2009

Effect of demyelinating ulnar nerve injury on strength and fatigue

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Effect of demyelinating ulnar nerve injury on strength and fatigue

(Spine Title: Effect of demyelinating nerve injury on skeletal muscle)

(Thesis Format: Integrated Article)

By

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Graduate Program in Kinesiology

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

2009

ABSTRACT

PURPOSE: The aim of the current study was to examine the effect of ulnar nerve conduction block on the strength and fatiguability of the first dorsal interosseous muscle (FDI). **METHODS:** Eight controls and nine patients presenting with ulnar nerve conduction block (CB) performed index finger abduction (FDI contraction) maximal voluntary contractions (MVC's) using a custom-built hand dynamometer to assess strength. Isometric FDI contractions held at 70% MVC until failure were used to assess fatiguability. Affected and healthy sides were tested to allow for comparison within individuals. **RESULTS:** CB affected side demonstrated significant decreases in strength and muscle endurance versus the unaffected side and controls. The extent of CB was positively correlated with the decrements in strength and endurance. **CONCLUSION:** The decrement in strength was due to an inability to recruit all of the available muscle fibres in the limb affected by CB. The decrease in endurance was possibly a result of frequency-dependent conduction block during sustained muscle contraction.

Keywords: Peripheral Neuropathy, Conduction Block, Ulnar Nerve, Demyelination, FDI, Fatigue, Strength

ACKNOWLEDGEMENTS

I will be forever appreciative of my experiences here at The University of Western Ontario as a graduate student. These past few years have afforded me great opportunities for academic and personal growth and those who have helped me along the way will not be forgotten. In the following passage I will attempt to recognize those who provided me with the many different brands of guidance and support that made this accomplishment possible.

I cannot overstate the gratitude I feel towards my thesis supervisor, Dr. Timothy Doherty, who constantly offered unparalleled levels of counsel, feedback and support. Tim, you foster a learning experience that is truly challenging, rewarding, and uniquely engaging. It can be stated without a shred of doubt in my mind that without you, this degree would not have been possible. Additionally, I assure you that I will always remember that "before" and "after" denote time, not anatomical position.

Another individual who is deserving of a heartfelt thank you is Dr. Charles Rice, our Grad Chair in the School of Kinesiology and a key member of my supervisory committee. Charles, your willingness to put on or take off your "Grad Chair hat" depending on the situation was more helpful than you know. I greatly appreciate your opinion, advice and, of course, your sense of humour which all aided in making these years so enriching and enjoyable. I hope you understand just how important a role you play for so many students here at Western, myself included.

To my comrades in lab, Mike Berger, Kendra Derry, Caitlin Symonette and Bradley Watson, I thank you for your friendship, your leadership, your support and for the pleasure of your company. You made life at the hospital infinitely more enjoyable and I wish you all the best of luck in your future endeavours, although I know none of you need it. In parting, I would just like you to note that if any of you ever need a subject for shocking or needle puncturing, I apologize, but I am not available.

A few of my irreplaceable friends are more than worthy of acknowledgment in this section and cannot be left out. To Davidson, Justin, Mayer, Dan, James, Quemyss and Chels: I thank you for your love and I thank you for the incredible memories. Keep your chins up, sticks on the ice, and I will see you around, sooner rather than later.

In closing, I give thanks to my family: Mom, Dad, Tyler and Karu. I owe you all more than I could ever hope to repay. Everything worthwhile that I have accomplished is a manifestation of the guidance and opportunities you have given me. Thank you for everything, and do not forget that I love you all deeply.

