Motor Unit Number Estimates and Quantitative Motor Unit Potentials Analysis Associated with Motor Deficits in Carpal Tunnel Syndrome

by

Joseph Nashed

A thesis submitted to the Department of Rehabilitation Science

In conformity with the requirements for

the degree of Master's of Science

Queen's University

Kingston, Ontario, Canada

(September , 2008)

Abstract

The purpose of this study was to determine the utility of decomposition-based quantitative electromyography (DQEMG) in detecting signs of motor unit loss and collateral sprouting in compression neuropathy. In order to accomplish this, needle- and surface-detected motor unit potential (MUP) morphological features, determined by DQEMG, were used to determine evidence of collateral sprouting. Evidence of motor unit loss was measured using motor unit number estimates (MUNEs).

Six subjects with severe carpal tunnel syndrome (CTS), eight subjects with mild CTS and nine healthy individuals with no known neuropathy participated in this cross sectional study. All subjects completed two phases of data collection: 1) an examination consisting of physical and electrophysiological tests to assess the presence and/or severity of CTS and 2) quantitative electromyography techniques to record MUNEs and MUP morphological characteristics. The needle-detected MUP parameters included peak-to-peak amplitude, duration and number of phases. The presence of satellite potentials was also investigated in the needle-detected MUPs. The surface-detected MUP parameters examined included peak-to-peak amplitude, duration and negative peak area. Kruskall-Wallace tests were used to determine group differences for all outcome measures.

The MUNEs were lower ($p<0.017$) in the severe CTS group as compared to those with mild or no CTS. This result suggests that individuals with severe CTS experience a decrease in the number of functioning motor units. Despite statistically similar surface-detected MUP morphology, there were significantly larger needle-detected MUP amplitudes ($p<0.017$) and satellite potentials ($p<0.05$) were present in the severe CTS

group as compared to the mild CTS group and healthy control group. These findings suggest there is collateral reinnervation in individuals with severe CTS. The results of this study support the use of DQEMG in future studies of compression neuropathies as an effective means to document the progression of motor deficits.

Acknowledgements

I wish to acknowledge the assistance, guidance, and expertise of many individuals who supported me throughout the past two years. I would like to extend my deepest sense of gratitude and appreciation to my supervisor Linda McLean. Thank you for being so patient with me. Her advice, encouragement and guidance helped develop my skills as a researcher. I would also like to extend my thanks and appreciation to Dr. Andrew Hamilton-Wright for his guidance and support over the last year and a half.

I would also like to thank the numerous individuals who graciously volunteered for this study. Thank you for your investment and contribution to our research.

I would like to thank all those people in the Motor Performance Lab and the School of Rehabilitation Therapy who have helped me over the past two years. Especially, for the friendship and support I received from other graduate students. I want to thank the grad room crew and particularly, Kristina Calder. Thank you for always being there. Finally, I would like to extend a special thank you to my family for the constant love, support, motivation and patience they have given to me, without you I would not be where I am today.

Table of Contents

Abstract ii
Acknowledgements iv
Table of Contents v
List of Figures ix
List of Tables x
List of Abbreviations xi
Chapter 1 Introduction 1
1.1 Introduction 1
1.1.1 Purpose 3
Chapter 2 Literature Review 4
2.1 The Median Nerve 4
2.1.1 Anatomy 4
2.1.2 Structure of a Peripheral Nerve 5
2.1.3 Physiology of a Motor Unit 6
2.1.3.1 Motor Unit and Action Potentials 6
2.1.3.2 Neuromuscular Junction 10
2.2 Carpal Tunnel Syndrome 11
2.2.1 Etiology of Carpal Tunnel Syndrome 11
2.2.1.1 Intrinsic Factors Associated with Carpal Tunnel Syndrome 11
2.2.1.2 Extrinsic Factors Associated with Carpal Tunnel Syndrome 12
2.2.1.3 Occupational Factors Associated with Carpal Tunnel Syndrome 12
2.2.2 Pathophysiology 13
2.2.2.1 Ischemia 14
2.2.2.2 Mechanical Nerve injuries 15
2.2.2.3 Motor Loss in Carpal Tunnel Syndrome 18
2.3 Clinical tests for carpal tunnel syndrome 19
2.3.1 Clinical Indicators 19
2.3.2 Nerve Conduction Studies 20
2.3.2.1 Compound Muscle Action Potentials 21

2.3.2.2 Sensory Nerve Evoked Potentials 22
2.3.2.3 Compound Nerve Evoked Potential 22
2.3.2.4 Classification of Carpal Tunnel Syndrome 23
2.4 Other Electrophysiological Techniques to Diagnose Motor Impairment 23
2.4.1 Quantitative Electromyographic Techniques to Examine Collateral Sprouting 24
2.4.2 Neurophysiological Techniques to Estimate Motor Axonal Loss 25
2.4.2.1 The Incremental Technique 26
2.4.2.2 Spike Triggered Average Technique 26
2.4.2.3 Statistical Technique 27
2.4.2.4 Reliability of MUNE Measures 27
2.5 Research Questions 27
Chapter 3 Methodology 29
3.1 Research Design and Subject Selection 29
3.1.1 Inclusion and Exclusion Criteria 29
3.2 Subject Screening and Medical History 30
3.2.1 Physical Examination 31
3.2.2 Nerve Conduction Studies 32
3.2.2.1 Electrode Configuration 32
3.2.2.2 Stimulus Intensity 33
3.2.2.3 Sensory Nerve Action Potentials 33
3.2.2.4 Compound Nerve Action Potentials 34
3.2.2.5 Compound Muscle Action Potentials 35
3.2.2.6 Stratification of Subjects with Carpal Tunnel Syndrome 37
3.3 Experimental Protocol 38
3.3.1 Acceptability Criteria of Needle and Surface Detected MUPs Used for Data Analysis 40
3.4 Outcome variables 41
3.4.1 MUP and SMUP Morphological Features 42
3.4.2 Satellite Potentials 42

3.4.3 MUNE 42
3.5 Statistical Analysis 43
3.5.1 Is there measurable evidence of collateral sprouting in individuals with severe CTS using MUP and SMUP morphological features determined by DQEMG software? 43
3.5.2 Is there evidence of motor axonal loss in individuals with severe CTS as measured using MUNE? 44
Chapter 4 Results 45
4.1 Subjects 45
4.2 Symptom Severity and Functional Deficits 48
4.3 Is there measurable evidence of collateral sprouting in individuals with severe CTS using MUP and SMUP morphological features determined by DQEMG software? 48
4.3.1 A Comparison of MUP Morphology Between Groups 48
4.3.2 A comparison of SMUP morphology between groups 52
4.4 Is there evidence of motor axonal loss in individuals with severe CTS as measured using MUNE? 54
Chapter 5 Summary and Discussion 57
5.1 Synopsis 57
5.2 Is there measurable evidence of collateral sprouting in individuals with severe CTS using MUP and SMUP morphological features determined by DQEMG software? 57
5.3 Is there evidence of motor axonal loss in individuals with severe CTS as measured using MUNE? 62
5.4 Considerations 65
5.4.1 Subjects 65
5.4.2 The use of Maximum Voluntary Contractions to estimate contraction effort during EMG data acquisition 66
5.4.3 Nerve Conduction Studies 67
5.4.4 Questionnaire and Physical Examination 68
5.5 Conclusions 68
Bibliography 70

Appendix A Advertisements 76
Appendix B Consent Form 77
Appendix C Questionnaire 81

List of Figures

Figure 4-1: Sample MUPT data identified by the DQEMG software. (a) needle-detected MUP and the corresponding quantifiable characteristics, (b) Surface-detected MUP and the corresponding quantifiable characteristics (c) An example of a MUP with a satellite potential..... 50

Figure 4-2: Box plots for MUP parameters (a) MUP amplitude, (b) MUP duration, (c) number of MUP phases, and (d) percentage of MUPs with satellite potentials for low-to-mid level contractions of the APB muscle..... 51

Figure 4-3: Box plots for SMUP parameters (a) SMUP amplitude, (b) SMUP duration, (c) SMUP area detected using the spike triggered average technique for low-to-mid level contractions of the APB muscle..... 52

Figure 4-4: Box plots of MUNE values (a) peak-to-peak amplitude MUNE, (b) negative peak amplitude MUNE, and (c) area MUNE calculated using the spike triggered average technique for low-to-mid level contractions of the APB muscle..... 56

List of Tables

Table 2-1: Summary of axon size and conduction velocity 7

Table 3-1: Summary of nerve conduction studies 36

Table 4-1: Median and interquartile ranges of CMAP measures. 47

Table 4-2: Median and interquartile ranges MUP and SMUP measures. 53

Table 4-3: Median and interquartile ranges of MUNE measures. 55

List of Abbreviations

CTS: Carpal Tunnel Syndrome

EMG: Electromyography

QEMG: Quantitative Electromyography

DQEMG: Decomposition Based Quantitative Electromyography

APB: Abductor Pollicis Brevis

CMAP: Compound Muscle Action Potential

SNAP: Sensory Nerve Action Potential

CNAP: Compound Nerve Action Potential

MU: Motor Unit

MUPT: Motor Unit Potential Train

MUP: Needle Detected Motor Unit Potential

SMUP: Surface Motor Unit Potential

MUNE: Motor Unit Number Estimate

MVC: Maximum Voluntary Contraction

NCS: Nerve Conduction Study

RMS: Root Mean Square

IDI: Inter-Discharge Interval

Chapter 1

Introduction

1.1 Introduction

Carpal tunnel syndrome (CTS) is a condition caused by localized compression of the median nerve at the wrist, specifically within the carpal tunnel. CTS is the most common peripheral nerve disorder with a population prevalence of 14% [1]. It is more prevalent in women compared to men [2]. Symptoms associated with CTS include numbness, tingling and/or burning in the distribution of the median nerve (digits 1 to 3 and the lateral ½ of digit 4), and in severe cases, progressive weakness of the thenar muscles. The nerve compression seen in CTS has been attributed to a variety of contributing factors including reduced space within the carpal tunnel (e.g. rheumatoid arthritis), increased intra-tunnel pressure [3, 4] or increased susceptibility of the nerve to pressure secondary to other conditions (e.g. diabetes milletus, hypothyroidism) [4]. Repetitive hand activity may produce symptoms over time due to thickening of the synovial lining of the tendons that share the carpal tunnel with the median nerve [5]. CTS symptoms are often exacerbated by activities that require repeated or sustained flexion and/or extension postures of the wrist, since these motions increase the amount of pressure on the tendons and nerves within the carpal tunnel [3].

The diagnosis of CTS is fairly simple, through subjective tests and evoked potential studies of nerve conduction velocity and response amplitudes [6-8]. Unfortunately the ability of current electrophysiological methods to investigate the underlying pathophysiology is limited. Nerve conduction studies and questionnaires are

used to measure the level of impairment or disability associated with CTS, however, they do not directly measure the pathological changes occurring within the motor unit pool [7, 9].

Electrophysiological studies of the changes that occur at the motor unit level in CTS might be of considerable value in providing insight into the extent of motor unit loss and neural re-organization resulting from nerve compression. Most clinical electromyography (EMG) studies subjectively assesses the level of motor unit involvement through determining the discharge frequency and size (amplitude and duration) of potentials from low threshold motor units, but these studies are not routinely performed in the assessment of CTS [7].

Quantitative EMG techniques [10] may be used to provide information about the re-organization of motor units following nerve injury and/or muscle disease. One particular quantitative EMG technique, decomposition-based quantitative electromyography (DQEMG), is a valid and reliable [11] method of obtaining electrophysiological data in healthy subjects, and has been used to assess motor unit complexity and firing rate and to estimate motor unit size and number [11-15]. The assessment of motor unit potential morphology and motor unit number estimates may provide insight into the pathophysiological process associated with nerve compression injury, however, the DQEMG system has not been tested or used in such a way.

1.1.1 Purpose

The purpose of this study was to gain a better understanding of the pathological mechanisms associated with motor nerve dysfunction in compressive neuropathies and determine the feasibility of using DQEMG in such research. Studying pathological changes in the abductor pollicis brevis (APB) muscle in individuals with severe CTS provides a convenient model to determine the feasibility of using DQEMG for this purpose. We sought to compare the quantitative EMG data obtained from individuals with severe CTS to those of healthy control subjects and subjects with mild CTS in order to quantify the neuromuscular changes that had occurred as a result of axonal compression. The following two research questions were addressed: 1) Using needle- and surface-detected motor unit potential morphological features determined by DQEMG software is there measurable evidence of collateral sprouting in individuals with severe CTS? 2) Is there evidence of motor axon loss in individuals with severe CTS as measured using motor unit number estimates?

Chapter 2
Literature Review

2.1 The Median Nerve

2.1.1 Anatomy

Carpal tunnel syndrome (CTS) is the result of localized compression of the median nerve at the wrist that may cause sensory dysfunction ranging from hypoesthesia to hyperesthesia and pain. Additionally, motor signs and symptoms in CTS can include atrophy and weakness of the thenar muscles [16].

The median nerve enters the hand through the carpal tunnel, which is surrounded by the carpal bones (hamate, pisiform, tubercle of trapezium, tubercle of the scaphoid) and the transverse carpal ligament. The transverse carpal ligament connects the radial and ulnar eminence of the wrist and is just under the skin. The median nerve and flexor tendons run relatively close to the carpal ligament. The radial component of the median nerve supplies sensory branches to the palmer surfaces of digits one to three as well as the lateral half of the fourth digit. The recurrent branch of the median nerve supplies motor innervation to the APB, the opponens pollicis and the superficial head of the flexor pollicis brevis muscles. The median nerve is very susceptible to compression, due to its location and its proximity to the transverse carpal ligament, and particularly due to the restricted space within the carpal tunnel [17, 18].

2.1.2 Structure of a Peripheral Nerve

A thorough understanding of the structure of a nerve, its components and associated physiology is important in order to properly understand the mechanisms related to peripheral neuropathies such as CTS. A peripheral nerve is comprised of numerous axons or nerve fibers whose cell bodies are located in either the anterior horn of the spinal cord (motor neuron) or the dorsal root ganglia (sensory neuron). The axons in the peripheral nervous system can be myelinated or unmyelinated. Myelinated fibers are axons surrounded by Schwann cells arranged in a longitudinal continuous chain, which insulate the axon [19]. Along myelinated nerve fibers, gaps in the myelin sheath, known as nodes of Ranvier, exist at evenly spaced intervals, enabling an especially rapid mode of electrical impulse propagation (saltatory conduction) [19]. Most motor and sensory nerve fibers within a peripheral nerve are myelinated [20]. Lying next to the myelinated nerve fibers are many unmyelinated fibers associated with one Schwann cell and these fibers conduct impulses much slower than myelinated fibers [19]. Peripheral nerve fibers are classified based on properties of their axons [20], including: axonal conduction velocity, mylenation and fiber size [20]. The larger the diameter of an axon, the greater the thickness of its myelin, and the greater the internodal distances, meaning that the largest fibers conduct impulses the most rapidly [20].

Alpha motor neurons, which innervate extrafusal muscle fibers, have A-alpha axons, which are large diameter, heavily myelinated fibers that conduct action potentials rapidly [20]. Sensory receptors are innverated by different types of nerve fibers including: A-beta, A-gamma, A-delta and C axons, which differ with respect to the

relative amount of myelin, fiber diameter and subsequently their conduction velocity (Refer to Table 1-1 for a summary of nerve fiber types and their properties) [20].

Myelinated and unmyelinated nerve fibers are organized together in fascicles, which are surrounded by the strong perineurial membrane. The fascicles are organized in groups, held together by a loose connective tissue called the epineurium. Between the nerve fibers and their basal membrane is an intrafascicular connective tissue known as the endoneurium. The quantity of the connective-tissue components may vary between nerves and also along the length of the same nerve [21, 22].

Peripheral nerves receive nutritional support through a well developed microvascular system [23]. The vessels enter the nerve trunk and proceed to divide into branches that run longitudinally in various layers of the epineurium. The vessels continue through the epineurium and connect at various points along the perineurial sheath. The vessels are thought to pass through the perineurium through a valve like system into the endoneurium, which primarily contains capillaries [23].

