahr scale is the most appropriate and typically used scale in determining PD in research studies, but the Hoehn & Yahr is not as accurate as the UPDRS scale in determining PD severity. Future studies exploring the effects of tendon vibration should consider PD severity and utilizing a more reflective scale of the current stage of the disease.

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Appendices

Appendix A: Ethics Approval

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

ETHICS CERTIFICATE OF FULL BOARD APPROVAL: AMENDMENT

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC CREB NUMBER:
Jennifer M. Jakobi	UBC/UBCO Health & Social Development/UBCO Health and Exercise Sciences	H11-01931
INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:		

Institution	Site
UBC	Okanagan
Other locations where the research will be conducted: N/A	

CO-INVESTIGATOR(S):
Kaylee Larocque
Chris McNeil
SPONSORING AGENCIES:
- Natural Sciences and Engineering Research Council of Canada (NSERC) - "Supraspinal and Sensory Contributions to Motoneuron Modulation during Steady Contractions in Men and Women"
PROJECT TITLE:
Motor Unit Activity and Force Steadiness in Functional Tasks and Isolated Contractions

REMINDER: The current UBC CREB approval for this study expires: November 20, 2014

AMENDMENTS BELOW REVIEWED AT REB FULL BOARD MEETING DATE: **April 8, 2014**				
AMENDMENT(S):				**AMENDMENT APPROVAL DATE:** **April 22, 2014**
Document Name		**Version**	**Date**	
Protocol:				
Protocol		02	April 9, 2014	
Consent Forms:				
Consent PD and Control		03	April 9, 2014	
Advertisements:				
Revised; deleted healthy and just state age		01	March 21, 2014	
PD_recruitment		01	April 9, 2014	
Other Documents:				
Overview of Addition of PD Population		01	March 21, 2014	

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The amendment(s) for the above-named project has been reviewed by the University of British Columbia Clinical Research Ethics Board, as presented in the documentation, and the accompanying documentation was found to be acceptable on ethical grounds for research involving human subjects

Approval of the Clinical Research Ethics Board by one of:

Dr. Peter Loewen, Chair
Dr. Stephen Hoption Cann, Associate Chair

Appendix B: Consent Form

THE UNIVERSITY OF BRITISH COLUMBIA | OKANAGAN

Faculty of Health and Social Development
3333 University Way
Kelowna, BC Canada V1V 1V7
Phone: 250-807-9906
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Subject Information and Consent Form

Motor Unit Activity and Force Steadiness in Functional Tasks

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                                              e-mail: chris.mcneil@ubc.ca

Emergency Telephone Number: **(250) 807-9884**

1. INVITATION TO PARTICIPATE

You are invited to participate in this study because you are between the ages of 18 and 100. This study will compare the effect of tendon vibration between persons with Parkinson's Disease and those without to better understand the contributions of reflex activity in the control of movement.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts.

If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reason for your decision.

If you do not wish to participate, you do not have to provide any reason for your decision.

3. WHO IS CONDUCTING THE STUDY?

Jennifer M. Jakobi, the lead investigator on this study and Kaylee Larocque, the MSc Student responsible for the execution of this study, invite you to be a subject in this motor unit and force steadiness experiment. This research is funded in part through NSERC and Internal funds from the University of British Columbia – Okanagan Campus.

4. BACKGROUND

Motor units are the basic functional unit of the neuromuscular system and they contribute to producing steady movements. Motor units are activated by information that is transmitted down the spinal cord from the brain as well as from feedback from muscles and joints. Force steadiness is the ability of a muscle to produce a specific and constant force level; which is necessary for many functional tasks. A concern with aging and in persons with Parkinson's Disease is the decrease in ability to maintain performance of daily living tasks. This research is being carried out for two reasons: to determine if differences in motor unit activity or force steadiness occur between a functional task and a standard anisometric (dynamic) contraction. A standard anisometric contraction is one in which movement is completed while performing a muscle contraction (Eg. bending at the elbow to the shoulder and returning the arm to the initial position). The difference between functional tasks and standard anisometric contractions is the intent and action of completing a task. The second reason is to evaluate the role of reflex feedback on force steadiness in persons with Parkinson's Disease and age-matched adults. Reflex feedback will be enhanced with the use of tendon vibration. Steadiness contributes to functional performance, but research to-date has not measured motor units or steadiness when reflex feedback is altered. Tendon vibration increases the amount of feedback that is transmitted to the spinal cord and in young adults vibrating the tendon has demonstrated an increased ability to control force. This research is being carried out to determine if tendon vibration enhances force control in Person's with Parkinson's Disease and age-matched adults.

5. PURPOSE

1. To determine if there are differences in motor unit activity and force steadiness between functional tasks and isolated muscle contractions.

2. To determine the influence of tendon vibration on motor unit activity and force steadiness in persons with Parkinson's Disease and age-matched adults.