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LIST OF ABBREVIATIONS

AAEM – American Association of Electrodiagnostic Medicine

ADQM – abductor digiti quini muscle

CB – conduction block

CIDP – chronic inflammatory demyelinating polyneuropathy

CMAP – compound muscle action potential

CMT – Charcot-Marie-Tooth disease

CTS – carpal tunnel syndrome

CV – conduction velocity

DCB – demyelinative conduction block

EMG – electromyography

FCU – flexor carpi ulnaris

FDB – frequency dependent conduction block

FDI – first dorsal interosseous muscle

FDP – flexor digitorum profundus

FDS – flexor digitorum superficialis

FPI – first palmar interosseous muscle

MMN – multifocal motor neuropathy

MRC – Medical Research Council

MVC – maximal voluntary contraction

NCS – nerve conduction study

nPamp – negative peak amplitude

nParea – negative peak area

RIHM – Rotterdam Intrinsic Hand Myometer

SCI – Spinal cord injury

SD – standard deviation

SNAP – sensory nerve action potential

SNCV – sensory nerve conduction velocity

TOS – thoracic outlet syndrome

TTF – time to fatigue

UNE – ulnar neuropathy at the elbow

1.0 GENERAL INTRODUCTION

Conduction Block

Conduction block is defined as the failure of a nerve impulse to propagate through a structurally intact axon (Sears & Bostock, 1981). Several possible mechanisms causing this phenomenon have been elucidated, the most important of which is demyelinative conduction block (DCB). DCB has been identified as the mechanism of conduction block in many different neuropathies including: Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and nerve entrapment syndromes (i.e. carpal tunnel syndrome [CTS], ulnar neuropathy at the elbow [UNE]) (Waxman & Brill, 1978; Brown & Feasby, 1984; Feasby *et al.*, 1985; Cappelen-Smith *et al.*, 2000). It is this failure to transmit nerve impulses that results in many of the so-called negative clinical deficits, such as weakness and numbness, observed in patients with neuropathy. Furthermore, the electrophysiological demonstration of conduction block is an essential aspect of diagnosing and localizing many of these disorders.

DCB is caused by the loss or injury of myelin surrounding the nerve. Myelin is the phospholipid substance encasing large, fast conducting motor and sensory nerves in what is termed the myelin sheath. The primary role of myelin in healthy nerves is to provide insulation, thus allowing for saltatory conduction to occur. The myelin sheath provides a low capacitance, high impedance insulation that helps limit leakage of current along the axonal internodal space (from one node of Ranvier to the next). At the onset of action potential propagation, sodium channels open at the node of Ranvier leading to an inward ionic current; this causes outward capacitative current at the following node to be

excited, also known as the driving current. This process leads to nodal membrane depolarization to threshold, activating sodium channels and starting another round of inward ionic current. The term internodal conduction time refers to the amount of time for the driving current at one node to activate current at the following node.

The driving current present within a neuron must be greater than the necessary threshold current for action potential transmission. Tasaki (1953) described this relationship as the neural safety factor for transmission, and mathematically defined it as the ratio of driving current to threshold current. Nerve conduction is successful only when the safety factor ratio is greater than unity, and it has been found that most healthy, myelinated nerves maintain safety factors of 5 or greater (Kaji, 2003).

If the myelin sheath is damaged (demyelination) the resistance is reduced and capacitance is increased leading to leakage of driving current out of the axon. As driving current is lost, the internodal conduction time increases as it takes longer to accumulate sufficient ionic charge to initiate an action potential at the subsequent node of Ranvier. This process leads to the overall slowing of conduction velocity in a nerve that has suffered sufficient demyelination. Conduction block can result from extensive demyelination resulting in a diminished driving current that is unable to bring the following node to threshold. That is, under these conditions, if the safety factor ratio is less than 1, action potential propagation will fail.

A second factor exacerbating conduction block in demyelinated fibres involves potassium channels located in the internode adjacent to the Node of Ranvier (paranodal region). These potassium channels are integral to healthy neural function in unmyelinated

nerve fibres as they help to repolarize the axon after the depolarization induced by sodium channel activation. In contrast, myelinated nerve fibres possess inactive potassium channels as repolarization is attained largely through the closing of sodium channels after action potential propagation. As a demyelinated axon is depolarized by a weakened driving current, the potassium channels are opened to help initiate repolarization. However, this action shortens the duration of current passing through the node, further reducing the driving current in an axon with an already impaired safety factor (Sherrat *et al.*, 1980). Studies have shown that chemicals, such as 4-aminopyridine, that extend the duration of the current through inhibition of the aforementioned potassium channels have been successful in improving symptoms in multiple sclerosis patients, a central nervous system condition highly associated with demyelination (Smith *et al.*, 2000).