2.1.3 Physiology of a Motor Unit

2.1.3.1 Motor Unit and Action Potentials

A motor unit (MU) is defined as a single α-motor neuron, and all muscle fibers innervated by it [24]. Activation of a motor neuron causes contraction of all of the muscle fibers innervated by that neuron; all of the motor units that innervate a single muscle are considered to be its motor unit pool. The number of muscle fibers innervated by each MU can vary. In general, the number of muscle fibers innervated by a MU is a function of a muscle's need for refined motion. Muscles requiring more refined motion are innervated

Table 2-1: Summary of axon size and conduction velocity

Myelinated fibers	Name and function of type of fiber	External Diameter (µm)	Conduction Velocity (m/s)
A-alpha or IA	Motor to skeletal muscle; sensory from muscle spindle proprioceptive endings	12-20	70-120
A-beta or IB	Sensory from tendons (tension); also Ruffini endings in skin	10-15	60-80
II	Sensory from Meissner's and pacinian corpuscles and similar endings in skin and connective tissue; from large hair follicles	5-15	30-80
A-gamma	Motor to intrafusal fibers of muscle spindles	3-8	15-40
A-delta or III	Sensory from small hair follicles and from free nerve endings for temperature and pain sensations	3-8	10-30
B	Preganglionic autonomic	1-3	5-15
Unmyelinated fibers	**Name and function of type of fiber**	**External Diameter (µm)**	**Conduction Velocity (m/s)**
C or IV	Pain & temperature; Olfaction; Postganglionic autonomic	0.2-1.5	0.5-2.5

Letters are used for any nerve; Roman numerals are for sensory fibers in dorsal spinal roots.

by motor units that innervate fewer muscle fibers [24]. In the median nerve, the motor neurons which extend past the carpal tunnel typically innervate the first and second lumbricals and the recurrent branch of the median nerve provides motor innervation to the abductor pollicis brevis (APB), opponens pollicis and the superficial head of the flexor pollicis brevis [17, 18]. The APB has been shown to contain approximately 177 MUs [11].

Muscle and nerve cells are electrically excitable. This is a unique characteristic not possessed by other cells in the body. The resting voltage across the axonal membrane of human skeletal muscle is approximately −70 mV, this voltage results mainly from a difference in concentrations of potassium and sodium inside and outside the cell [25, 26]. A depolarization of the axonal membrane creates an action potential. As an action potential passes through a point on the axonal membrane, the voltage rises to approximately +50 mV in one millisecond, then returns to −70 mV, typically with an undershoot [26, 27]. Action potentials are triggered when an initial depolarization reaches a 'threshold level'. If the threshold level of depolarization occurs (~ -55 mV in most mammals), an action potential is generated. This depolarization opens voltage-sensitive sodium channels, which allow sodium ions to flow inwards, further depolarizing the membrane [26, 27]. During the millisecond that the voltage-gated sodium channels remain open, sodium ions rush into the cell in that localized region. The depolarization of the membrane opens up more of the voltage-gated sodium channels in adjacent portions of the membrane. In this way, a wave of depolarization sweeps along the cell, because it dramatically raises the voltage at a localized area of the axonal membrane, causing a similar rise at adjacent areas. The action potential is often described as 'traveling' down

the axon [26, 27]. The speed at which the action potential travels down an axon varies depending on the diameter of the axon as well as the presence of myelin. As previously described, in myelinated fibers (i.e. motor neurons) the action potential propagates down the axon in saltatory fashion, whereby the action potentials are only generated at the nodes of Ranvier where the axon is exposed. The action potential is often described as 'jumping' from node to node [26, 27]. By contrast, in unmyelinated fibers, the action potential moves continuously down the axon like a wave [26, 27].

After initiation of an action potential, a refractory period occurs, and is divided into two phases, the absolute and relative refractory periods. Refractory periods are the amount of time taken for a cell membrane to be capable of becoming excited, which is typically 1-2 ms [26, 27]. The absolute refractory period is defined as the interval of time in which an action potential absolutely cannot be initiated, regardless of the stimulus intensity, and it is caused by inactivation of the sodium channels. The relative refractory period immediately follows the absolute refractory period, during which an action potential is inhibited, but not impossible to elicit if adequate stimulus intensity is applied. As such, with repeated stimuli, the nerve has a maximum firing frequency, typically between 5-50 Hz, that is dependent on the action potential duration and the associated absolute refractory period duration [28, 29].

The action potential proceeds along the axon until it reaches the axon terminals, of the synaptic junction. The synapses are specialized structures where neurotransmitter chemicals are released in order to allow the axon to communicate with its target muscle cell. The transmission of an action potential from its motor nerve to its associated muscle fibers via the neuromuscular junction is described below.

2.1.3.2 Neuromuscular Junction

Upon reaching the terminal axon, voltage-gated calcium channels are activated, which allows calcium ions to flow inward from the extracellular fluid into the motor neuron's cytosol [27, 30]. The influx of calcium ions provokes the extracellular release of neurotransmitters, specifically acetylcholine. Acetylcholine diffuses across the synaptic cleft and binds to receptors on the post-synaptic muscle fiber membrane (sarcolemma) [27, 30]. The receptors, when activated, cause voltage-gated sodium channels to open which allow sodium ions to flow inward causing an end plate potential [27, 30]. Similar to the action potential produced on the axonal membrane, a threshold must be reached in order to produce an action potential within the muscle fiber. The interior of a resting muscle fiber has a resting potential of approximately −95 mV [27]. If the end plate potential reaches the threshold voltage of approximately −50 mV, an action potential is generated in the muscle fiber [27, 30]. The action potential sweeps along the muscle fiber, similarly to that which happens along an unmyelinated axon. As the action potential passes along the muscle fiber, the sarcoplasmic reticulum releases ionic calcium which interacts with the myofibrils to induce muscular contraction. Stimulation of the motor neuron causes contraction of all of the muscle fibers innervated by that neuron [27].

The motor deficits associated with nerve compression injuries can stem from demyelinating or degenerating axons at the site of compression, which can prevent or slow action potentials from being transmitted beyond the point of compression and ultimately to those muscle fibers innervated by the injured axons. The weakness or atrophy often described by individuals with severe CTS is likely a result of the prolonged

compression of the median nerve which can cause a loss of motor units within the APB, opponens pollicis and the superficial head of the flexor pollicis brevis.

2.2 Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is a condition caused by localized compression of the median nerve at the wrist, specifically within the carpal tunnel. CTS is the most common peripheral nerve disorder with a population prevalence of 14% [1]. It is more prevalent in women compared to men [2]. Symptoms associated with CTS include numbness, tingling and/or burning in the sensory distribution of the median nerve (digits 1 to 3, and the lateral aspect of digit 4), and in severe cases, progressive weakness of the thenar muscles [16].

2.2.1 Etiology of Carpal Tunnel Syndrome

Peripheral neuropathy is the result of a variety of intrinsic factors, extrinsic mechanical factors, disease states, metabolic factors, and epidemiological factors. One or several of these may be involved in the development of symptoms of CTS in a given individual.

2.2.1.1 Intrinsic Factors Associated with Carpal Tunnel Syndrome

Intrinsic factors are those that increase the volume of the contents within the carpal tunnel, which leads to an increase in interstitial pressure causing compression of the median nerve. Increased retention of body fluids during pregnancy, cardiac insufficiency, or other medical conditions have been implicated in the development of CTS [31]. Diabetes, hemophilia and myeloma have also been linked to CTS [4, 32].

Patients who undergo chronic hemodialysis also have a high incidence of CTS. Suggested mechanisms for the development of CTS in hemodialysis patients include increases in body fluid and distal stenosis [33]. Inflammatory conditions such as rheumatoid arthritis and gout have also been implicated in cases of CTS. A tenosynovitis of the flexor tendons associated with these inflammatory conditions can cause a reduction of space within the carpal tunnel making the median nerve more susceptible to compression [16].

2.2.1.2 Extrinsic Factors Associated with Carpal Tunnel Syndrome

Extrinsic factors include those which reduce the dimensions of the carpal tunnel and may result in increased interstitial pressure since the volume of the contents are unchanged. For example, CTS has been observed to occur in association with wrist fractures, scaphoid fractures or subluxation or wrist arthritis [34]. Structural changes, however, are not the only extrinsic factors that cause CTS. Wrist position has been shown to affect the pressure measured within the carpal tunnel [35]. Sustained flexion and/or extension postures of the wrist have been shown to increase the amount of pressure on the tendons and nerves within the carpal tunnel [3].

2.2.1.3 Occupational Factors Associated with Carpal Tunnel Syndrome

Workers engaged in tasks that require repetitive flexion and extension of the wrist, strong grip or exposure to vibration are at a higher risk of developing CTS than other workers. Tanaka et al. [36] estimated the prevalence of self-reported CTS among workers using the Occupational Health Supplement of the 1988 National Health Interview Survey. They concluded that the risk factor most strongly associated with

medically confirmed CTS was exposure to repetitive bending/twisting of the hands or wrists at work [36]. A critical review regarding work-related CTS was performed by the National Institute of Occupational Health and Safety in 1997 [37], which summarized the findings of over 30 epidemiologic studies and concluded that there was strong evidence of a positive association between the development of CTS and the combined factors of high force demands with repetition, and high force demands combined with wrist flexion and extension postures. Furthermore, the Workplace Safety and Insurance Board of Ontario reported that in 2005 hand and wrist pain accounted for the second greatest number of lost time claims in Ontario, second only to number of lost time claims due to back pain [38].

2.2.2 Pathophysiology

Two pathological mechanisms are believed to be involved in compressive neuropathies: ischemia and mechanical compression. Ischemic changes (reduced vascular flow) associated with CTS are believed to occur with acute compression while mechanical changes (i.e. axonal loss) associated with CTS are believed to occur due to chronic compression [39]. These ischemic and mechanical changes may explain why the relief of symptoms is so variable with respect to time following median nerve decompression surgery. In patients with milder symptoms, immediate relief (usually within hours to days) may be attributed to the restoration of the intraneural vascular flow to an otherwise healthy nerve. Prolonged recovery times (weeks to months) may be related to the typically slow resolution of intraneural edema. Recovery of function that

takes months may reflect the time required for remyelenation and regeneration of axons across more severe nerve compression sites [40, 41].

2.2.2.1 Ischemia

Ischemia is typically related to acute nerve compression, whereby there is a sudden increase in interstitial pressure within the carpal tunnel that can result in occlusion of blood flow and subsequent axonal conduction block. This condition is most often completely reversible. Following the release of the compression, normal nerve conduction is usually restored [42, 43]. Many animal studies have demonstrated retarded axonal and epidural flow when an isolated but intact nerve segment is compressed using a small pneumatic cuff [44-46]. Local nerve compression was studied by Rydevik et al. [45] in the rabbit tibial nerve using small, inflatable cuffs placed around the nerve through a small incision [45]. They examined the effects of graded extraneural compression which was induced, in vivo, in the tibial nerve of a rabbits and a microscopic technique was used to observe changes in intraneural microcirculation. Pressures of 20–30 mm Hg were found to interfere with venous blood flow while pressures of 35–50 mm Hg reduced capillary flow. Pressures above 60 mm Hg caused complete ischemia. Circulation was restored within the first minute after releasing the pressure, however edema was present [45]. The pressures of 35-50 mm Hg, which caused reduced capillary flow, are similar to the pressures that have been recorded in the in individuals with carpal tunnel syndrome [3]. Unfortunately, the effect of pressure on nerve conduction velocity was not monitored.

With the use of a miniature pressure cuff, Ludborg et al. [47] induced an extraneural pressure of 30 mm Hg around the sciatic nerves of rats for periods of two, four, six, and eight hours. The endoneurial fluid pressure was measured by direct micropipette measurement techniques at one or 24 hours after removal of the cuff, and the nerves were then subjected to histological analysis. Endoneurial edema, associated with a three-fold increase in endoneurial fluid pressure, was observed after compression at 30 mm Hg for eight hours. Furthermore, the endoneurial pressures at twenty-four hours after release of the cuff were higher with larger durations of compression. The authors concluded that increasing either the duration of compression or the compression pressure is associated with greater edema formation and greater sustained intraneural pressures [47]. Such an increase in endoneurial fluid pressure may interfere with intrafascicular capillary flow, and thereby constitute an important pathophysiological mechanism in nerve compression injuries. When endoneural edema forms in this space, the pressure in the fascicle increases, remains high, and interferes with the endoneurial microcirculation [47, 48]. The ischemic effects associated with CTS cannot be ignored. To further complicate matters ischemia is often superimposed with mechanical injury.

2.2.2.2 Mechanical Nerve injuries

One of the key characteristics of chronic compressive neuropathies, such as CTS, is demyelination. The loss of myelin, which is critical to normal conduction of neural impulses, appears to result primarily from mechanical disruption of the internodal segments. A reduction in nerve conduction velocity in patients with carpal tunnel syndrome is presumed to result from a focal disturbance in myelin, and demyelination

has been observed and documented [49, 50]. The myelin segments are distorted and damaged proximal and distal to the site of compression [51]. If the compression is relieved, then Schwann cells will remyelinate the axon. However, remyelination causes an increase in the number of nodes of Ranvier, which can permanently slow the conduction velocity at the site of remyelination [51].

Extensive demyelination and persistent compression, as is the case in severe CTS, can eventually result in axonal damage and Wallerian degeneration distal to the site of injury [52, 53]. Wallerian degeneration is best understood in the context of axonal transection, and is initiated 48 to 96 hours after traumatic nerve injury. In severe cases of CTS, Wallerian degeneration can occur if the axon is fully transected but has a completely intact endoneurium and stroma. In this case, recovery can occur through axonal regrowth along the endoneurial tubes [52]. If the injury involves both the axon and endoneurial tubes, but the surrounding perneurium is intact, recovery depends on how well sprouts can cross the site of the lesion and find the appropriate endoneurial tubes [52], however this type of lesion is not typical in those individuals with CTS [53]. After an axon has grown to and connected with its target cell (in the case of a motorneuron and a muscle fibre), the diameter of the axon may increase as it matures [52].

Mechanical axonal injuries are typically classified in one of two ways: 1) axonal lesions in continuity (i.e. demyelination), or 2) as loss of continuity (i.e. axonal loss) [52]. Complete nerve transection does not typically occur in CTS. The recovery of axonal lesions associated with demyelination is often rapid and complete, whereas recovery following axonal loss depends on several factors such as the type of injury, the site of the

lesion and the time interval between injury and treatment. Acute compression is often associated with the demyelination of mainly large fibers [54] which, if severe or prolonged, may result in Wallerian degeneration [50]. The distinction between axonal lesions in continuity and with loss of continuity is often simplified to demonstrate the clinical implications in each case. However, chronic nerve entrapment is likely associated with combined demyelination and axonal degeneration, and this type of lesion has been observed in animal models [49, 55].

Powell et al. [55] induced nerve compression in the sciatic nerves of 91 rats with an inflatable miniature plexiglass compression device which was surgically implanted. The experiment was designed to study the pathogenesis of lesions in nerve entrapment syndrome. In one group, a pressure of 80 mm Hg was applied and the nerve was excised for histological analysis at intervals of 4 hours and 1, 2, 7, 10, 14, and 28 days. In another, smaller group of animals, pressures of 10 mm Hg and 30 mm Hg were applied and the follow-up intervals were 5, 6, and 7 days. Edema was visible in the subperineurial space within four hours in all compression subgroups, and it persisted for the entire duration of the study. Axonal degeneration was associated with the degree of endoneurial edema and was primarily noted in the nerves subjected to 80 mm Hg of compression and, to a lesser extent, in those subjected to 30 mm Hg of compression. Axonal degeneration was rarely seen in the nerves subjected to 10 mm Hg of compression. Demyelination was observed at 7 and 10 days, and was followed by remyelination at 14 and 28 days following relief of pressure. Demyelination was prominent in the nerves subjected to 30 mm Hg of compression and, to a lesser extent, in those subjected to 10 mm Hg of

compression. The authors concluded that the 'dose-response' pattern observed in acute nerve compression, holds true in chronic cases as well [55].

CTS, whether acute or chronic, is thought to be predominantly demyelinating [56]. As described above, extensive demyelination and persistent compression can eventually result in axonal damage and Wallerian degeneration distal to the site of injury [52, 53]. Furthermore, damage to motor nerve fibers causes changes to occur at the neuromuscular junction [57]. Nerve terminals and junction end-plates break down, causing neuromuscular transmission to fail, even before nerve conduction fails [58]. Denervation follows and is associated with considerable muscle fiber atrophy [59].