6. WHO CAN PARTICIPATE IN THE STUDY?

Individuals with Parkinson's Disease and age-matched adults between the ages of 18 and 100 years. Individuals will be English speaking.

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

Those individuals who have current or previous sensory or motor neuropathy, myopathy or any cardio respiratory conditions, beyond that associated with Parkinson's Disease, that impact exertion should not participate in this study. Recreationally active individuals who train for more than 1 hour, 3 times per week or for any longer duration cannot participate in this study. Individuals outside the age limits are not able to participate.

8. STUDY OVERVIEW

The study is taking place in Kelowna, B.C. at the University of British Columbia Okanagan in the Neuromuscular Physiology Lab. There will be approximately 30 persons with Parkinson's Disease and 30 age-matched adults involved in this study. Each participant will complete, in a randomly selected order, each of the two types of contractions outline below.

Prior to the experimental procedures maximal effort contractions with no change in joint angle (isometric) and with maximal velocity (anisometric contraction) will be collected to determine work rate and work velocity. The maximal isometric contractions will be held for 3-5 seconds, whereas the maximal velocity contractions are executed in approximately 6 seconds.

You will be asked to come into the lab on a minimum of one occasion for a duration of approximately 2 hours. Baseline measures will be collected first followed by the muscle contraction trials. Each trial will consist of 3 attempts totaling 6 muscle contractions.

One type of muscle contraction is an isolated contraction and the other is an isolated contraction with vibration applied to the opposite arm. For example, if you are holding the right arm steady the tendon of the left arm will be vibrated.

The task with and without vibration will each be performed 3-5x to record the most steady contraction.

Protocol Overview:

You will enter the lab on the testing day and fill out the **Pre-experiment Screening Questionnaire.**

Surface electrodes will then be placed over the muscles involved the flexion and extension of the elbow. These muscles are located on the front and the back of your upper arm. For each muscle

measured 3 adhesive surface electrodes, 2 placed directly over the muscle and one to serve as a ground which will be placed over a boney surface (ie the elbow, shoulder, wrist, etc).

Intramuscular fine wire electrodes will then be inserted directly into the short and long head of the biceps brachii. In order to insert these wires a small needle will be inserted into your arm and then removed with the thin wires being left in. You will feel a prick when the needle is inserted and may feel slight discomfort when the wires are first inserted.

Once all wires are connected the experimental protocol will begin. In a random order the following two trials will occur:

Functional Task Contraction; Two movements
Water Jug
- You will be given a water jug weight approximately 1 Kg.
- At a specific velocity, you will be asked to raise the water jug and pour a glass of water (however, the jug will be blocked from actually pouring water so the weight does not change), and return the jug to the table.
- You will perform this task with your dominant hand
- Three – five trials will be given
- Intramuscular and Surface EMG will be recorded throughout the trials to measure muscle and motor unit activity.

Cup Lifting

- You will be given a weighted cup
- At a specific velocity, you will be asked to raise the cup to your lips, hold, then return the cup to the table top.
- You will perform this task with your dominant hand
- Three – five trials will be given
- Intramuscular and Surface EMG will be recorded throughout the trials to measure muscle and motor unit activity.

Isolated Contractions: 1 of either anisometric or isometric
Anisometric Contraction
- Subject will be set up in the Biodex dynamometer which is a machine that will measure the torque, velocity, and position of your elbow.
    o For this set up you will sit in seat with your arm supported by a comfort pad while gripping a handle which you will move during the contractions. The seat consists of straps – similar to seatbelts but crossing both sides of your body – which will hold the subject in place and prevent additional movement.
- You will resist an approximate 1 Kg weight and asked to perform a biceps flexion contraction at a pre-determined rate.
- You will perform this contraction with your dominant hand.
- Three trials will be given
- Intramuscular and Surface EMG will be recorded throughout the trials to measure muscle and motor unit activity.

Isolated Contractions: with and without tendon vibration
- Subject will be set up in the dynamometer which is a machine that will measure force
  - For this set up you will sit in seat with your arm supported by a comfort pad while gripping a handle which you will pull up against. The seat consists of straps – similar to seatbelts to ensure consistent body positioning.
- You will pull up and hold a low force contraction steady for approximately 6sec.
- This steady contraction will be done without tendon vibration and with tendon vibration applied to the opposite arm.
- Intramuscular and Surface EMG will be recorded throughout the trials to measure muscle and motor unit activity.

Both of these tasks allow a within comparison, as MU measures have never been made when the tendon on the contralateral arm is vibrated. Measures of the MU indicate the necessary activity within the muscle to perform the desired movement. The wires pick up the electrical activity of your muscle and provide information about both the recruitment (activation) of your motor units as well as the rate at which they discharge and the activation of these motor units influence force steadiness.