Although conduction for a single action potential will fail under conditions featuring extensive demyelination of an axon, it is also known that conduction block can occur in nerves that have suffered only some demyelination in conjunction with the application of a high-frequency stimulus. This phenomenon has been termed frequency-dependent conduction block (FDB). FDB has been demonstrated in many investigations examining both central and peripheral nerves in response to both high-frequency nerve stimulation and maximal voluntary contractions (Bostock & Grafe, 1985; Inglis *et al.*, 1998; Cappelen-Smith *et al.*, 2000). Nerve axons that are subject to a high rate of impulses (either voluntarily or through electrical stimulation) become hyperpolarized (hypoexcitable) thus requiring greater levels of stimulus to reach threshold. In healthy, myelinated axons, conduction is still successful in these instances due to the neural safety

factor which provides sufficient driving current to reach threshold even in hyperpolarized axons. However, axons that have been subject to demyelination have impaired safety factors (diminished driving current due to leakage) that may not be able to reach nodal threshold in hyperpolarized axons (Brown & Watson, 2002). Thus, whereas a single action potential would be propagated, or low-frequency impulses can be maintained, a sufficiently demyelinated nerve may have conduction failure when required to fire at a high rate.

Clinically, conduction block in the peripheral nervous system is diagnosed through the use of basic electrodiagnostic procedures, in particular, the motor nerve conduction study (NCS). The NCS is used to determine if any conduction block is present in a nerve, and it can be used to identify the 1-2 cm segment where the nerve is damaged (Miller, 1979). The motor NCS is performed by electrically stimulating a peripheral nerve of interest and recording from a skeletal muscle innervated by that nerve using electromyographic (EMG) equipment. Several measurements are recorded during this process including the time taken for the electrical impulse to travel from the site of stimulation to the muscle, known as the latency (ms). Also recorded is the size of the response at the muscle, termed compound muscle action potential (CMAP). Specifically, the negative peak amplitude (nPamp) (mV) and negative peak area (nParea) (mVms) of the CMAP are measured. By stimulating at two or more different locations along the same nerve, and by measuring the distance between stimulation sites, and the recording electrode the conduction velocity of the nerve can be determined. If the conduction velocity is found to be less than normal values (usually 50 m/s in upper limb nerves), then it is known that the nerve has suffered some conduction slowing, indicative of

demyelination. Also, by examining the CMAP size parameters elicited from stimulation sites distal and proximal to a potential area of demyelination (e.g. the elbow for UNE), it can determined if conduction block is present. The definition of what actually represents a meaningful decline in CMAP amplitude or area remains a contentious issue, with some studies calling for decreases in amplitude and area as high as 50% (Rhee *et al.*, 1990; Weber, 1997), while the AAEM guidelines stipulate a CMAP amplitude reduction of 20% or greater in ulnar neuropathy at the elbow (Campbell *et al.*, 1999). However, it has been determined that changes in nParea is a more accurate identifier of conduction block than nPamp, due to the inability of nPamp measurements to differentiate conduction block from temporal dispersion in some cases (Olney & Miller, 1984).

1.1 Ulnar Neuropathy at the Elbow

Ulnar nerve compression at the elbow is recognized as the second most common nerve entrapment in the upper extremity, exceeded in incidence only by carpal tunnel syndrome (CTS). A recent study reported the annual incidence of ulnar neuropathy at the elbow as 24.7 cases per 100,000 person years (Mondelli *et al.*, 2005). It is characterized by an impairment of function in the affected upper extremity due to loss of sensation, reduced dexterity, weakness, and, less commonly, pain (Campbell, 1997). Over the past two decades there has been an increase in the incidence of compressive neuropathies of the upper extremities (Latinovic *et al.*, 2006). The early diagnosis and treatment of these neuropathies is important as a late presentation decreases the odds of a full recovery and favourable clinical outcome.

1.1.1 Anatomy of Ulnar Neuropathy at the Elbow

The ulnar nerve is susceptible to damaging compression at the elbow over a wide area beginning approximately 10 cm proximal to the elbow and ending 5 cm distally. Over that approximately 15 cm span the ulnar nerve is most often impinged at one of five different locations (Posner, 1998).