2.2.2.3 Motor Loss in Carpal Tunnel Syndrome

During the first few days after denervation the size of muscle fibers and their ability to contract rapidly decreases. The rate of muscle fiber atrophy after denervation, varies in different muscles and with different species [57]. Patients with severe CTS often have motor deficits which accompany the more traditional sensory symptoms. Motor impairments can stem from demyelination and in more severe cases, axonal loss causing denervation of the abductor pollicis brevis, opponens pollicis and the superficial head of the flexor pollicis brevis, they are observed through thenar atrophy and are measured through loss of pinch and grip strength [60].

Reinnervation of the denervated neuromuscular junctions is an important part of recovery from motor fiber axon damage [57]. Reinnervation occurs in two ways: 1) sprouting of undamaged axons in close physical proximity to the denervated fibers, and 2) axonal regeneration from the site of nerve injury [57].

Quantification of axonal loss and the degree of collateral sprouting could in fact prove to be a valuable tool in the assessment of compression neuropathies in terms of extent of injury, recovery mechanisms, and rate of recovery.

2.3 Clinical tests for carpal tunnel syndrome

2.3.1 Clinical Indicators

The clinical diagnosis of CTS is based on a combination of clinical signs and symptoms and is often confirmed by abnormal nerve conduction studies. The condition must be differentiated from conditions that produce similar symptoms such as cervical radiculopathy or median nerve compression at the elbow or in the proximal forearm and this differentiation is heavily based on a patient subjective reports. The classic symptoms of CTS include pain, numbness or paraesthaesia in the thumb, index, middle and radial half of the ring fingers. Wrist pain, digital weakness, inability to pinch strongly and frequent dropping of objects are also common complaints particularly when the condition has been present for a long period of time [16].

Two clinical maneuvers that have been widely used in clinical examination are Phalen's test [6] and Tinel's sign [8]. Tinel's sign involves tapping lightly with a rubber mallet or the examiner's index finger directly over the median nerve within the carpal tunnel proximal to the middle wrist crease. A reproduction of the patient's complaint of parethesia radiating to the tip of the thumb or any of the first three fingers indicates the possibility of injury of the median nerve within the carpal tunnel [8].

Phalen's wrist flexion test is also commonly employed in making a diagnosis of CTS. For this provocative maneuver, the patient allows the wrists to fall into full flexion

letting the fingers dangle downward. If a tingling sensation in the median nerve distribution starts within a minute, it is considered a positive sign for the presence of CTS [6]. Although these tests are commonly used by many clinicians, due to the widely reported differences in their specificity and sensitivity, they are not adequate to confirm a diagnosis of CTS [61]. Basing diagnostic decisions solely on these signs and symptoms can lead to confusion with other common disorders that have similar symptoms, such as tendonitis and/or cervical radiculopathy [62].

Carpal tunnel syndrome can be confused with other disorders that present similar symptoms. Cervical radiculopathy can often mimick the symptoms associated with CTS, thus making a diagnosis of CTS difficult. Unfortunately, there are no universally accepted criteria for the diagnosis of cervical radiculopathy [63]. In most cases, the patient's history and physical examination are considered sufficient to make the diagnosis although the sensitivity and specificity of these techniques are not known [64]. Rotation or bending of the head/neck towards the symptomatic side can be used as a clinical indicator of cervical radiculopathy, the test is considered positive if there is an increase in pain or paraesthesia during or following the movement [65].

2.3.2 Nerve Conduction Studies

Electrodiagnostic methods are considered by some to be the "gold standard" for the diagnosis of CTS, because they are a quantitative method of measuring the integrity of a nerve [7]. Nerve conduction studies (NCS) involve stimulating the peripheral nerves and recording the evoked response from the muscle (muscle action potential) or nerve (sensory/mixed nerve action potential), as described in further detail below.

Measurements of axonal conduction times and the amplitude and duration of evoked potentials are clinically valuable in the assessment of peripheral nerve function [66]. Many factors need to be taken into consideration when conducting and interpreting electrodiagnostic tests. Age, height, skin temperature, and methodological variations have all been found to impact normative values [67].

2.3.2.1 Compound Muscle Action Potentials

In assessing the integrity of motor nerves, the nerves are stimulated supramaximally, causing the simultaneous depolarization of all axons. The resultant action potentials travel orthodromically down the motor axon, evoke synaptic transmission at the neuromuscular junction and result in a compound muscle action potential (CMAP). The CMAP is measured through electrodes placed on the skin surface over the target muscle. The time (in milliseconds) it takes for the impulse to travel from the stimulation point and to depolarize the muscle is defined as the distal motor latency. While motor latency measurements are generally considered the most important metric, the shape of the CMAP can also provide valuable information. The area and amplitude of the CMAP is correlated with the number of functioning muscle fibers within the muscle [59]. A prolonged CMAP duration reveals marked slowing of the conduction velocity in some of the nerve fibers, which occurs in cases of demyelination. A low amplitude CMAP reveals evidence of severe impairment however, it is difficult to differentiate demyelination from axonal loss in CTS using only a CMAP, since both conduction block and motor unit loss can cause a reduction in amplitude. Furthermore, demyelination and axonal loss often occur simultaneously [62].

2.3.2.2 Sensory Nerve Evoked Potentials

Sensory nerve conduction may be measured by stimulating a mixed nerve proximally (e.g. wrist) and recording with surface electrodes placed at a distal site (e.g. a digit) where only sensory axons are present (antidromic). It can also be measured by stimulating a distal site (e.g. digit) and recording the resultant potential proximally (orthodromic). There is no significant difference between the anti- or orthodromic methods, with respect to latency, for a sensory nerve action potential (SNAP) [68]. However, antidromic stimulation has the advantage of producing SNAPs of greater amplitude as compared to the orthodromic method [68]. The resulting SNAP is the sum of the action potentials evoked within the myelinated sensory fibers of the nerve of interest. Sensory nerve action potential latency is measured as the transmission time along a predetermined length of nerve.

2.3.2.3 Compound Nerve Evoked Potential

A compound nerve action potential (CNAP) may be measured by stimulating a distal portion of a mixed nerve (sensory and motor nerve fibers) (e.g. palm) and recording from the skin surface over a proximal site along the nerve (e.g. wrist). The nerve conduction velocity and CNAP amplitude are determined with the same techniques as the sensory nerve conduction studies. A CNAP provides slightly more information as compared to SNAPs, which only record from sensory nerve fibers and CMAPs, which only records from muscle fibers, because they record from a portion of mixed nerve (all axons within a given nerve). The sensory muscle afferent fibers (Ia fibers), which supply the muscle spindles, are the largest and fastest afferent fibers within a nerve and are only

recorded during the CNAP (Refer to Table 2-1) [26]. Furthermore, evoking a CNAP through palmar stimulation is more sensitive than antidromic or orthodromic stimulation of digital fibers in establishing the diagnosis of CTS [69]. The combination of SNAPs, CNAPs and CMAPs are useful in examining the integrity of a nerve and are often used to classify such neuropathic disorders as CTS.

2.3.2.4 Classification of Carpal Tunnel Syndrome

Stevens [7] proposed the following criteria to classify the severity of CTS:

Mild: prolonged sensory distal latency and SNAP/CNAP amplitude reduction;

Moderate: prolonged median motor and sensory distal latencies;

Severe: changes seen in moderate category with either an absent SNAP from the median nerve, or low amplitude or absent thenar CMAPs.

2.4 Other Electrophysiological Techniques to Diagnose Motor Impairment

In addition to the nerve conduction techniques described above, quantitative electromyography (EMG) may be used to provide more information regarding the nature of the injury and recovery process. This is not necessary for the clinical diagnosis of CTS and will not affect management decisions, but may be useful in research situations. For the purpose of this study, quantitative EMG will be used to examine collateral sprouting and estimate motor axonal loss.

2.4.1 Quantitative Electromyographic Techniques to Examine Collateral Sprouting

For quantitative electromyography (QEMG), a needle electrode is inserted into the muscle and records the electrical activity of muscle fibers at rest and during voluntary contractions. The electrode observes the summed muscle fiber activity from each motor unit as a motor unit potential (MUP). The amplitude of the MUP is a function of the number of muscle fibers belonging to that motor unit as well as the proximity of the needle to the active fibers [70]. The duration of the MUP is influenced by the number and location of more distant fibers belonging to the same motor unit as well as the dispersion of the neuromuscular junction [70]. Quantifiable morphologic characteristics of MUPs include: amplitude (V), duration (ms), the number of crossings of the baseline (number of phases) or the number of direction changes seen in the MUP waveform (turns) [70].

Collateral sprouting occurs when surviving motor axons reinnervate muscle fibers which are no longer innervated. This can be identified in quantitative EMG studies by the presence of small, polyphasic satellite potentials following a MUP and/or long-duration polyphasic MUPs. As the newly formed axonal sprouts mature, their electrical contribution is incorporated into the parent MUP, resulting in abnormally long, large and complex waveforms [71, 72].

Traditional clinical needle EMG studies not only examine motor unit morphology but, typically perform observations of resting activity and of the recruitment frequencies of MUPs while the needle is in situ. Although rest observations and are difficult to quantify they are useful clinically. At rest, the muscle should be electromyographically quiet [70]. Insertional activity is the electrical response of the muscle membrane to stimulation caused by the insertion of the EMG needle. An increase in the duration of

insertional activity develops 3-4 weeks after denervation and persists until the muscle fiber degenerates completely or is reinnervated by an axon [70]. Because the presence of increased insertional activity is dependent on the duration since injury, its absence does not necessarily infer an absence of denervation injury [70]. The rate, also known as recruitment frequency, is a measure of the frequency of the first MUP at the time the second MU is recruited. An increase in recruitment frequency often indicates that there is muscle fiber loss related to a myopathic process. Inspection of the interference pattern during a strong contraction effort is also helpful in evaluating disease processes. In denervation processes, there is a reduction in the number of MUPs produced by the patient with muscle contraction, resulting in a more sparse interference pattern than would normally be seen, and in myopathy, the amplitude of the peaks in the interference pattern is reduced.

2.4.2 Neurophysiological Techniques to Estimate Motor Axonal Loss

Motor unit number estimation (MUNE), as the name suggests, is a technique used to estimate the number of motor units and consequently the number of functioning axons within a muscle [11]. A number of MUNE methods have been described, but only three types are commonly used. In all cases the size of the CMAP is divided by the average size of surface recorded single motor unit potentials (SMUP) using the same electrodes. The differing MUNE methods measure the SMUP sizes in different ways and are described below in section 2.4.2.1. For the purpose of this study, the second method (Section 2.4.2.2) described will be used to evaluate axonal loss. MUNE Methods

2.4.2.1 The Incremental Technique

In this approach stimulation of the motor nerve starts at a sub-threshold level. Gradually, the stimulus intensity is increased incrementally by 1 mA until a muscle response is seen, representing the first motor unit activated. The stimulus intensity is increased incrementally by 1 mA, causing an increase in the recorded responses. Each increase in the recorded response is assumed to represent the addition of one additional motor unit to the muscle potential. The amplitude of the resultant response is divided by the number of increments to yield an average surface motor unit potential; this value is divided into the maximum CMAP amplitude to give the estimate of the number of motor units [73].

2.4.2.2 Spike Triggered Average Technique

The spike triggered averaging method utilizes both an intramuscular electrode and surface electrodes simultaneously to detect electromyographic (EMG) signals during minimal isometric contraction [74]. The needle-detected MUPs are used as triggering sources to select specific sections of the surface EMG signal, which are averaged to produce an SMUP [74]. The CMAP size related parameter (e.g. peak-to-peak amplitude, negative peak amplitude and area) is divided by the same size related parameter of the average SMUP [74]. For the purpose of this study, MUNEs were generated using an average SMUP template detected through a decomposition-based quantitative electromyography program (DQEMG) [12]. Several MUPs were recorded by a surface electrode as the individual performed a series of low to moderate level contractions ranging from 5 to 50% of their maximum voluntary contraction (MVC). The surface

detected EMG signal was then decomposed into its constituent MUP trains. The average SMUP size related parameters were used as the denominator below the same CMAP size related parameter in order to estimate the total number of motor units within the muscle.

2.4.2.3 Statistical Technique

Groups of 30 sequential submaximal CMAPs are recorded at one stimulus intensity level. As long as the size distribution of each group follows a Poisson distribution, then the variance in area of the submaximal CMAPs equals the mean area for the individual SMUPs that contribute to this variance. The CMAP is then divided by the resultant mean SMUP determined by the variance [75].

2.4.2.4 Reliability of MUNE Measures

There is no gold standard for determining a MUNE, and most MUNE methods generate similar estimates for the numbers of motor units present in a muscle. A critically important factor is the reliability of the measurement. There have been relatively few studies looking at test-retest reliability of MUNE measurements [11, 76]. Thus, no firm conclusions about the relative reliability of the different measurements can be made however, the spike triggered averaging technique in conjunction with DQEMG has been deemed valid and reliable for use in the thenar muscles [11].

2.5 Research Questions

The purpose of this cross-sectional study was to develop a better understanding of the underlying pathophysiological mechanisms involved in severe CTS. The following questions were addressed in this study:

1. Is there measurable evidence of collateral sprouting in individuals with severe CTS using MUP and SMUP morphological features determined by DQEMG software?

2. Is there evidence of motor axon loss in individuals with severe CTS as measured using MUNE?

The tests for CTS typically include motor, sensory, and mixed NCSs in the median and ulnar nerves in the symptomatic arm. Electrophysiological data pertaining to the ongoing changes occurring at the motor unit level may be of considerable value, in providing insight into the extent of MU loss and reorganization resulting from prolonged nerve compression.

Chapter 3
Methodology

3.1 Research Design and Subject Selection

The study received ethics approval form the Queen's University Research Ethics Board (REH-408-07). In order to address the research questions, a cross sectional study was designed. Three groups of subjects were recruited: individuals with severe CTS (motor involvement), individuals with mild CTS (no motor involvement) and individuals with no signs or symptoms of CTS. Men and women between the ages of 18-60 were recruited through advertisements (Appendix A) which were placed in Kingston General Hospital, Hotel Dieu Hospital and Providence Care in Kingston, ON. Subjects were also recruited through referral by a physician (Dr. Faris) in the Physical Medicine and Rehabilitation department at Providence Care. The recruitment period was from August 1st, 2007 to June 15th, 2008.

3.1.1 Inclusion and Exclusion Criteria

A reduction in nerve conduction velocity has been associated with increased age, particularly after the age of 60 [67]. Thus, only those between the ages of 18 - 60 were considered for participation. Subjects were selected on the basis of a clinical and electrophysiologically (described in section 3.2) confirmed diagnosis of CTS and were classified as mild or severe. Subjects with CTS were required to have symptoms including: hand paraesthesia and hypoesthesia or pain in the first three digits [16]. All participants were required to have normal conduction through the median nerve in the

forearm and radial nerve as described in section 3.2.2.3. Those with clinical or electrophysiological evidence of radiculopathy were excluded (described later in 3.2.1). Furthermore, subjects were excluded if they had conditions which would increase the susceptibility of their nerves to compression neuropathies (e.g. diabetes milletus, hypothyroidism, hypertension) [4]. Subjects recruited to the control group were required to have no past or present history of neuropathy and to meet the same exclusion criteria as above.

3.2 Subject Screening and Medical History

The consent form was reviewed with each subject by the investigator to ensure they understood all aspects of the study prior to providing written consent (Appendix B). Individuals who agreed to volunteer in the study participated in one evaluation session which lasted approximately one hour. Demographic data were documented for each subject, including height, weight, age, occupation and handedness. Subjects then completed the Brigham and Women's Carpal Tunnel Questionnaire[9] (Appendix C) to quantify the functional limitations associated with their condition, which was used for descriptive purposes. The Brigham and Women's Carpal Tunnel Questionnaire is a two part questionnaire which examines symptom severity and functional status in individuals with CTS [9]. This questionnaire has been found to be reliable [77] (Cronbach alpha, 0.89 and 0.91 for severity of symptoms and functional status, respectively) and sensitive to functional change.