The tendon at the elbow on the opposite side of the body will be vibrated. This vibration has been described as a deep tickle or wave. The vibration device is a slender and rigid tube that is placed onto the tendon with slight pressure. At the elbow it feels very similar to leaning on a washing machine that is off balance and 'shaking'. This vibration is used to send reflex information back to the spinal cord. This reflex information whether from the biceps (front) or triceps (back) in the arm gives the spinal cord different pieces of excitatory or inhibitory information to deal with and will help us understand reflex contribution to steady movements.

Once you have completed these contractions the surface electrodes will be removed and the fine wire electrode will be pulled out of the muscle. A slight discomfort may be experienced as the wire is removed; however, it is removed very quickly.

You are then free to leave; the experimenters will address any questions or concerns you have.

9. WHAT ARE MY RESPONSIBILITIES?

The only responsibility of you, the subject, is to refrain from becoming involved in the study if the criteria for participation are not met. Additionally, if at any time you feel uncomfortable with the measures taken you can terminate the experiment.

10. WHAT ARE THE POSSIBLE HARMS AND SIDE EFFECTS OF PARTICIPATING?

Discomfort may be experienced when inserting and removing the fine wire electrodes. When inserting needles there is always a risk for infection however all needles will be sterilized and gloves will be worn by the experimenter at all times to minimize risk. One arm will be used for

all testing procedures so slight muscle soreness may present the next day in that arm. The other arm that is vibrated has no lasting sensations once the vibration is removed.

11. WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

There are no direct and immediate benefits of this research to you. In the long-term information gained will assist in understanding force steadiness. Vibration might provide an additional means to increase force control in persons with Parkinson's Disease.

The researchers can provide you with the results of the study. These results will be accessible via the web on the researcher's website.

There is a potential benefit to the aging population as it may prove to be beneficial to perform functional tasks opposed to weight lifting routines to maintain the ability to perform functional tasks of daily living.

12. WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

If new information arises during the research study that may materially affect your willingness to remain in the study, you would be advised of this information via phone contact.

13. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

Your participation in this research is entirely voluntary. If at any time you feel the need to withdraw from the study you are free to do so with no penalty. You may withdraw without providing any explanation of your reason for doing so.

You do not have to submit a request to withdraw in writing.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will be retained for analysis. By law, this data cannot be destroyed.

14. WHAT HAPPENS IF SOMETHING GOES WRONG?

Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities.

1. In the event you become injured or unexpectedly ill while participating in this study, necessary medical treatment will be available at no additional cost to you, as per your provincial health care plan.

2. In Canada, healthcare is provided through a system of provincial insurance. You do not waive any of your legal rights to compensation by signing this consent form.

If an emergency does occur we are equipped with a medical gurney (bed and linen for comfort and appropriate supplies are available to address a multitude of needs e.g.). In situations where additional care is warranted e.g.) blood pressure response indicative of medical care, a telephone call is immediately placed for a first responder team, and also a nurse is brought in for consultation immediately until the first responders arrive. The subject is never left unattended, and reassurance is consistently offered.

15. CAN I BE ASKED TO LEAVE THE STUDY?

If you are not complying with the requirements of the study or for any other reason, the Principal investigator may withdraw you from the study. On receiving new information about the technique being utilized your research investigator might consider it to be in your best interests to withdraw you from the study without your consent if they judge that it would be better for your health.

16. AFTER THE STUDY IS FINISHED

Results of this project may be published as a part of Kaylee Larocque's MSc Thesis and in peer reviewed manuscript (paper). Any data included will not be linked to a specific participant. Your data will be assigned a personal identification number to ensure anonymity in both the analysis and documentation of results. The raw data obtained in this study will only be available to the main research investigator, Dr. Jakobi. Data will be kept for 5 years following the study in a locked room on password protected computers.

17. WHAT WILL THE STUDY COST ME?

The study will not cost you anything to participate in; neither will you receive any remuneration for your participation.

18. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

19. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, you can contact Kaylee Larocque at **(250) 807-9190** or by email at kayleelarocque@hotmail.ca**.**

20. WHO DO I CONTACT IF I HAVE QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT DURING THE STUDY?

If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services by email at RSIL@ors.ubc.ca or by phone at 1-877-822-8598. **This project has been reviewed and approved by the UBC Clinical Research Ethics Board.** This Board aims to help protect the rights of research subjects.

SUBJECT CONSENT TO PARTICIPATE

I understand that this is not a contract of participation and by signing this document I am not giving up any legal rights. I understand that I will receive a copy of this signed form.

- I have read and understood that subject information and consent form
- I have had sufficient time to consider the information provided and to ask for advice if necessary
- I have had the opportunity to ask questions and have had satisfactory responses to my questions
- I understand that all of the information collected will be kept confidential and that the result will only be used for scientific objectives
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive
- I understand that I am not waiving any legal rights as a result of signing this consent form
- I understand that there is no guarantee that this study will provide any benefits to me
- I have read this form and I freely consent to participate in this study
- I have been told that I will receive a dated and signed copy of this form.

SIGNATURES

Printed name of subject	Signature	Date

Printed name of witness	Signature	Date

Printed name of investigator	Signature	Date

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