Anatomically, from proximal to distal, the first potential location of ulnar entrapment occurs at the distal length of the medial intermuscular septum of the arm. In the middle third of the arm, the ulnar nerve pierces the medial intermuscular septum and descends along the medial head of the triceps. Along this course the ulnar nerve first becomes vulnerable to compression proximally at the arcade of Struthers for approximately 8 cm distally until the medial epicondyle. The arcade of Struthers is a thin aponeurotic band extending from the medial head of the triceps to the medial intermuscular septum. It has been found to be present in approximately 70% of individuals (Spinner & Kaplan, 1976). The arcade is formed by superficial muscle fibres of the triceps, deep fascia of the arm, and the internal brachial ligament. In this area the ulnar nerve can be compressed by the arcade itself, the hypertrophied medial head of triceps (usually only in body builders), or, in the absence of the arcade, the edge of the intermuscular septum (Posner, 1998).

The second most proximal site of ulnar nerve compression at the elbow occurs just proximal to the medial epicondyle of the humerus. Ulnar compressive neuropathy in this region develops usually secondary to a fracture of the humerus, particularly due to a malunited supracondylar fracture or other deformity of the bone. Ulnar neuropathy as a

consequence of humeral fracture was first described by Mouchet in 1914. It became to be known as tardy ulnar palsy, a term that eventually was used too generally to describe ulnar entrapment at the elbow, rather than only to refer to ulnar complications as a result of humeral bone damage.

A third and probably most common area of entrapment is the olecranon groove. This groove is covered by a fibroaponeurotic band, and is anteriorly bordered by the medial epicondyle and laterally bordered by the ulnohumeral ligament and olecranon itself. During its course through the groove the ulnar nerve is accompanied by several major blood vessels including the inferior and superior ulnar collateral arteries and the posterior recurrent ulnar artery. The nerve is especially vulnerable at this location due to the wide variety of potential causes of entrapment. The three main categories of conditions that cause compression at the olecranon groove are: lesions within the groove, conditions outside the groove, and factors that predispose the nerve to displace from the groove. Potential lesions within the groove are highly varied and can arise from soft tissue tumours, synovitis due to rheumatoid arthritis, arthritic spurs, fracture fragments, infections and haemorrhaging due to bleeding disorders. Common conditions outside of the groove that lead to nerve compression are found in individuals who lean on their flexed elbow for extended periods of time. Classic examples of this are found in patients who are confined to their beds and truck drivers who lean their arm on their window frame while driving (Piligian *et al.*, 2000). Other conditions outside of the groove that can cause entrapment include improper arm positioning during elbow surgery (this usually only aggravates a pre-existing ulnar condition) and an anomalous anconeous epitrochlearis muscle that arises from the olecranon and inserts on the medial epicondyle

(Alvine & Schurrer, 1987). This muscle is normally found as the epitrochleoanconeuous ligament in most humans. The third category of ulnar nerve injury at the olecranon groove is caused by the nerve shifting out of the groove during elbow flexion and then returning to its normal position upon extension. During this subluxation the nerve usually shifts onto the tip of the epicondyle or just anterior to it. This condition can be caused by a traumatic tear or congenital deformity of the fibroaponeurotic covering of the groove. Congenital hypoplasia of the trochlea or malconvalescent deformity of the medial epicondyle can also lead to this third category of nerve damage. Finally, the 20% of the population that experience bilateral hypermobility of the ulnar nerve at the olecranon groove are also predisposed to nerve damage due to friction over the medial epicondyle during flexion and extension as well as inadvertent injury during an injection at the site to treat medial epicondylitis.

The fourth area of ulnar nerve entrapment in the elbow occurs within the cubital tunnel which passes through the humeral and ulnar heads of the flexor carpi ulnaris muscle. The roof of this tunnel is formed by a fibrous band referred to as Osbourne's ligament, while its floor is composed of the medial collateral ligament of the elbow. The term "cubital tunnel syndrome" can be used to describe entrapment neuropathy to the ulnar nerve at this location; however it is often less accurately used to describe all ulnar neuropathies at the elbow. In terms of ulnar neuropathy, the cubital tunnel and previously mentioned olecranon groove are the sites of highest incidence. In the cubital tunnel, the ulnar nerve is at risk of damage during flexion of the elbow, during which Osbourne's ligament becomes stiff and taut while the medial collateral ligament relaxes, bulging medially, thus compressing the ulnar nerve against Osbourne's ligament (Vanderpool *et*