The first part of the questionnaire is a symptom severity scale, which consists of eleven questions with multiple-choice responses, scored from 1 point (mildest) to 5

points (most severe). The symptom severity score is calculated as the mean of the scores for the eleven individual items [9]. Eight activities comprise the functional status scale. The answers are rated from 1 point (no difficulty with activity) to 5 points (cannot perform the activity at all). The score for the functional status is calculated as the mean of these eight items [9].

3.2.1 Physical Examination

Subjects were then assessed using Tinel's sign [8] and Phalen's test [6] (as described in section 2.4.1) and the result of each test (positive/negative) was recorded for descriptive purposes. Cervical radiculopathy was assessed by means of the cervical compression and distraction tests [65]. The cervical compression test involved pressure being applied in a caudal direction to the head of the subject. If symptoms began or were exacerbated when the pressure was applied this was considered a positive test for radiculopathy and the potential subject was excluded [65]. Similarly, the cervical distraction test was performed on each subject by gently placing both hands on the side of the head and lifting slightly, thus reducing any pressure applied to cervical nerve roots [78]. If symptoms of pain or paraesthaesia diminished during or following the distraction test, it was considered a positive test for radiculopathy and the subject was excluded. Subjects were also asked to perform a series of movements as follows: rotating their neck to the right and left, lateral bending their neck to the right and left and finally, fully flexing and extending their head and neck [78]. Each position was held at the end of the available range of motion for 30 seconds. If pain or paraesthaesia began or were exacerbated with these neck movements, this was considered to be a positive sign for

radiculopathy and subjects would have been excluded, however, the range of movement tests produced no symptoms in any subject. A total of two subjects were excluded from the study due to suspicion of radiculopathy following positive compression and distraction tests.

3.2.2 Nerve Conduction Studies

Nerve conduction studies (NCS) were performed using the Comperio (Neuroscan Medical Systems, El Paso,. Texas) clinical EMG system. Palmar temperatures were monitored and maintained above 30°C for all testing. Prior to electrode placement, the hand under investigation was thoroughly cleaned using compound rubbing alcohol (Life^{TM}, Toronto, ON) and cosmetic pads (Life^{TM}, Toronto, ON). Surface EMG signals were detected using self-adhering electrocardiogram electrodes (refer to section 3.2.2.1 for electrode placement) (Harris Healthcare, Hudson, MA) cut in half to measure 1 cm x 3 cm. A full-sized (2 cm x 3 cm) electrode was placed on the posterior aspect of the hand to serve as a reference. Signals were amplified (Neuroscan Medical Systems, El Paso, TX) with a bandpass filter of 5 Hz – 5 kHz, digitized and stored using the Comperio Software by Neuroscan.

3.2.2.1 Electrode Configuration

Subjects sat with their arms comfortably supported on a pillow on their lap during data collection. Conductive gel was applied to the tips of the stimulator anode and cathode probe before applying a stimulus to the skin surface. In the case of SNAPs and CNAPs, a bipolar electrode configuration was used with an inter-electrode distance of 3

cm. In contrast, a monopolar configuration was used to record CMAPs. The active surface electrode was positioned over the motor point of the APB, with the reference surface electrode positioned over the first metacarpophalangeal joint. The motor point was determined by placing the cathode portion of a stimulating probe on the belly of the APB. With the train rate on the stimulator set at 3 Hz and the stimulation duration set at 100 ms, the motor point was determined as the region of the muscle where the smallest electrical stimulus produced a visible muscle twitch.

3.2.2.2 Stimulus Intensity

For all nerve conduction studies, the stimulus current was initially set to zero and increased incrementally until maximum potential amplitude was achieved. Supramaximal stimulation was delivered at an intensity of 120% of that intensity which produced the maximum potential amplitude, and ten of each of the CMAPs, SNAPs and CNAPs were emsemble averaged respectively, to ensure a clean and reliable waveforms. SNAP and CNAP latency was measured from the peak of the stimulus artifact to the negative peak of the respective waveforms. CMAP latency was measured from the peak of the stimulus artifact to the onset of the waveform. The following seven nerve conduction tests were performed on each participant. Refer to Table 3-1 for a summary of the nerve conduction tests performed:

3.2.2.3 Sensory Nerve Action Potentials

Median and Ulnar SNAPs: Measured antidromically, the surface electrodes were positioned over the proximal and distal phalanges of digit four. SNAPs were elicited with stimulation of both the median and ulnar nerve at the wrist (13 cm proximal to the

recording electrodes). Following an elicited response, the primary investigator visually inspected the waveform to ensure it had a distinct onset, negative peak and positive peak. Prolongation of the median nerve SNAP of digit four relative to the ulnar nerve SNAP of digit four >0.5 ms was considered abnormal [26].

Radial SNAP: Measured antidromically, the surface electrodes were positioned distal to the anatomical 'snuff box' and proximal to the metacarpophalengeal joint of digit one. Again, an average of ten SNAPs was recorded and measured as described above. This test has a normal upper limit of 2.9 ms, exceeding this limit suggests the possibility of radial neuropathy and subjects with this finding were be excluded from the study. Those with radial nerve latencies greater than median nerve latencies were excluded from the study due to suspicion of radial neuropathy [26].

3.2.2.4 Compound Nerve Action Potentials

Median and Ulnar CNAPs: Measured orthodromically, the surface electrodes were positioned over the nerve 8 cm proximal to the stimulation site (lateral and medial aspect of the hand; mid-palmar for the ulnar and median nerves respectively). A CNAP was elicited by stimulation of the mixed nerve in the mid-palmar region and was verified and ensemble averaged as discussed above. A comparison between median and ulnar nerve mid-palmar sensory latency was made and a difference greater than 0.4 ms between median and ulnar nerve latencies was considered abnormal and was used to classify CTS [26]. The criteria for stratification are provided in detail in section 3.3.3.6.

3.2.2.5 Compound Muscle Action Potentials

CMAP of the APB by stimulation at the wrist: Measured orthodromically, the active surface electrode was positioned over the motor point of the APB, 7 cm proximal to the stimulation site (which was proximal to the carpal tunnel). Following a maximal elicited response, the waveform was inspected to ensure it had a distinct onset, negative peak and positive peak. As with the SNAPs and CNAPs, an ensemble average of ten CMAPs was then recorded. Latency was measured from the peak of the stimulus artifact to the onset of the resultant CMAP. This test has an normal upper limit of 4.4 ms in terms of latency, and a normal lower limit of 4mV for amplitude [26] and was used to stratify individuals with CTS (see section 3.3.3.6).

CMAP of the APB by stimulation at the antecubital fossa: Measured orthodromically, the active surface electrode was positioned over the motor point of the APB. A maximum CMAP was elicited from the antecubital fossa, in a similar technique as described in 3.2.2.5 above, and ten CMAPs were ensemble averaged. This test was considered normal if the conduction velocity exceeded 49 m/s [26] and was used to ensure normal conduction of the median nerve within the forearm. Subjects with slowed conduction from the cubital fossa were excluded from the study.

Table 3-1: Summary of nerve conduction studies

Nerve (Response Type)	Distance from stimulation to recording site	Stimulation Site	Recording Site
Median (CNAP)	8 cm	Mid Palm	Proximal to the wrist
Ulnar (CNAP)	8 cm	Mid Palm	Proximal to the wrist
Median (SNAP)	13 cm	Proximal to the wrist	Lateral aspect of digit 4
Ulnar (SNAP)	13 cm	Proximal to the wrist	Medial aspect of digit 4
Radial (SNAP)	10 cm	Radial aspect of forearm	Distal to anatomical snuff box
Median (CMAP)	7 cm	Proximal to the wrist	Motor point of APB
Median (CMAP)	Variable	Anticubital Fossa	Motor point of APB

3.2.2.6 Stratification of Subjects with Carpal Tunnel Syndrome

In all cases (SNAPs, CNAPs and CMAPs) markers indicating the negative peak onset, the negative peak, the negative-peak termination, and the positive peak were automatically positioned by the software. Following visual confirmation of marker locations, (and manual adjustments by the investigator if required), the software calculated size related parameters of the CMAP/CNAP/SNAPs including negative-peak area, negative-peak amplitude, and peak-to-peak amplitude. For the purposes of this study, the subjects were stratified into three groups on the basis of the severity of the nerve conduction studies, as listed below. Only subjects who fell into one of the following three groups were included in the study [7, 26]:

1) Healthy: No electrophysiological evidence of impairment .

2) Mild CTS: prolongation of sensory distal latencies (median mid palmer latency >2.2 ms or prolongation of the median mid-palmar CNAP relative to the ulnar mid-palmar CNAP >0.4 ms or a difference in latency >0.5 ms between median and ulnar SNAPs of digit four); and no other positive findings [7, 26].

3) Severe CTS: prolongation of both median motor (>4.4 ms) and sensory distal latencies (median mid palmer latency >2.2 ms or prolongation of the median mid-palmar CNAP relative to the ulnar mid-palmar CNAP >0.4 ms or a difference in latency >0.5 ms between median and ulnar SNAPs of digit four);

with either an undetectable SNAP/CNAP or a low amplitude (< 4 mV) or absent thenar CMAP and no other positive findings [7, 26].

Individuals with moderate CTS, as indicated by prolonged median motor (>4.4 ms) and sensory distal latencies (median mid palmer latency >2.2 ms or prolongation of the median mid-palmar CNAP relative to the ulnar mid-palmar CNAP >0.4 ms or a difference in latency >0.5 ms between median and ulnar SNAPs of digit four) [7, 26]; were excluded from participation.

3.3 Experimental Protocol

EMG signals were acquired using custom software (AcquireEMG) on the Neuroscan Comperio system (Neuroscan Medical Systems, El Paso, TX). Intramuscular signals were detected using disposable concentric needle electrodes (Model 740 38-45/N; Ambu Neuroline, Baltorpbakken, Ballerup, Denmark) and amplified (Neuroscan Medical Systems, El Paso, TX) with a bandpass of 10 Hz to 10 kHz. Surface signals were detected by self-adhering 1 cm x 3 cm electrocardiogram electrodes (Harris Healthcare, Hudson, MA) and amplified (Neuroscan Medical Systems, El Paso, TX) with a bandpass of 5 Hz to 5 kHz. The same electrode configuration used to record the CMAPs was maintained.

Prior to insertion of the concentric needle, the first digit was immobilized manually by the examiner while the other digits were held in an extended position, to allow manual resistance to be applied during voluntary contractions of the APB while minimizing movement artifact. Subjects were then asked to perform an isometric maximum voluntary contraction (MVC) by pushing their thumb into the examiner's

resistance for 10 s. The root mean square (RMS) value of the EMG signal over 1 s intervals was calculated and the highest RMS value across the 10 s was determined to be their MVC. Subsequent contractions were described as a percentage of the MVC.

A concentric intramuscular electrode (Model 740 38-45/N; Ambu Neuroline, Baltorpbakken, Ballerup, Denmark) was inserted into the APB such that the tip of the electrode was located within the muscle and beneath the surface electrode. Subjects were asked to perform a low level isometric contraction for a 30 s interval while the needle and surface data were acquired with sampling rates of 31,250 and 3125 Hz respectively. With the needle in situ the subject was instructed to increase the contraction force, in an isometric fashion, until MUPs from several active motor units were detected. Data were acquired when AcquireEMG found the average peak acceleration of the individual MUPs in the EMG interference pattern was above 30 kV/s^2 [13]. If this acceleration was not attained the subject was asked to relax the muscle and the needle was then repositioned. Once a suitable needle location had been found data collection began.

Several such contractions were maintained, each for a period of 30 s. Subjects were instructed to maintain the contraction intensity as consistently as possible throughout each data acquisition period. Following each contraction the needle position was adjusted to collect from more superficial, intermediate, or deep portions of the muscle. Data collection from submaximal contractions continued until at least 30 acceptable MUPs had been detected. Five to eight contractions were required to obtain 30 or more MUP trains. The acceptability criteria are listed below.

A MUP template was calculated using median-trimmed averaging and a SMUP was estimated using spike triggered averaging [13]. To be included in subsequent

analyses, a SMUP had to be temporally aligned (within 10 ms) with its corresponding MUP and verified as a distinct waveform with respect to the RMS of the signal baseline. Markers indicating the onset, negative peak, positive peak and end of the MUP waveforms, and markers indicating the onset, negative peak onset, negative peak, positive peak, and end of the SMUP waveforms were automatically determined by the software, but were visually inspected for accuracy, and manually repositioned if incorrectly placed.

3.3.1 Acceptability Criteria of Needle and Surface Detected MUPs Used for Data Analysis

After EMG signal acquisition was complete, decomposition was accomplished using DQEMG^{TM} software whereby the surface and needle acquired data were decomposed into their constituent SMUP and MUP trains respectively. To do this, the DQEMG program identifies unique waveforms through calculating the slope and acceleration of the leading edge of the needle-detected signal. The signals sampled are therefore very dependent on the proximity of the needle tip to the active muscle fibers of a given motor unit. Firing rate information is also used for classification, since a MU usually fires at pseudo-regular intervals. If a MUP with similar slope or acceleration characteristics is identified as firing within the expected interdischarge interval after the last MUP from that bin was identified, then it is assigned to the same bin. Through slope, acceleration and firing rate information, a decision rule is used to determine whether subsequent MUPs belong to an existing bin, or should be given a new bin. Ultimately

several bins of signals with similar characteristics are created In each bin, a template for the representative MUP is created based on ensemble averaging samples in that bin.

The surface MUP signals are determined somewhat differently. These signals are identified through spike triggered averaging of the needle-detected MUPs assigned to each bin. As such, the needle-detected signal is used to trigger the recording of its corresponding surface-detected signal. The surface-detected signal morphology is therefore less dependent on the proximity of the needle to the active fibers within the motor unit.

Motor unit potential trains (MUPTs) obtained following decomposition of the needle-detected EMG data were evaluated through visual inspection during off-line analysis. Two interrelated criteria were used to determine the acceptability of a given MUPT: the variability in the instantaneous firing rate versus time plot, and the inter-discharge interval (IDI) histogram. An acceptable train had at least 50 MUPs, a consistent firing rate plot in the physiological range (8–30 Hz), as well as an IDI histogram with a Gaussian-shaped main peak and a coefficient of variation of <0.3 [12]. Any MUPTs that did not meet all of these criteria were excluded from the analysis. Finally, the decomposed MUPTs are reviewed and assessed, to confirm that the decomposition of each contraction is acceptable and the landmark positions on the MUAP templates are valid.

3.4 Outcome variables

The following outcome variables were used to assess collateral sprouting and axonal loss in the aforementioned groups.

3.4.1 MUP and SMUP Morphological Features

An average MUP and SMUP template was produced for each subject. The MUP parameters examined included peak-to-peak amplitude, duration and area. The SMUP parameters examined included peak-to-peak amplitude, duration and negative peak area.

3.4.2 Satellite Potentials

A satellite potential is a late component of the MUP, The most commonly accepted definition for the satellite potential is that it is a late spike, usually an action potential (AP) from a single muscle fiber, distinct from the main MUP spike but time-locked to it [70]. Acceptable MUPs (section 2.4.1) were visually assessed off-line for the presence of satellite potentials. Signal components were regarded as satellites if they were time-locked to the main MUP spike and occurred after the MUP terminal wave. The number of satellite potentials evident in the MUPs of each subject were counted and converted to a percentage of an individual's total number of MUPs using the equation below:

$$\%\ \ of\ \ \ Satellite\ \ \ Potentials \equiv \frac{\#\ \ of\ \ \ MUPs\ \ \ with\ \ \ Satellite\ \ \ Potentials}{Total\ \ \ Number\ \ of\ \ \ MUPs} \times 100$$

3.4.3 MUNE

MUNE techniques are used to measure the number of motor units within a given muscle. Three MUNE calculations were performed, using the following morphological feature of the attained SMUPs: peak-to-peak amplitude, negative peak amplitude and negative peak area. The MUNE calculations are described in section 2.4.2.

3.5 Statistical Analysis

Data analysis was performed using MINITAB® Statistical Software (v.15). The MUP and SMUP data were averaged for each individual to provide average MUP and SMUP morphological values (amplitude, duration, number of phases and area) for each volunteer respectively. All results were presented as a median value and their corresponding interquratile range (IQR). Significant group differences were determined using Kruskall-Wallace tests for both the results of the administered questionnaires and the attained demographic data (sex, age and MVC force). The alpha level was initially set to 0.05, but adjusted for multiple comparisons. The specific research questions were addressed as described below:

3.5.1 Is there measurable evidence of collateral sprouting in individuals with severe CTS using MUP and SMUP morphological features determined by DQEMG software?