al., 1968). Studies have shown that Osbourne's ligament stretches approximately 40% from full extension to complete flexion; or 5 mm for every 45° of flexion (Vanderpool *et al.*, 1968). Also, during flexion the tunnel has been reported to change its general shape from oval to "flattened elipse" (Apfelberg & Larson, 1973). These changes occurring in the tunnel cause a great increase in pressure (up to 7 times greater) during flexion, with an additional increase in cubital tunnel pressure (up to 20 times greater) with flexor carpi ulnaris contraction during flexion (Werner *et al.*, 1985). These large increases in pressure can constrict intraneural circulation and cause mechanical deformation of the ulnar nerve, eventually leading to nerve damage. The potential for occluded neural circulation has been previously demonstrated in studies which show that at 20 - 30 mmHg of pressure, flow is impaired within venules draining the nerve, however at this pressure capillary and arterial flow remains unaffected (Ogata & Naito, 1986). With further increases in pressure come more detriments to neural circulation, at 60 – 80 mmHg, venule, capillary and arterial flow stops entirely, thus causing the nerve to become ischemic (Ogata & Naito, 1986). If the pressure is released within two hours, studies have shown that circulation is returned almost immediately and the nerve can resume normal functioning within a few hours. However, if pressure is maintained for a prolonged period of time (greater than 2 hours), the ischemia can result in long-term or irreparable nerve damage (Lundborg & Dahlin, 1992).

The fifth and most distal major site of ulnar nerve impingement at the elbow occurs immediately distal to the cubital tunnel as the nerve exits the flexor carpi ulnaris muscle. As the nerve exits the FCU it must pierce a layer of fascia (the flexor pronator aponeurosis) to continue its course between the flexor digitorum superficialis (FDS) and

flexor digitorum profundus (FDP) muscles. The flexor pronator aponeurosis can constrict the nerve, leading to an entrapment syndrome (Amadio & Beckenbaugh, 1986).

While it is important to recognize the anatomical features involved, standard electrodiagnostic techniques typically are unable to localize ulnar compression sites to an exact anatomical feature. Thus, when discussing this condition it is more appropriate to describe it in a generalized fashion as ulnar neuropathy at the elbow (UNE), rather than by specific anatomical sites (i.e. cubital tunnel syndrome).

1.1.2 Signs and Symptoms of Ulnar Neuropathy at the Elbow

The symptoms associated with focal ulnar neuropathy at the elbow may arise acutely or insidiously, with an acute development sometimes associated with a specific traumatic event. Symptoms usually include numbness and paraesthesia in the hand, pain in the medial aspect of the elbow, and in certain instances, dysesthesias radiating from the elbow distally to the wrist (Campbell, 1997). The numbness usually presents in the hand at the fifth finger, and the ulnar aspect of the fourth finger (Folberg *et al.*, 1994). The aforementioned elbow pain is normally associated with overuse of the forearm flexors, particularly flexor carpi ulnaris, which can irritate the nerve during contraction. Some cases of ulnar nerve compression are associated with an impairment of hand function, particularly in terms of increased fatiguability and weakness (Eversmann, 1993). Patients often describe an impaired ability to open jars or bottles and experience a lack of muscular endurance during some repetitive hand-oriented tasks. Symptoms observed in the intrinsic hand muscles are usually first described as "clumsiness" and a lack of dexterity, gradually developing into a weakened grip and pinch (as determined by

Froment's sign, a test of adductor pollicis function). Studies describing the motor deficits in patients have reported 20% with weakness in FCU, 56% in FDP, 75% in abductor digiti minimi, and 84% in first dorsal interosseous (Stewart, 1987). In the most advanced stages of ulnar neuropathy at the elbow, pronounced motor loss is witnessed through atrophied intrinsic hand muscles and clawing of the fourth and fifth digits, known as the "ulnar claw hand deformity" (Eversmann, 1993). The ulnar clawing forms as a result of the paralysis of the interossei and lumbrical muscles of the fourth and fifth fingers. This leads to flexion of the interphalangeal joints and hyperextension of the metacarpalphalangeal joints, causing the ulnar clawing to form. Patients at this stage of ulnar neuropathy often are observed having great difficulty in making a fist with their affected hand (Robertson & Saratsiotis, 2005).

1.1.3 Diagnosis of Ulnar Neuropathy at the Elbow

The first steps taken when diagnosing ulnar neuropathy at the elbow usually include a complete physical examination and a history of the patient, particularly in relation to activities at work or leisure that aggravate their symptoms. The physical examination begins at the neck moving distally along the arm, concluding at the hand and has been described in detail by Posner (1998). When examining the neck, any findings of a limited range of motion, especially when accompanied by pain, may indicate a disease of the cervical discs or arthritis, rather than ulnar neuropathy at the elbow. The brachial plexus is then tested to examine any possibilities of thoracic outlet syndrome. Procedures such as Roo's test (overhead exercise test that elicits paraesthesia and obliterates the radial pulse in thoracic outlet syndrome patients) are used to determine whether a problem exists within the brachial plexus that could be causing the patient's symptoms.

Moving distally along the arm, the elbow is inspected for any visible or palpable signs of deformity. The ulnar nerve itself is palpated for any subluxations, dislocations, or enlargements. Any focal sites of tenderness along the course of the ulnar nerve may be markers of the specific site of compression. The next step usually involves administration of the elbow flexion test, where the patient is asked to maintain elbow flexion and wrist extension for 1 to 3 minutes (to this date, no consensus has been made as to a precise time frame). The test is considered positive if paraesthesia develops in the ulnar nerve's distribution at any point during the test. Unfortunately this test has been found to be more sensitive than specific with 10% of "healthy individuals" reporting as false-positives. Impairment in sensory function of the ulnar nerve usually presents in the little finger and ulnar-half of the ring finger. However it is important to note that this sensory deficit can extend to the middle finger, or be limited to the little finger in some cases. Observation of numbness in the dorsum of the hand and little finger can be a key differential between a diagnosis of ulnar nerve compression at the elbow, or at the wrist. Generally when the nerve is compressed at the wrist (as it passes through Guyon's canal) the dorsum of the hand will not be impacted by any sensory deficits. This is due to the dorsal sensory branch of the ulnar nerve branching off approximately 5 cm proximally from the ulnar styloid, where it runs backwards underneath the flexor carpi ulnaris muscle, passes through the deep fascia and runs distally along the ulna crossing the wrist at the dorso-ulnar aspect of the hand. Thus the dorsal sensory branch avoids compression at Guyon's canal by bypassing it, allowing continued sensory innervation of the dorsum of the hand. Physical examinations are typically followed up by electrodiagnostic studies to confirm diagnoses.

1.1.4 Electrodiagnosis of UNE

When the classical signs of UNE are observed in a patient, in particular numbness of the 4th and 5th digits brought on my pressure or flexion at the elbow, diagnosis of UNE is relatively certain. However, UNE can still be confused with other neurological conditions such as radiculopathies and occasionally CTS, making the diagnosis less straightforward. To better elucidate the underlying problem, electrodiagnostic studies are employed to confirm or rule out UNE, to measure the extent of the nerve damage, and to detect any other possible nerve lesions. Electromyographic (EMG) techniques are also useful in defining the type of pathology involved, differentiating among segmental demyelination, axonal degeneration, and other nerve abnormalities (Daube, 1985). This information is important as it can be relevant to the type of treatment recommended (Haig *et al.*, 1999).

In suspected UNE cases, the objective of EMG is to detect ulnar nerve damage, and to localize it to the elbow. Motor nerve conduction studies (NCS) are employed, by recording from the first dorsal interosseous (FDI) muscle or hypothenar eminence, and by electrically stimulating the ulnar nerve at the wrist, below the elbow, and above the elbow (Payan, 1969). The prime indication of UNE in NCS is focal slowing or block of nerve conduction across the elbow segment. The conduction velocity of the nerve is quantified by comparing differences in the distance and latencies between sites of stimulation (Bostock & Rothwell, 1997). Velocities falling below 45 - 48 m/s across the elbow are typically considered indicative of UNE, especially when accompanied by normal CV in the forearm segment. Conduction block may also be found across the elbow, as discussed previously, providing further information on the extent of the damage to the ulnar nerve.

The absence of slowing or block across the elbow leaves the diagnosis of UNE in doubt (Campbell, 2000).