MUP and SMUP morphological features (Refer to section 3.4.1) were compared among the three groups using Kruskall-Wallace tests. The percentage of satellite potentials was compared between the three groups as well. The α-level was adjusted to account for multiple comparisons ($\alpha = 0.05/3$) separately for MUP and SMUP data, and was therefore set at $\alpha = 0.017$ in each case. The percentage of motor unit potentials with satellite potentials were analyzed using the following α-level $\alpha = 0.05$. Post hoc analyses were performed using Mann-Whitney U tests.

3.5.2 Is there evidence of motor axonal loss in individuals with severe CTS as measured using MUNE?

MUNE were compared among the three groups using Kruskall-Wallace tests. Three MUNE calculations were performed, based on the following morphological feature of the SMUP: peak-to-peak amplitude, negative peak amplitude and negative peak area. The α-level was adjusted to account for multiple comparisons ($\alpha = 0.05/3$), and was therefore set at $\alpha = 0.017$ in each case. Post hoc analyses were performed using Mann-Whitney U tests.

Chapter 4
Results

4.1 Subjects

Twenty seven subjects volunteered to participate in the study. Two subjects were excluded after screening because of suspected radiculopathy and two others were excluded due to confounding conditions (pregnancy and rheumatoid arthritis, respectively). The nine men and fourteen women who remained were between 25-60 years of age and were stratified by severity of CTS into the following three groups: 9 healthy individuals (4 men, 5 women), 8 individuals with mild CTS (2 men, 6 women) and 6 individuals with severe CTS (3 men, 3 women). There were no differences in median age or sex between the groups (Severe CTS: 53 (IQR: 41.25-52.5) years, mild CTS: 46 (IQR: 41.25-52.5) years and control: 43 (IQR: 30-53.5) years; $p>0.05$). During the EMG data acquisition the severe CTS group contracted at a significantly higher percentage of their MVC as compared to the mild CTS and healthy groups (Severe CTS: 39.6 (IQR: 31.95-44) %MVC, mild CTS: 13.6 (IQR: 8.06-21.39) %MVC and control: 10.04 (IQR: 8.48-21.13) %MVC; $p>0.05$). The intensity, measured in pulses per second (PPS) of the contractions did not significantly differ between groups (Severe CTS: 10.52 (IQR: 1.23-12.56) PPS, mild CTS: 12.86 (IQR: 11.58-14.95) PPS and control: 12.71 (IQR: 11.45-15.5) PPS; $p>0.05$). Three MUNE calculations were performed, and based on the morphological features of the recorded CMAPs and SMUPs. Significant group differences were found for all CMAP characteristics (negative-peak amplitude, peak-to-peak amplitude and negative-peak area; $p<0.05$) as identified in Table 4-1. Post hoc

analysis revealed significant group differences between the healthy control group and both the mild and severe CTS groups for all three morphological features ($p<0.05$).

Table 4-1: Median and interquartile ranges of CMAP measures

Group	Peak-to-peak Amplitude (μV)	Negative-peak Amplitude (μV)	Negative-peak Area (μVms)
Healthy	19797 (17790-23458)*	11830 (10741-12922)*	31468 (29964-41797)*
Mild CTS	12940 (10447-14175)**	7518 (6824-8889)**	22114 (17452-28462)**
Severe CTS	10053 (8242-15437)**	6447 (4884-8311)**	21749 (15994-31206)**

*** denotes a significant difference from parameters notated with ****

4.2 Symptom Severity and Functional Deficits

Significant group differences were found for severity of symptoms scores between groups (Severe CTS: 4.0 (IQR: 3.18-4.45), mild CTS: 3.09 (IQR: 2.36-4.00), control: 1.0 (IQR: 1.00-1.05); $p<0.05$). Post hoc analysis revealed significant group differences between the healthy control group and both the mild and severe CTS groups ($p<0.05$). Similarly, significant group differences were found for the functionality scores of the questionnaire (Severe CTS: 3.4 (IQR: 2.6-4.1), mild CTS: 1.2 (IQR: 1.0-2.1), control: 1.0 (IQR: 1.0-1.2); $p<0.05$). Post hoc analysis revealed significant group differences between the severe CTS group and the healthy control groups ($p<0.05$). The results of the specific analysis related to each experimental question are presented below.

4.3 Is there measurable evidence of collateral sprouting in individuals with severe CTS using MUP and SMUP morphological features determined by DQEMG software?

The results of the MUP and SMUP morphological features that were compared between groups are listed below. Refer to Figure 4-1 for a sample of MUPT data.

4.3.1 A Comparison of MUP Morphology Between Groups

Significant group differences were found for MUP amplitude and duration ($p<0.017$) as identified in Table 4-2. Post-hoc analysis revealed that individuals in the severe CTS group demonstrated larger peak-to-peak amplitude MUPs as compared to those individuals with mild CTS and those who were healthy (Figure 4-2a; $p<0.017$).

There was no difference in peak-to-peak amplitude between those with mild CTS and healthy individuals (Figure 4-2a; $p>0.017$).

MUP durations were significantly different between the severe CTS groups as compared to the mild group such that the severe group demonstrated longer duration MUPs (Figure 4-2b; $p<0.017$). No significant difference in duration was found between the severe CTS group and the healthy group (Figure 4-2b; $p>0.017$). Similarly, no difference in MUP duration was found between mild CTS and healthy groups (Figure 4-2b; $p>0.017$). No group differences were found in the number of MUP phases between any of the three groups (Figure 4-2c; $p>0.017$).

Significant group differences were found for the percentage of total MUPs with satellite potentials (Figure 4-2d; $p<0.017$) as shown in Table 4-2. Post-hoc analysis revealed that the severe CTS group demonstrated a greater percentage of MUPs with satellite potentials as compared to the mild CTS and healthy groups, who both demonstrated no MUPs with satellite potentials (Figure 4-2d; $p<0.017$).

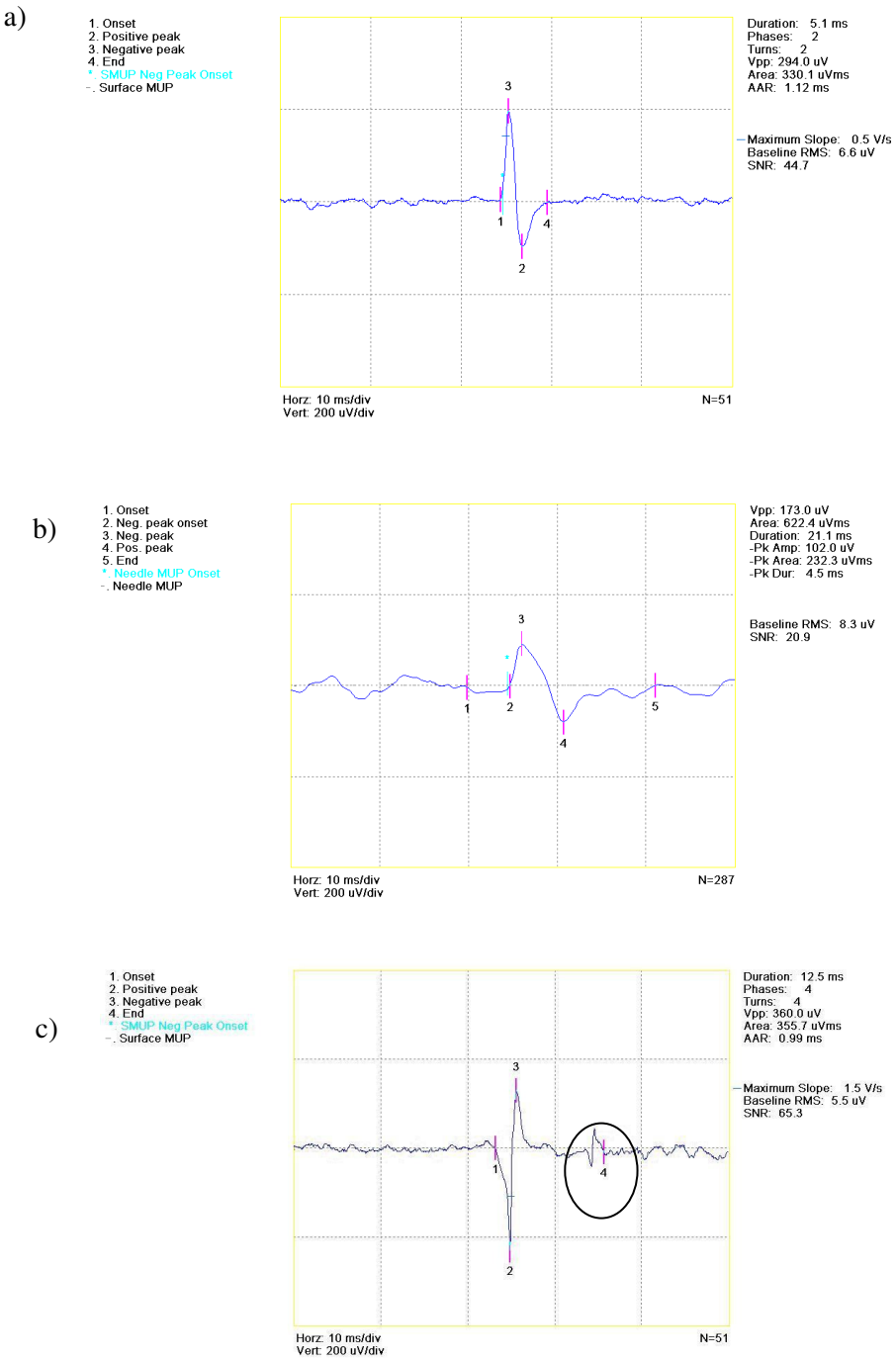

Figure 4-1: Sample MUPT data identified by the DQEMG software. (a) needle-detected MUP and the corresponding quantifiable characteristics, (b) Surface-detected MUP and the corresponding quantifiable characteristics (c) An example of a MUP with a satellite potential. The satellite potential is circled and occurs approximately 10 ms after the main MUP. Calibrations for all panels: 10 ms/div and 200 µV/div

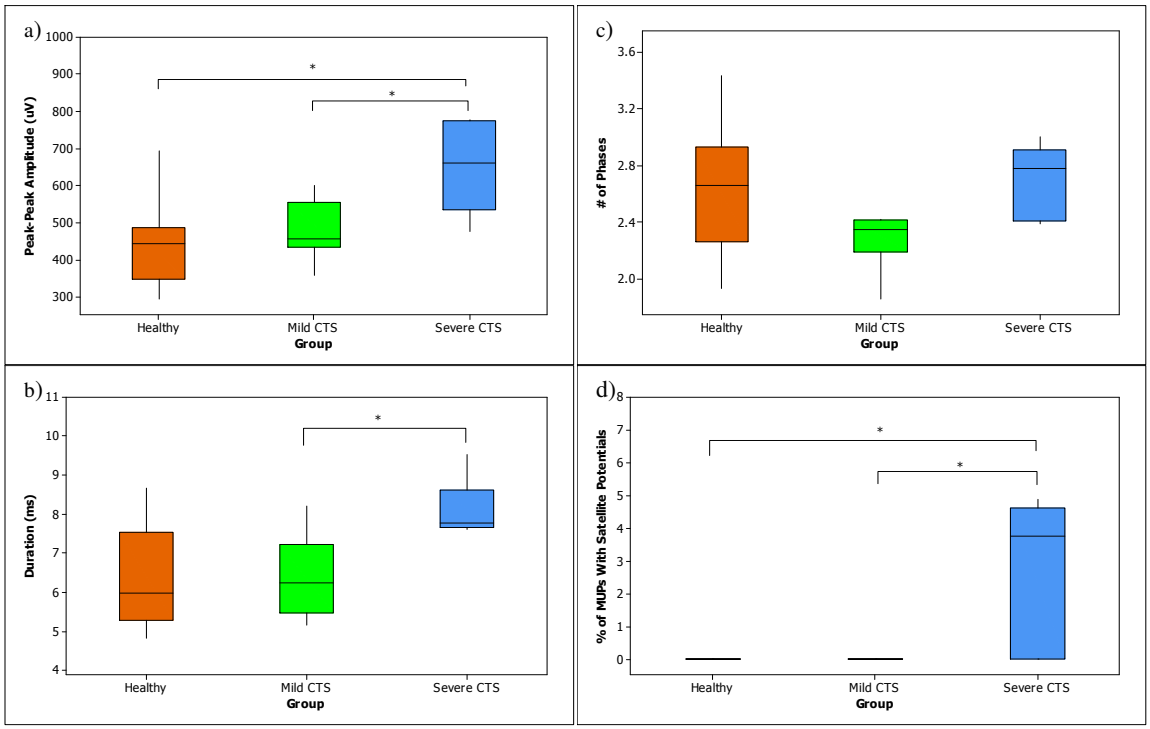

Figure 4-2: Box plots for MUP parameters (a) MUP amplitude, (b) MUP duration, (c) number of MUP phases, and (d) percentage of MUPs with satellite potentials for low-to-mid level contractions of the APB muscle. The boxes represent the interquratile range with the bar within each box representing the median value. The whiskers extend to the maximum and minimum data points within 1.5 box heights from the top and bottom of the box respectively (* denotes significant differences between groups)

4.3.2 A comparison of SMUP morphology between groups

The Kruskall-Wallace tests failed to reveal any significant differences between groups for any SMUP parameters (amplitude, area, duration) ($p>0.017$) as identified in Table 4-2 and Figure 4-3.

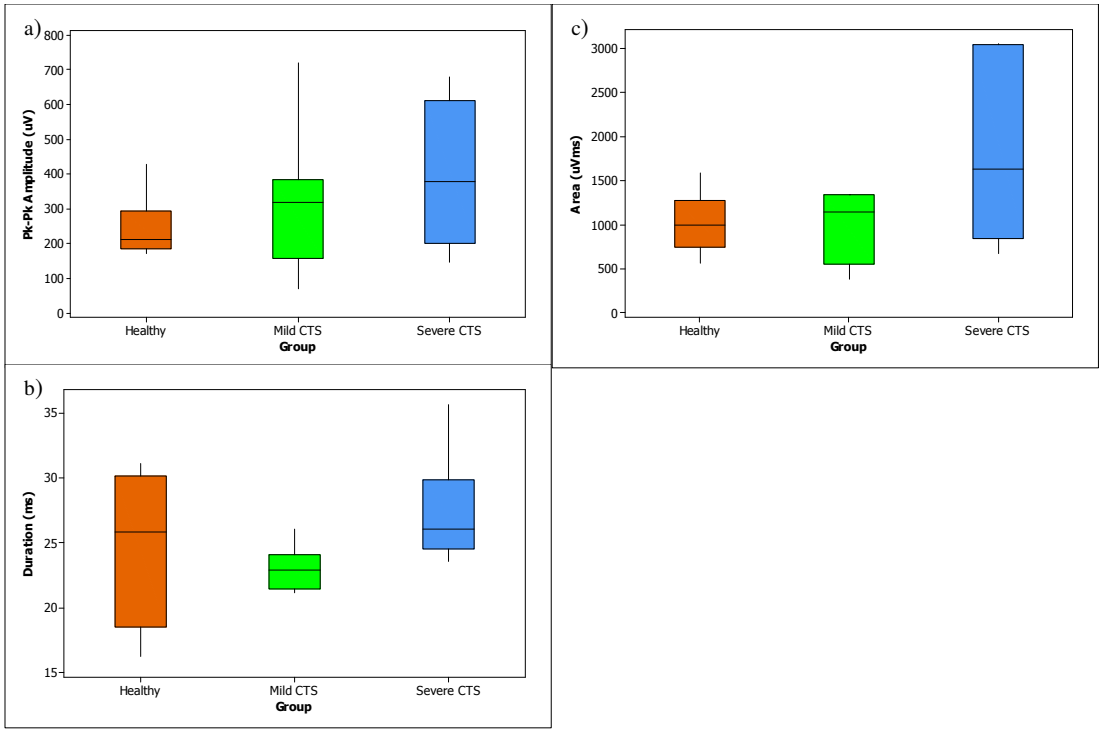

Figure 4-3: Box plots for SMUP parameters (a) SMUP amplitude, (b) SMUP duration, (c) SMUP area detected using the spike triggered average technique for low-to-mid level contractions of the APB muscle. The boxes represent the interquratile range with the bar within each box representing the median value. The whiskers extend to the maximum and minimum data points within 1.5 box heights from the top and bottom of the box respectively (* denotes significant differences between groups)