Sensory conduction studies can be used to aid the identification of focal slowing in patients with ulnar nerve entrapment at the elbow. Typically, these studies involve recording the sensory nerve action potential (SNAP) from the 5th digit, which is ulnar innervated, to provide evidence of sensory axonal involvement. The amplitude and area of the SNAP provide information regarding the number and size of functioning sensory axons. The benchmark for an abnormal SNAP response is less than 50% of the amplitude of the SNAP on the asymptomatic side (Raynor *et al.*, 1994). Abnormally low SNAP responses are attributed to temporal dispersion, conduction block, and significant loss of large myelinated axons by focal demyelination (Bostock & Rothwell, 1997). Loss of CMAP amplitude or area and evidence of acute or chronic denervation on needle EMG of ulnar innervated muscles indicates axonal involvement and a greater degree of severity than primarily demyelinating lesions.

1.2 First Dorsal Interosseous (FDI): a useful model to study strength and fatigue

The first dorsal interosseous (FDI) is a bipennate, intrinsic muscle of the hand responsible for abduction of the index finger. It is the largest of the dorsal interossei, and the most important muscle for abduction force production of the index finger. It originates on the radial side of the second metacarpal and the proximal half of the ulnar side of the first metacarpal. It inserts on the radial side of the base of the second proximal phalanx (index finger) and the extensor expansion (the aponeurosis of extensor muscles

that run into the back of the hand). Similar to all of the other dorsal and palmar interosseous muscles, the FDI is innervated by the ulnar nerve. This point is important to note because both the FDI and its antagonist, the first palmar interosseous (FPI), will be activated with any electrical stimulation of the ulnar nerve and these muscles produce opposing forces.

The FDI has long been for a popular choice in neuromuscular investigations for several reasons. It has a very distinct and superficially located muscle belly creating favourable conditions for both surface and needle EMG recording. The ulnar nerve is easily accessible at multiple locations along the arm readily allowing for transcutaneous electrical stimulation. Also, the FDI has a distinct and unique mechanical function that is relatively easy to measure given its near-unipolar pull of the index-finger (in contrast to other muscles of the hand, especially those of the thenar eminence). Finally, FDI is a muscle that is finely controlled making it ideal for studies that require minimal extraneous movement and specific sub-maximal force outputs.

For the reasons listed above, FDI has been used extensively to help understand various questions pertaining to neuromuscular physiology and thus much is known about its properties. Carpentier *et al.* (2001) established a mean maximal voluntary contraction force output for FDI of 26.8±1.7 N during isometric finger abduction in 8 healthy, young adults (aged between 21 and 41 years). These findings were closely followed by Taylor *et al.* (2003) who found the mean isometric force output of FDI to be 26.6 ±5.8 N in 10 healthy, young adults (mean age 29.4±4.4 years).

Various studies have shown that FDI is a muscle that suffers from little to no central activation deficit (Thomas *et al.* 1989; Kalmar & Cafarelli, 2004; Eichelberger & Bilodeau, 2007). Thomas *et al.* (1989) found that healthy participants were able to maintain maximal voluntary activation of FDI during a 5 minute continuous maximal contraction. More recently, it has been found that FDI is not susceptible to central fatigue at most contractile intensities. Eichelberger & Bilodeau (2007) found no central fatigue in index finger abduction during isometric contractions at 75%, 60%, and 45% of MVC. However central fatigue may become a factor during prolonged, low intensity FDI contractions, as a decrease of over 10% was measured in central activation ratio during prolonged isometric contractions at 30% MVC.

The effect of joint angle (index finger position) on FDI force output has also been investigated. Zijdewind and Kernell (1994) found index finger abduction force to be greatest at the minimal abduction angle (resting finger position). Force output was found to decrease by approximately 50% when the finger was held in a neutral position (50% abduction/adduction), and a further decrease of 10% when held in the maximally abducted position. The main reasons for the differences in force output stem from changes in: (1) moment arm, (2) muscle length, and (3) passive tension. Placing the index finger in the adducted position would result in a decrease in moment arm for the FDI muscle which would serve to decrease FDI force production, provided there were no changes in other parameters. In this same adducted position, the FDI muscle length would be increased where it is at, or near its optimal length for maximal force development. Finally, maintaining index finger adduction increases passive tension (reducing muscle

slack) in the FDI muscle, thus increasing the efficiency of extrinsic force output (Zijdewind & Kernell, 1994).