Table 4-2: Median and interquartile ranges MUP and SMUP measures

Group	Needle-detected MUPs				Surface-detected MUPs		
	% Satellite Potentials	Amplitude (μV)	Duration (ms)	No. of Phases	Amplitude (mV)	Area (mVms)	Duration (ms)
Control	0 (0-0)**	442 (384-487)**	5.9 (5.3-7.5)	2.7 (2.3-2.9)	211 (184-294)	993 (746-1279)	25.9 (18.5-30.1)
Mild CTS	0 (0-0)**	457 (433-554)**	6.2 (5.5-7.2)**	2.3 (2.2-2.4)	319 (156-383)	1140 (551-1337)	22.9 (21.5-24.0)
Severe CTS	3.8 (1.2-4.6)*	661 (540-774)*	7.9 (7.7-8.6)*	2.7 (2.4-2.9)	379 (200-610)	1626 (837-3048)	26.1 (24.5-29.9)

*** denotes a significant difference from parameters notated with ****

4.4 Is there evidence of motor axonal loss in individuals with severe CTS as measured using MUNE?

Three MUNE calculations were performed, based on the following morphological feature of the SMUP: peak-to-peak amplitude, negative peak amplitude and negative peak area. The results are summarized in Table 4-3. Significant group differences were found for MUNEs calculated using amplitude measures (i.e. peak-to-peak amplitude and negative peak amplitude) (Figure 4-4; $p<0.017$). Post-hoc analysis revealed that the severe CTS group demonstrated lower MUNEs as compared to the healthy group (Figure 4-4a; $p<0.017$). Similar to the MUNE computed using peak-to-peak amplitude, post-hoc analysis revealed that the severe CTS group demonstrated lower MUNEs computed using negative peak amplitude as compared to the healthy control group (Figure 4-4b; $p<0.017$). No group differences were found for MUNEs calculated using negative peak area (Figure 4-4c; $p>0.017$).The mild CTS group MUNE values fell between the control group and the severe CTS group but was not statistically different from either group for any of the MUNE calculations.

Table 4-3: Median and interquartile ranges of MUNE measures

Group	Pk-Pk MUNE	Neg Pk MUNE	Area MUNE
Control	147 (110-199)**	138 (102.5-166)**	131 (109.5-167)
Mild CTS	77 (70-138)	73 (68.3-102)	76.0 (64.5-160.3)
Severe CTS	53 (23-85)*	47.5 (19.8-76.3)*	49.5 (24.5-106.3)

*** denotes a significant difference from parameters notated with ****

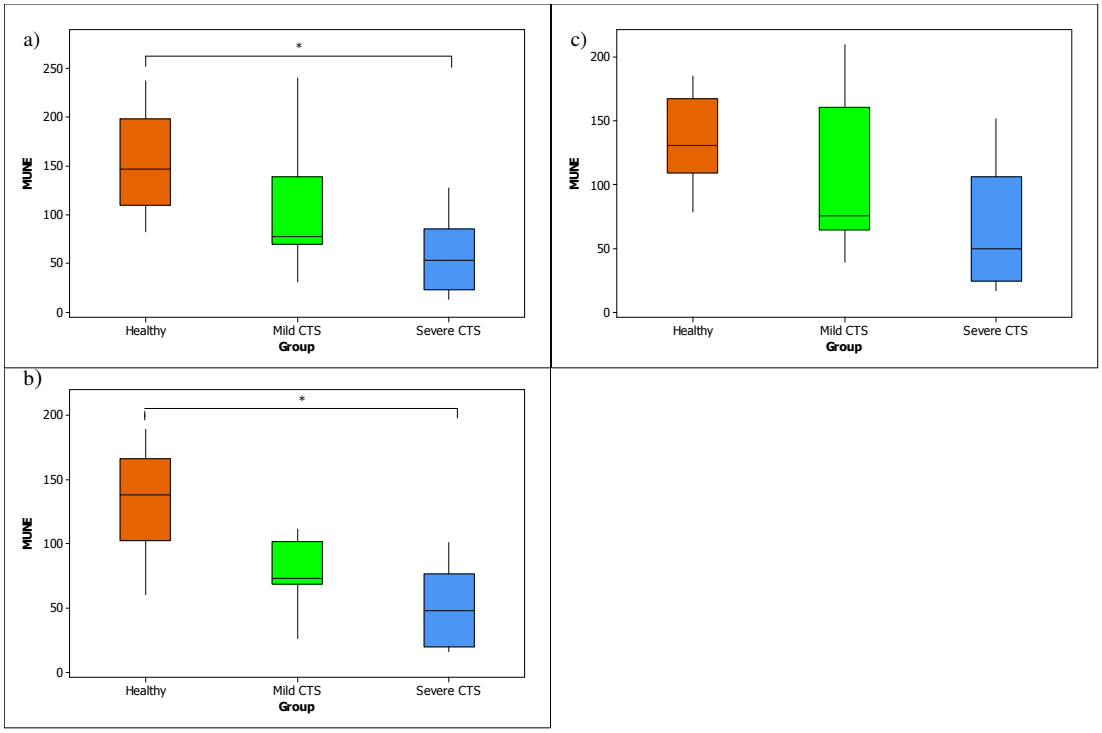

Figure 4-4: Box plots of MUNE values (a) peak-to-peak amplitude MUNE, (b) negative peak amplitude MUNE, and (c) area MUNE calculated using the spike triggered average technique for low-to-mid level contractions of the APB muscle. The boxes represent the interquratile range with the bar within each box representing the median value. The whiskers extend to the maximum and minimum data points within 1.5 box heights from the top and bottom of the box respectively (* denotes significant differences between groups)

Chapter 5
Summary and Discussion

5.1 Synopsis

The purpose of the study was to use DQEMG as a means of obtaining electrophysiological data that are representative of the pathophysiology associated with motor deficits in CTS. Measurable evidence of collateral sprouting was assessed using MUP and SMUP morphological features. Evidence of axonal loss was measured using MUNE measures. The results indicate that the subjects with severe CTS demonstrate measurable evidence of collateral sprouting and MU loss.

5.2 Is there measurable evidence of collateral sprouting in individuals with severe CTS using MUP and SMUP morphological features determined by DQEMG software?

Shape characteristics of MUPs provide insight into the underlying pathophysiology of neuromuscular diseases [10, 79]. For example, in individuals with neuropathy, classic EMG findings include MUPs with increased durations and amplitudes due to collateral reinnervation [10]. In this case the number of turns and phases may either be normal or increased [10]. The most common type of reinnervation is that occurring after partial nerve lesions, which takes place by collateral sprouting. Early in the collateral sprouting process, MUPs are either normal in size or larger than normal. In this stage, the action potential from the newly innervated muscle fibers usually occur late in the MUP waveform, as satellite potentials. They occur late due to a reduced

action potential propagation velocity caused by muscle fiber atrophy and the initially small, thin and poorly myelinated axonal twigs which innervate the muscle fibers [10]. At later stages of reinnervation, the individual spike components become more stable, with long duration and high amplitude [10]. The stability occurs as a result of the electrical contribution of recruited muscle fibers becoming incorporated into the parent motor unit [10], which occurs when the muscle fiber properties become similar to those of the parent motor unit and when the axonal sprout matures.

The observed MUP morphological differences between the severe CTS group as compared to the mild CTS and healthy groups suggests that the orphaned muscle fibers in individuals with severe CTS undergo collateral sprouting. In the current study, peak-to-peak amplitudes, which are thought to be representative of motor unit size [80], were significantly larger in individuals in the severe CTS group as compared to the mild CTS and healthy groups.

The larger peak-to-peak amplitudes may be due to the reorganization of motor units via collateral sprouting. It should be noted, however, a variety of factors influence amplitude including: electrode type, electrode location and contraction level [15, 81, 82]. Comparing the MUP amplitude values between studies can be difficult because the characteristics of the detected MUP are dependent on the electrodes used, aned the level and type of contraction. Although differences in needle-detected MUP amplitudes between groups were found in the current study, Nelson et al. [81] compared MUP characteristics and hand dominance using monopolar needle electrodes in the APB and abductor digiti minimi muscles. The median amplitude values of the healthy group of the

present study was considerably lower than those observed by Nelson et al. [81]. For example, median APB concentric needle-detected MUP amplitude of the healthy group in the current study 442 μV was far less than that reported for the APB of Nelson's healthy subjects 911.8 μV using a monopolar needle [81]. The contrast in the amplitudes recorded between the two studies is largely due to the difference in recording apparatus used. Monopolar needle electrodes record MUPs with larger amplitudes because the potentials seen by the needle tip are referenced to those seen by a surface electrode located at a point remote from the active motor units. Concentric needle electrodes reference the potentials seen by the needle tip to those seen by the needle cannula, and therefore these potentials have more cancellation of potential amplitude as compared monopolar recordings.

Both surface-recorded and needle-recorded MUP duration is thought to be influenced by motor unit size [80], however needle-detected MUP durations are also heavily dependent on the distance of the active motor unit to the recording electrode. In the current study, the severe CTS group had significantly longer MUP durations as compared the mild CTS group, yet the MUP duration values of the mild CTS group were not different from those of the healthy control group (Figure 4-1b). A significant difference in MUP duration between the severe CTS group and healthy individuals was expected but was not observed. This might have been related to the high amount of variability inherent in the MUP duration measures. The MUP duration is defined by the initial and terminal phases of the MUP signal. The DQEMG^{TM} program automatically places the markers at the signal onset and at the end of the signal. The marker locations

are then validated by the researcher and, in cases where there is a discrepancy between marker locations determined automatically and those that the researcher deems appropriate, the marker location is moved. Determining the terminal point of the MUP is not always obvious, and such, researchers have found , lower reliably in determining MUP onset and end markers [70, 83-85] as compared to the reliability in determining the peaks [84-86]. Calder et al. [86] recently examined the reliability of MUP morphological features and concluded that the within-subject reliability of both MUP duration (ICC: -0.29) and the number of phases (ICC: -0.69) were unreliable in the investigation of healthy populations. Thus, MUP duration may not an accurately depiction of the underlying pathophysiology associated with the motor deficits seen with CTS.

The results of the current study offer no evidence that the needle-detected MUPs recorded from severe CTS patients have a larger number of phases than those of healthy subjects and individuals with mild CTS. As mentioned above, this may be related to the lower reliability in MUP complexity measures [84-86]. It appears that the pathology of an underlying neuromuscular condition is not reflected in the number of phases of MUPs. Also using DQEMG, Boe et al. [87] failed to find a difference in complexity between healthy individuals and those with the neurogenic condition ALS.

To our knowledge, this is the first investigation that used QEMG to quantify and examine MUP satellite potentials in individuals with CTS. The results of the present study showed that the severe CTS group had a larger percentage of MUPs with satellite potentials as compared to both the mild CTS and healthy groups.

Satellite potentials are seen in both neuropathies and myopathies [88, 89]. The proposed explanations for the occurrence of satellite potentials involve pathological mechanisms leading to an increased action potential propagation time along regenerating axons and their branches and/or along atrophic muscle fibers. The causes of increased action potential propagation time may include: the existence of extremely long and/or slender collateral axon sprouts, aberrant endplate positions because of collateral reinnervation, immature endplates with slow neuromuscular transmission; and small diameter muscle fibers resulting from atrophy. Collateral sprouts may in some instances even innervate two different muscles [90]. The observed late potentials in neuropathies could in some cases be due to the unusual separation of the end-plates within the motor unit. Regardless of the mechanism, satellite potentials appear to reflect an immature reinnervation process.

The sum of the MUP results obtained using DQEMG, suggest that individuals with severe CTS undergo continual collateral sprouting, most likely in an attempt to compensate for axonal loss. Although the percentage of satellite potentials was small relative to the number MUPs detected, a significant difference was detected among groups. This difference suggests that satellite potentials may have some diagnostic value however, further research is required to determine the validity and reliability of satellite potentials as a measure of collateral sprouting,

Although MUP morphological characteristics offer insight into the size of the motor units, they are influenced by the limitations of the needle electrode used to detect them [80]. Estimating motor unit size and shape using surface EMG electrodes is thought

to be a more accurate representation, as there is a greater number of muscle fibers per motor unit contributing to the EMG signal [91, 92]. Despite the absence of significant differences among the groups, the median values of the SMUP characteristics found in this work reflects similar processes as seen in the concentric needle-detected MUP data This finding is particularly evident in Figure 4-3, which shows the trend towards SMUPs with larger amplitudes and areas in patients with severe CTS. The lack of statistical significance seen in the SMUP parameters can attributed to the large within-group variability and perhaps a larger sample may have produced significant differences between groups.

Overall, DQEMG appears sensitive enough to determine relative MUP characteristic differences between groups of differing CTS severities. The needle- and surface-detected MUP morphological features suggest that individuals with severe CTS undergo collateral sprouting. Collateral sprouting occurs secondary to motor axon loss as a compensatory effect, which was investigated by the second research question discussed below.

5.3 Is there evidence of motor axonal loss in individuals with severe CTS as measured using MUNE?

MUNEs provide information related to the number of functioning motor axons in a given motor unit pool [74, 75, 93, 94]. This information is useful when evaluating the extent of motor unit loss associated with motor neuron disease or peripheral neuropathy and when assessing the course and outcome of treatment for these disorders [75, 87, 95]. In fact, decomposition based spike triggered averaging, specifically using DQEMG, has

been found to be a valid, reliable and practical tool for obtaining a MUNE [11]. Boe et al. [11] have established normative MUNEs values determined using SMUP negative-peak amplitude (177 +/- 98 μV) and area (269+/- 104 μVms) for APB muscle. The median MUNE values of the healthy group in the current study falls within the typical range observed for this muscle [11]. For example, the median MUNE calculated using negative-peak amplitude in the current study (Refer to Table 4-3) is within one standard deviation of that reported in healthy subjects by Boe et al. [11].

The results of this study indicate that there were significant differences between the severe CTS and healthy groups for the MUNE measures derived from the peak-to-peak, and negative peak amplitudes of the CMAPs and the average SMUP.. This result suggests that individuals with severe CTS have undergone extensive axonal loss relative to the healthy group. The lack of difference exhibited between the mild CTS group and either the severe CTS group or the healthy group supports the hypothesis that individuals within the mild CTS group had some motor deficits, most likely caused by demyelination, as it typically occurs first in compressive neuropathies [96].

MUNEs calculated based on amplitude characteristics are limited in that they disregard temporal dispersion, which may offer insight in the synchronicity of muscle fiber action potentials. The MUNEs calculated using the area measure take temporal dispersion into account. That said, the results of this study showed no significant differences between the groups when MUNEs were calculated using area measures but differences seen when amplitude measures were used. Regardless of the morphological feature used to calculate the MUNEs, all three methods followed a similar trend whereby

lower MUNEs were estimated in the severe CTS group (Table 4-3). The median MUNE values calculated using SMUP area were of similar magnitude to those calculated using amplitude measures (Table 4-3) however there was large variability associated with the MUNEs calculated based on the SMUP area measure, as is illustrated in Figure 4-4c. The small sample size may have limited the statistical power to detect differences between groups with this high variance.

The MUNEs were calculated using both CMAP and SMUP morphological characteristics. SMUP morphological features failed to find significant differences among groups (Table 4-3), however, significant differences were found for CMAP morphological features between the healthy group and both the mild and severe CTS groups (Table 4-1). This finding suggests that MUNE calculations were highly influenced by CMAP amplitude. Unlike other neuropathic conditions, such as ALS, where the neuropathy is known to be demyelinating in nature, nerve compression injuries can cause conduction block through both demyelination and axonal loss, both of which can affect the shape characteristics of a CMAP, making it difficult to determine which pathology is most responsible for the observed changes to a CMAP. Despite uncertainty as to the underlying cause, the results of the MUNE calculations suggest that the amplitude based measures are sensitive enough to detect differences in the number of healthy or functioning motor units in a given muscle, and determined lower MU numbers in the severe CTS group.

5.4 Experimental Considerations

5.4.1 Subjects

Subject recruitment for this study proved to be very difficult despite the high incidence of CTS. The recruitment efforts were limited particularly by the exclusion criteria that required individuals between the ages of 18-60 and to have no other confounding pathology. Consequently, the number of subjects who participated in each group was smaller than originally planned, however, the subject numbers are consistent with other published literature. Greening et al. found differences in longitudinal nerve movement when only seven control subjects were compared to eight subjects with non-specific arm pain group (wrist flexor group)[14] and Boe et al.[24] found differences in motor unit number estimates (MUNE) comparing only 10 healthy subjects to 9 patients with amyotrophic lateral sclerosis (ALS). Nonetheless, using non-parametric analysis the data collected had sufficient statistical power to detect differences in many of the measures studied.

Although age and sex were not significantly different between groups, ideally subjects would have been matched by age and sex. The small number of subjects recruited in each group prevented subject matching by age and sex. The results from this study cannot be generalized to individuals who are outside of the specified age range or those with conditions which would cause CTS as a secondary pathology.

5.4.2 The use of Maximum Voluntary Contractions to estimate contraction effort during EMG data acquisition

The needle evaluation consisted of individuals contracting their APB muscles at low levels of their MVC while the needle was in situ. For the individuals in the healthy and mild CTS groups this was not problematic. For most individuals in the severe CTS group the contractions needed to produce data of adequate quality (section 3.4.1) were at a much higher percentage of their MVC as compared to the other two groups. It can be argued that contracting at a higher level (%MVC) activated larger motor units [15, 97]. The size principle, as described by Henneman et al. [97] dictates the recruitment order: the smaller fatigue-resistant slow twitch motor units are recruited before the larger fast twitch fatigable motor units. The differences in contraction levels were not surprising since individuals with severe CTS are thought to have axonal loss due to prolonged compression [19, 52] and thus, they could generally generate lower MVCs. Boe et al. [87] found that those individuals with amytrophic lateral sclerosis (ALS), a degenerative motor neuron disease, generated lower MVCs as compared to healthy individuals [87]. Similar to the study by Boe et al. [87], intensity was used to properly assess whether or not the three test groups activated a similar number of motor units during the isometric contractions. The intensity of the contractions signifies the number of pulses per second viewed by DQEMG. The intensity was found to be similar among the three groups ($p>0.05$), which suggest that similar numbers of motor units were active during data collection.

5.4.3 Nerve Conduction Studies

Nerve conduction studies (NCS) were used to stratify individuals by severity of CTS. A wide variety of NCS techniques exist and, although the specificities of the techniques are high and comparable, their sensitivities have been noted to be variable [98]. In fact, the literature suggests that the sensitivities of the motor and mixed NCS are particularly lower than those of sensory NCS [98, 99]. Jablecki et al. reported the pooled sensitivities and specificities of a variety of NCS techniques from studies that met a predefined set of quality assurance criteria [98]. The comparison of the median and ulnar sensory conduction between wrist and ring finger proved to be the most sensitive diagnostic test, with a lower pooled sensitivity of 0.85[98]. By contrast, comparisons of median and ulnar mixed nerve conductions between the wrist and palm and motor conduction studies of median nerve across the wrist were reported to have pooled sensitivities of 0.71 and 0.63, respectively [98]. Significant differences were found for the CMAP characteristics between the healthy group and both the mild and severe CTS groups. The CMAP characteristics may be responsible for the significant differences among the groups with respect to MUNE calculations. Furthermore, the analysis of the CMAP morphological features failed to find significant differences between the mild and severe CTS groups which support the hypothesis that individuals in the current study with mild CTS had undetected motor deficits and those individuals with severe CTS may not have been truly severe. That said, the methods used for stratification were selected because they were the best methodology available, and by excluding individuals with evidence of moderate CTS, we attempted to create a clear separation among groups.

5.4.4 Questionnaire and Physical Examination

The clinical outcome measures revealed that there were similar severity of symptoms scores between the severe CTS group and mild CTS group as compared to the healthy control group. The severe CTS group had significantly reduced functional scores compared to the healthy control group however, the mild CTS group were not significantly different from either the severe CTS group or the healthy control group. The median symptom severity and functional scores of the severe and mild CTS groups (section 4.1) were within one standard deviation of the mean values of the preoperative CTS group (Symptom severity: 3.4 ± 0.67; Functional scores: 3.0 ± 0.93) recorded by Levine et al [9]. The questionnaire was developed for use with a heterogeneous population and was intended for use in tracking symptom and functional changes following intervention [9]. That said, the symptom severity and functional scores showed similar trends to much of the electrophysiological data presented in this work, where the mild CTS scores were between those of the control group and those of the severe CTS group.

5.5 Conclusions

The purpose of this study was to gain a better understanding of the pathological mechanisms associated with motor nerve dysfunction in compressive neuropathies and determine to the feasibility of using DQEMG in such research.

The MUNEs computed in this study suggest that individuals with severe CTS experience a loss of functioning motor units. The significantly larger MUP amplitudes and the presence of satellite potentials in individuals with severe CTS suggest that

orphaned muscle fibers in individuals with severe CTS undergo collateral reinnervation. The lower MUNEs in the mild CTS group suggest they are experiencing the initial signs of motor deficits likely caused by demyelination as it typically occurs prior to axonal loss. It appears MUNEs may be a sensitive measure to estimate the number of functioning motor units within a given muscle. That said, the CMAP characteristics found similar differences to the MUNEs among groups, which suggest that it may provide similar information as MUNEs however, CMAPs are far less invasive. These results support the use of DQEMG in future studies of compression neuropathy as an effective means to document the severity of motor deficits.

Bibliography

1. Atroshi, I., et al., *Prevalence of carpal tunnel syndrome in a general population.* JAMA, 1999. **282**(2): p. 153-8.
2. de Krom, M.C., et al., *Carpal tunnel syndrome: prevalence in the general population.* J Clin Epidemiol, 1992. **45**(4): p. 373-6.
3. Gelberman, R.H., et al., *The carpal tunnel syndrome. A study of carpal canal pressures.* J Bone Joint Surg Am, 1981. **63**(3): p. 380-3.
4. Spinner, R.J., J.W. Bachman, and P.C. Amadio, *The many faces of carpal tunnel syndrome.* Mayo Clin Proc, 1989. **64**(7): p. 829-36.
5. Armstrong, T.J., et al., *Some histological changes in carpal tunnel contents and their biomechanical implications.* J Occup Med, 1984. **26**(3): p. 197-201.
6. Phalen, G.S., *The carpal-tunnel syndrome. Seventeen years' experience in diagnosis and treatment of six hundred fifty-four hands.* J Bone Joint Surg Am, 1966. **48**(2): p. 211-28.
7. Stevens, J.C., *AAEM minimonograph #26: the electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine.* Muscle Nerve, 1997. **20**(12): p. 1477-86.
8. Tinel, J., *Le signe du fourmillement dans les lesion des nerfs peripheriques.* La Presse Medicale, 1915. **23**(47): p. 388-89.
9. Levine, D.W., et al., *A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome.* J Bone Joint Surg Am, 1993. **75**(11): p. 1585-92.
10. Stalberg, E., et al., *Quantitative motor unit potential analysis.* J Clin Neurophysiol, 1996. **13**(5): p. 401-22.
11. Boe, S.G., D.W. Stashuk, and T.J. Doherty, *Motor unit number estimation by decomposition-enhanced spike-triggered averaging: control data, test-retest reliability, and contractile level effects.* Muscle Nerve, 2004. **29**(5): p. 693-9.
12. Stashuk, D.W., *Decomposition and quantitative analysis of clinical electromyographic signals.* Med Eng Phys, 1999. **21**(6-7): p. 389-404.
13. Stashuk, D., *EMG signal decomposition: how can it be accomplished and used?* J Electromyogr Kinesiol, 2001. **11**(3): p. 151-73.
14. Doherty, T.J. and D.W. Stashuk, *Decomposition-based quantitative electromyography: methods and initial normative data in five muscles.* Muscle Nerve, 2003. **28**(2): p. 204-11.
15. Boe, S.G., et al., *Decomposition-based quantitative electromyography: effect of force on motor unit potentials and motor unit number estimates.* Muscle Nerve, 2005. **31**(3): p. 365-73.
16. Atroshi, I., et al., *Symptoms, disability, and quality of life in patients with carpal tunnel syndrome.* J Hand Surg [Am], 1999. **24**(2): p. 398-404.
17. Netter, F., *Atlas of the human body*. 2003, CIBA-GEIGY Corp: Summit, N.J. p. 455-66.
18. Gray, H., *Gray's Anatomy: The Anatomical Basis of Clinical Practice*, S. Standring, Editor. 2005, Elsevier Churchill Livingstone: New York, NY. p. 847-87.
19. Sunderland, S., *The nerve lesion in the carpal tunnel syndrome.* J Neurol Neurosurg Psychiatry, 1976. **39**(7): p. 615-26.

20. Whitwam, J.G., *Classification of peripheral nerve fibres. An historical perspective.* Anaesthesia, 1976. **31**(4): p. 494-503.
21. Gray, H., *Gray's Anatomy: The Anatomical Basis of Clincial Practice*, S. Standring, Editor. 2005, Elsevier Churchill Livingstone: New York, NY. p. 43-50.
22. Sunderland, S., *Nerves and Nerve Injuries*. 1978, Churchill Livingstone: New York, NY. p. 69-98.
23. Lundborg, G., *Structure and function of the intraneural microvessels as related to trauma, edema formation, and nerve function.* J Bone Joint Surg Am, 1975. **57**(7): p. 938-48.
24. Burke, R.E., *Motor units: anatomy physiology, and functional organization.*, in *Handbook of physiology. The Nervous System.* 1981, American Physiological Society: Bethesda, Md. p. 345-422.
25. Hille, B., *Ion Channels of Excitable Membranes*. 1992, Sinauer Associates: Sunderland, MA. p. 63-80.
26. Preston, D.C. and B.E. Shapiro, *Electromyography and Neuromuscular Disorders*. 2005, Elsevier Butterworth Heinmann: Philadelphia, PA. p. 117-42.
27. Silverthorn, D.U., *Human Physiology: An Integrated Approach*. 2004, Pearson Benjamin Cummings: San Francisco, CA. p. 240-75.
28. Bellemare, F., et al., *Motor-unit discharge rates in maximal voluntary contractions of three human muscles.* J Neurophysiol, 1983. **50**(6): p. 1380-92.
29. Kukulka, C.G. and H.P. Clamann, *Comparison of the recruitment and discharge properties of motor units in human brachial biceps and adductor pollicis during isometric contractions.* Brain Res, 1981. **219**(1): p. 45-55.
30. McArdle, J.J., *Overview of the Physiology of the Neuromuscular Junction*, in *The Neuromuscular Junction*, R.A. Brumback and J. Gerst, Editors. 1984, Futura: Mount Kisco, NY. p. 65-102.
31. Padua, L., et al., *Carpal tunnel syndrome in pregnancy: Multiperspective follow-up of untreated cases.* Neurology, 2002. **59**(10): p. 1643-6.
32. Solomon, D.H., et al., *Nonoccupational risk factors for carpal tunnel syndrome.* J Gen Intern Med, 1999. **14**(5): p. 310-4.
33. Schwarz, A., et al., *Carpal tunnel syndrome: a major complication in long-term hemodialysis patients.* Clin Nephrol, 1984. **22**(3): p. 133-7.
34. Lee, D.J., J. Fechter, and S.B. Schnall, *Old displaced fracture of the scaphoid. An unusual cause of carpal tunnel syndrome.* Orthop Rev, 1993. **22**(7): p. 842-4.
35. Werner, R., et al., *Intracarpal canal pressures: the role of finger, hand, wrist and forearm position.* Clin Biomech, 1997. **12**(1): p. 44-51.
36. Tanaka, S., et al., *The US prevalence of self-reported carpal tunnel syndrome: 1988 National Health Interview Survey data.* Am J Public Health, 1994. **84**(11): p. 1846-8.
37. Bernard, B.P., *Musculoskeletal disorders and workplace factors: A critical review of epidemiological evidence for work-related musculoskeletal disorders of the neck, upper extremity and low back.* 1997, National Institue for Occupational Safety and Health. p. 97-141.
38. *Workplace Safety and Insurance Board Statistical Supplement 2005*. [cited.
39. Burnett, M.G. and E.L. Zager, *Pathophysiology of peripheral nerve injury: a brief review.* Neurosurg Focus, 2004. **16**(5): p. E1.
40. Lundborg, G. and L.B. Dahlin, *The pathophysiology of nerve compression.* Hand Clin, 1992. **8**(2): p. 215-27.

41. Sugimoto, H., N. Miyaji, and T. Ohsawa, *Carpal tunnel syndrome: evaluation of median nerve circulation with dynamic contrast-enhanced MR imaging.* Radiology, 1994. **190**(2): p. 459-66.
42. Lundborg, G., et al., *Median nerve compression in the carpal tunnel--functional response to experimentally induced controlled pressure.* J Hand Surg [Am], 1982. **7**(3): p. 252-9.
43. Gelberman, R.H., et al., *Carpal tunnel syndrome. A scientific basis for clinical care.* Orthop Clin North Am, 1988. **19**(1): p. 115-24.
44. Lundborg, G., *Ischemic nerve injury. Experimental studies on intraneural microvascular pathophysiology and nerve function in a limb subjected to temporary circulatory arrest.* Scand J Plast Reconstr Surg Suppl, 1970. **6**: p. 3-113.
45. Rydevik, B., G. Lundborg, and U. Bagge, *Effects of graded compression on intraneural blood blow. An in vivo study on rabbit tibial nerve.* J Hand Surg [Am], 1981. **6**(1): p. 3-12.
46. Dahlin, L.B. and G. Lundborg, *The neurone and its response to peripheral nerve compression.* J Hand Surg [Br], 1990. **15**(1): p. 5-10.
47. Lundborg, G., R. Myers, and H. Powell, *Nerve compression injury and increased endoneurial fluid pressure: a "miniature compartment syndrome".* J Neurol Neurosurg Psychiatry, 1983. **46**(12): p. 1119-24.
48. Lundborg, G. and L.B. Dahlin, *Anatomy, function, and pathophysiology of peripheral nerves and nerve compression.* Hand Clin, 1996. **12**(2): p. 185-93.
49. Ochoa, J. and L. Marotte, *The nature of the nerve lesion caused by chronic entrapment in the guinea-pig.* J Neurol Sci, 1973. **19**(4): p. 491-5.
50. Gilliatt, R.W., *Chronic nerve compression and entrapment*, in *The physiology of peripheral nerve disease*, A.J. Sumner, Editor. 1980, Saunders: Philadelphia, PA. p. 316–39
51. Ochoa, J., T.J. Fowler, and R.W. Gilliatt, *Anatomical changes in peripheral nerves compressed by a pneumatic tourniquet.* J Anat, 1972. **113**(Pt 3): p. 433-55.
52. Sunderland, S., *Nerves and Nerve Injuries*. 1978, Churchill Livingstone: New York, NY. p. 69-98.
53. Rosenbaum, R.B. and J. Ochoa, *Carpal Tunnel Syndrome and other disorders of the median nerve*. 2002, Elsevier Butterworth Heinemann: Woburn, MA. p. 193-212.
54. Gilliatt, R.W., *Acute compression block*, in *The physiology of peripheral nerve disease*, A.J. Sumner, Editor. 1980, Saunders: Philadelphia, PA. p. 287-315.
55. Powell, H.C. and R.R. Myers, *Pathology of experimental nerve compression.* Lab Invest, 1986. **55**(1): p. 91-100.
56. Mackinnon, S.E., et al., *Chronic human nerve compression--a histological assessment.* Neuropathol Appl Neurobiol, 1986. **12**(6): p. 547-65.
57. Miller, R.G., *AAEE minimonograph #28: injury to peripheral motor nerves.* Muscle Nerve, 1987. **10**(8): p. 698-710.
58. Gilliatt, R.W. and R.H. Westgaard, *Nerve--muscle interactions: some clinical aspects.* Electroencephalogr Clin Neurophysiol Suppl, 1978(34): p. 547-53.
59. Engel, A.G. and H.H. Stonnington, *Trophic functions of the neuron. II. Denervation and regulation of muscle. Morphological effects of denervation of muscle. A quantitative ultrastructural study.* Ann N Y Acad Sci, 1974. **228**(0): p. 68-88.
60. Geere, J., et al., *Power grip, pinch grip, manual muscle testing or thenar atrophy - which should be assessed as a motor outcome after carpal tunnel decompression? A systematic review.* BMC Musculoskelet Disord, 2007. **8**: p. 114.
61. Gerr, F. and R. Letz, *The sensitivity and specificity of tests for carpal tunnel syndrome vary with the comparison subjects.* J Hand Surg [Br], 1998. **23**(2): p. 151-5.

62. Jablecki, C.K., et al., *Literature review of the usefulness of nerve conduction studies and electromyography for the evaluation of patients with carpal tunnel syndrome. AAEM Quality Assurance Committee.* Muscle Nerve, 1993. **16**(12): p. 1392-414.
63. Wainner, R.S. and H. Gill, *Diagnosis and nonoperative management of cervical radiculopathy.* J Orthop Sports Phys Ther, 2000. **30**(12): p. 728-44.
64. Honet, J.C. and M.R. Ellenberg, *What you always wanted to know about the history and physical examination of neck pain but were afraid to ask.* Phys Med Rehabil Clin N Am, 2003. **14**(3): p. 473-91.
65. Spurling, R.G. and S. W.B., *Lateral rupture of the cervical intervertebral discs: a common cause of shoulder arm pain.* Surgery, Gynaecology and Obstetrics, 1944. **78**: p. 350-8.
66. Hilburn, J.W., *General principles and use of electrodiagnostic studies in carpal and cubital tunnel syndromes. With special, attention to pitfalls and interpretation.* Hand Clin, 1996. **12**(2): p. 205-21.
67. Stetson, D.S., et al., *Effects of age, sex, and anthropometric factors on nerve conduction measures.* Muscle Nerve, 1992. **15**(10): p. 1095-104.
68. Goddard, D.H., et al., *Measurement of nerve conduction--a comparison of orthodromic and antidromic methods.* Clin Rheumatol, 1983. **2**(2): p. 169-74.
69. Mills, K.R., *Orthodromic sensory action potentials from palmar stimulation in the diagnosis of carpal tunnel syndrome.* J Neurol Neurosurg Psychiatry, 1985. **48**(3): p. 250-5.
70. Stalberg, E., et al., *Quantitative analysis of individual motor unit potentials: a proposition for standardized terminology and criteria for measurement.* J Clin Neurophysiol, 1986. **3**(4): p. 313-48.
71. Dorfman, L.J., *Quantitative clinical electrophysiology in the evaluation of nerve injury and regeneration.* Muscle Nerve, 1990. **13**(9): p. 822-8.
72. Erminio, F., F. Buchthal, and P. Rosenfalck, *Motor unit territory and muscle fiber concentration in paresis due to peripheral nerve injury and anterior horn cell involvement.* Neurology, 1959. **9**: p. 657-71.
73. McComas, A.J., et al., *Electrophysiological estimation of the number of motor units within a human muscle.* J Neurol Neurosurg Psychiatry, 1971. **34**(2): p. 121-31.
74. Brown, W.F., M.J. Strong, and R. Snow, *Methods for estimating numbers of motor units in biceps-brachialis muscles and losses of motor units with aging.* Muscle Nerve, 1988. **11**(5): p. 423-32.
75. Daube, J.R., *Estimating the number of motor units in a muscle.* J Clin Neurophysiol, 1995. **12**(6): p. 585-94.
76. Lomen-Hoerth, C. and R.K. Olney, *Comparison of multiple point and statistical motor unit number estimation.* Muscle Nerve, 2000. **23**(10): p. 1525-33.
77. Gay, R.E., P.C. Amadio, and J.C. Johnson, *Comparative responsiveness of the disabilities of the arm, shoulder, and hand, the carpal tunnel questionnaire, and the SF-36 to clinical change after carpal tunnel release.* J Hand Surg [Am], 2003. **28**(2): p. 250-4.
78. Magee, D.J., *Orthopedic Physical Assessment*. 2002, Saunders. Philadelphia, PA. p. 133-147.
79. Stashuk, D. and W.F. Brown, *Quantitative electromyography*, in *Neuromuscular function and disease: basic, clinical, and electrodiagnostic aspects*, W.F. Brown, C. Bolteon, and M. Aminoff, Editors. 2002, WB Saunders: Philadelphia. PA. p.311-48

80. Nandedkar, S.D., et al., *Analysis of amplitude and area of concentric needle EMG motor unit action potentials.* Electroencephalogr Clin Neurophysiol, 1988. **69**(6): p. 561-7.
81. Nelson, R.M., et al., *Comparison of motor unit action potential characteristics and hand dominance using monopolar needle electrodes in the abductor pollicis brevis and abductor digiti minimi muscles.* Electromyogr Clin Neurophysiol, 2003. **43**(1): p. 17-22.
82. Howard, J.E., K.C. McGill, and L.J. Dorfman, *Properties of motor unit action potentials recorded with concentric and monopolar needle electrodes: ADEMG analysis.* Muscle Nerve, 1988. **11**(10): p. 1051-5.
83. Stalberg, E. and H. Erdem, *Quantitative motor unit potential analysis in routine.* Electromyogr Clin Neurophysiol, 2002. **42**(7): p. 433-42.
84. Takehara, I., et al., *Reliability of quantitative motor unit action potential parameters.* Muscle Nerve, 2004. **30**(1): p. 111-3.
85. Chu, J., et al., *Skill and selection bias has least influence on motor unit action potential firing rate/frequency.* Electromyogr Clin Neurophysiol, 2003. **43**(7): p. 387-92.
86. Calder, K.M., et al., *Reliability of quantitative EMG analysis of the extensor carpi radialis muscle.* J Neurosci Methods, 2008. **168**(2): p. 483-93.
87. Boe, S.G., D.W. Stashuk, and T.J. Doherty, *Motor unit number estimates and quantitative motor unit analysis in healthy subjects and patients with amyotrophic lateral sclerosis.* Muscle Nerve, 2007. **36**(1): p. 62-70.
88. Finsterer, J. and B. Mamoli, *Satellite potentials as a measure of neuromuscular disorders.* Muscle Nerve, 1997. **20**(5): p. 585-92.
89. Lang, A.H. and V.S. Partanen, *"Satellite potentials" and the duration of motor unit potentials in normal, neuropathic and myopathic muscles.* J Neurol Sci, 1976. **27**(4): p. 513-24.
90. Esslen, E., *Electromyographic findings on two types of misdirection of regenerating axons.* Electroencephalogr Clin Neurophysiol, 1960. **12**: p. 738-41.
91. Stalberg, E., *Macro EMG, a new recording technique.* J Neurol Neurosurg Psychiatry, 1980. **43**(6): p. 475-82.
92. Stalberg, E. and P.R. Fawcett, *Macro EMG in healthy subjects of different ages.* J Neurol Neurosurg Psychiatry, 1982. **45**(10): p. 870-8.
93. Daube, J.R., *Motor unit number estimates--from A to Z.* J Neurol Sci, 2006. **242**(1-2): p. 23-35.
94. Doherty, T., et al., *Methods for estimating the numbers of motor units in human muscles.* J Clin Neurophysiol, 1995. **12**(6): p. 565-84.
95. Doherty, T.J. and W.F. Brown, *The estimated numbers and relative sizes of thenar motor units as selected by multiple point stimulation in young and older adults.* Muscle Nerve, 1993. **16**(4): p. 355-66.
96. Keir, P.J. and D.M. Rempel, *Pathomechanics of peripheral nerve loading. Evidence in carpal tunnel syndrome.* J Hand Ther, 2005. **18**(2): p. 259-69.
97. Henneman, E., G. Somjen, and D.O. Carpenter, *Excitability and inhibitability of motoneurons of different sizes.* J Neurophysiol, 1965. **28**(3): p. 599-620.
98. Jablecki, C.K., et al., *Practice parameter: Electrodiagnostic studies in carpal tunnel syndrome. Report of the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation.* Neurology, 2002. **58**(11): p. 1589-92.
99. Chang, M.H., et al., *Comparison of sensitivity of transcarpal median motor conduction velocity and conventional conduction techniques in electrodiagnosis of carpal tunnel syndrome.* Clin Neurophysiol, 2006. **117**(5): p. 984-91.

Appendix A

Advertisements

Do you have

Carpal Tunnel Syndrome?

We are investigating nerve function in individuals with carpal tunnel syndrome and differences in recovery when surgery has and

Queen's UNIVERSITY

If you are aged 18-60 and either…

- have mild or severe carpal tunnel syndrome and have not yet had surgery, OR
- Healthy and have no known neurological deficits

then you may qualify for this study and we would like your help!

We will use a technique called *electromyography to study signals* from the muscles in your hand.

This study is led by Drs. Linda McLean and Andrew Hamilton-Wright of the School of Rehabilitation Therapy at Queen's University

If you would like more

Andrew Hamilton-Wright
Tel: 533 6000 x74756
email:

Andrew Hamilton-Wright Tel: 533 6000
Andrew Hamilton-Wright Tel: 533 6000
Andrew Hamilton-Wright Tel: 533 6000
Andrew Hamilton-Wright Tel: 533 6000
Andrew Hamilton-Wright Tel: 533 6000
Andrew Hamilton-Wright Tel: 533 6000
Andrew Hamilton-Wright Tel: 533 6000

Appendix B

Consent Form

Subject Name: _____

Subject Identifier: _____

Date of Collection: _____

TITLE OF PROJECT: Injury and repair in carpal tunnel syndrome

BACKGROUND INFORMATION:

You are being **invited** to participate in a research study directed by Drs. L. McLean and A. Hamilton-Wright to investigate nerve injury and repair in carpal tunnel syndrome. Dr. Hamilton-Wright will read through this consent form with you, will describe all procedures in detail and will answer any questions you may have. This study has been reviewed and approved for ethical compliance by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

DETAILS OF THE STUDY:

1. Aim of the study:

A small but significant portion of individuals who undergo surgery for carpal tunnel syndrome have symptoms that do not improve after surgery and recovery. Through this study we are investigating the extent of nerve injury and the healing process in people

with carpal tunnel syndrome, in order to provide insight into what is going wrong in problematic cases.

2. Description of visits, dosage, tests to be performed as part of the study:

. One visit to the Motor Performance Laboratory will be required. At this time a routine clinical assessment will be performed to determine the severity of the carpal tunnel syndrome you are experiencing. You may have undergone this assessment previously if you have seen a physiatrist for your carpal tunnel syndrome. Electrical impulses will be delivered to the nerve in your wrist and the conducted nerve signals will be recorded at the muscles and nerves or your hand. Next, an electromyographic analysis will be performed that will examine the structure and function of one of the muscles controlling your thumb on the symptomatic arm. This examination will require placing a small needle into the thumb muscles and having you perform slight contractions of 10 to 30 seconds each. The entire visit will last approximately 1 hour. We will provide you with a parking permit while you are attending this session.

3. Risks/Side-Effects:

Some people find the needle based examination uncomfortable, and you are free to withdraw from the study at any time. There are no other short- or long-term risks or side effects known to occur as a result of the techniques used in this study. If however you feel that you have any unusual symptoms associated with the study experience, please report them immediately to the researchers.

4. Benefits

e.g. While you may not benefit directly from this study, results from this study may improve our understanding of <u>carpal tunnel syndrome,</u> and may benefit patients in the future.

5. Exclusions:

You will not be considered for this study if you: are less than 18 or greater than 60 years of age, if you have any other neurological disorder such as multiple sclerosis or stroke, if you have diabetes mellitus, or if you have suffered an injury to the affected limb that might interfere with the study results.

6. Confidentiality

. All information obtained during the course of this study is strictly confidential and your anonymity will be protected at all times. You will be identified by subject number only. All data recorded on paper will be stored in a locked filing cabinet and will be available only to Drs. Hamilton-Wright and McLean. All electronic data will be stored free from your identity and will remain on the computer in the Motor Performance Laboratory and will be backed up at the Queen's University secure server. You will not be identified in any publication or reports.

7. Voluntary nature of study/Freedom to withdraw or participate:

Your participation in this study is voluntary. You may withdraw from this study at any time and your withdrawal will not affect your future medical care with any physician at any hospital.

8. Liability:

"**In the event that you are injured as a result of the study procedures, medical care will be provided to you until resolution of the medical problem.**
By signing this consent form, you do not waive your legal rights nor release the investigator(s) and sponsors from their legal and professional responsibilities."

SUBJECT STATEMENT AND SIGNATURE SECTION:

9. I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given

sufficient time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form. I will receive a copy of this consent form for my information.

If at any time I have further questions, problems or adverse events, I can contact

Dr. A. Hamilton-Wright at (613) 533 6000, extension 74756

Dr. L. McLean at (613) 533 6000, extension 36101

or

Dr. E. Culham (Director) at (613) 533 6000, extension 36727

If I have questions regarding my rights as a research subject I can contact Dr. Albert Clark, Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at (613) 533-6081

By signing this consent form, I am indicating that I agree to participate in this study.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

STATEMENT OF INVESTIGATOR:

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

_____ _____

Signature of Principal Investigator Date

Appendix C

Questionnaire

A Self-Administered Questionnaire for the Assessment of Severity of Symptoms and Functional Status in Carpal Tunnel Syndrome

Ref: DW Levine, BP Simmons, MJ Koris, LH Daltroy, GG Hohl, AH Fossel, JN Katz, *J Bone Joint Surg Am.* 1993;75:1585-1592

The following questions refer to your symptoms for a typical twenty-four-hour period during the past two weeks (circle one answer to each question):

How severe is the hand or wrist pain that you have at night?

1. I do not have hand or wrist pain at night
2. Mild pain
3. Moderate pain
4. Severe pain
5. Very severe pain

How often did hand or wrist pain wake you up during a typical night in the past two weeks?

1. Never
2. Once
3. Two or three times
4. Four or five times
5. More than five times

Do you typically have pain in your hand or wrist during the daytime?

1. I never have pain during the day
2. I have mild pain during the day
3. I have moderate pain during the day
4. I have severe pain during the day
5. I have very severe pain during the day

How often do you have hand or wrist pain during the daytime?

1. Never
2. Once or twice a day
3. Three to five times a day
4. More than five times a day
5. The pain is constant

How long, on average, does an episode of pain last during the daytime?

1. I never get pain during the day
2. Less than 10 minutes
3. 10 to 60 minutes
4. Greater than 60 minutes
5. The pain is constant during the day

Do you have numbness (loss of sensation) in your hand?

1. No
2. I have mild numbness
3. I have moderate numbness
4. I have severe numbness
5. I have very severe numbness

Do you have weakness in your hand or wrist?

1. No weakness
2. Mild weakness
3. Moderate weakness
4. Severe weakness
5. Very severe weakness

Do you have tingling sensations in your hand?

1. No tingling
2. Mild tingling
3. Moderate tingling
4. Severe tingling
5. Very severe tingling

How severe is numbness (loss of sensation) or tingling at night?

1. I have no numbness or tingling at night
2. Mild
3. Moderate
4. Severe
5. Very severe

How often did hand numbness or tingling wake you up during a typical night during the past two weeks?

1. Never
2. Once
3. Two or three times
4. Four or five times
5. More than five times

Do you have difficulty with the grasping and use of small objects such as keys and pens?

1. No difficulty
2. Mild difficulty
3. Moderate difficulty
4. Severe difficulty
5. Very severe difficulty

On a typical day during the past two weeks have hand and wrist symptoms caused you to have any difficulty doing the activities listed below? Please circle one number that best describes your ability to do the activity.

Activity	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Cannot Do at All Due to Hand or Wrist Symptoms
Writing	1	2	3	4	5
Buttoning of clothes	1	2	3	4	5
Holding a book while reading	1	2	3	4	5
Gripping of a telephone handle	1	2	3	4	5
Opening of jars	1	2	3	4	5
Household chores	1	2	3	4	5
Carrying of grocery bags	1	2	3	4	5
Bathing and dressing	1	2	3	4	5