As previously mentioned, the ulnar nerve innervates both FDI and its direct antagonist FPI; this is an important factor to consider when conducting studies involving these muscles when direct ulnar nerve stimulation is used. The resultant force from these two muscles in response to electrical stimulation of the ulnar nerve has also been elucidated. In a resting finger position (no finger abduction), supramaximal ulnar nerve stimulation at 30 Hz was found to produce only 51% of maximal voluntary force (Zijdewind & Kernell, 1994). It was concluded that the remaining 49% of force output was negated by concurrent contraction of FPI, the index finger adductor. Additionally, the same stimulus intensity applied to the ulnar nerve with the index finger in an abducted position elicited a reversed direction of action, adduction. These factors are important to consider when using FDI as a model designed to study neuromuscular function, particularly involving force output and fatigue. More specifically, the twitches elicited for the purposes of the interpolated twitch technique could be attenuated, particularly in when compared to studies involving muscles that are not innervated by the same motor nerve as their antagonist. While much is known of the functional and contractile properties of FDI in healthy, young humans, no investigations to date have directly quantified the impact of impaired ulnar nerve function (i.e. conduction block) on FDI strength and fatigue.

1.3 Effect of Focal Nerve Injury on Strength and Fatigue

It is well known that individuals who suffer from focal peripheral nerve injury (i.e. carpal tunnel syndrome, or ulnar neuropathy at the elbow) may present with weakness of the muscles innervated by the injured nerve (Kuhlman & Hennessey, 1997; Simpson, 2002; Schreuders *et al.* 2004; Tamburin *et al.*, 2008). Tamburin *et al.* (2008) examined 320 patients diagnosed with carpal tunnel syndrome. Using manual strength testing and the 1-5 MRC scale, hand weakness was found in 113 upper limbs (56%). Of these 113 weak patients, 48 were classified as mild; 54 as moderate; 9 as severe; and 2 as very severe weakness. The degree of weakness, however, was not compared to the results of electrophysiological studies. Also the subjectivity of manual strength testing cannot be ignored as a factor in these results. For example, Brandsma *et al.* (1995) found manual strength testing to have an interobserver reliability as low as 0.72, and intraobserver reliability as low as 0.71, indicating this measure is subject to a fair degree of variability in repeated measures. Use of more objective measures, including grip strength and key pinch dynamometers, have also demonstrated significant weakness in patients presenting with focal, demyelinating neuropathies (Kuhlman & Hennessey, 1997; Geere *et al.*, 2007). However, these measures have been called into question as they fail to adequately isolate individual, potentially affected muscles supplied by other nerves. When the muscles of interest were isolated using a custom designed dynamometer, the Rotterdam Intrinsic Hand Myometer (RIHM), no correlation has been found between grip/pinch strength measurements and isolated, intrinsic hand muscle strength recovery (Schreuders *et al.*, 2004). The mechanism of weakness measured in these studies is thought to be due to an inability to maximally recruit and fire all motor units due to demyelination resulting

in conduction block or pain-induced inhibition of motor unit firing (Sohn *et al.,* 2000). It is clear these studies are often subject to various limitations: (1) subjective testing is often the only measure used (manual muscle strength), (2) the objective tests employed often fail to isolate the muscle or muscle group of interest adequately (i.e. key pinch test), and (3) the strength tests are not directly compared with the electrophysiological measures of nerve damage (i.e. motor nerve conduction studies).

Although the loss of strength related to focal nerve damage has been shown using many different techniques, muscular fatigue under these conditions has not been quantified so universally. Ozcakar *et al.* (2005) examined 23 patients with thoracic outlet syndrome (TOS) and 15 healthy controls with isokinetic muscle testing for strength and fatigue. TOS typically involves the compression, and subsequent damage of the lower trunk of the brachial plexus. They found both groups to have similar muscle strengths; however they determined the patient group to have greater fatigue ratios on the symptomatic side versus their asymptomatic side, and versus controls. However, it is not clear how closely these findings can relate to other peripheral, focal neuropathies as the fatigue in TOS could be affected by vascular compression, and not solely nerve damage (Dorazio & Ezzel, 1979; Etheredge *et al.*, 1979). Muscular fatigue has also been subjectively associated with instances of conduction block in studies examining neuropathies such as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (Bissay *et al.,* 2008). Bissay *et al.* (2008) described a CIDP patient, suffering from conduction block in various motor nerves, who complained of disabling fatigue and the inability to sustain physical effort. This may lend credence to the notion that conduction block and fatigue are related, however in this study fatigue was not quantified in any

form and the generalized nature of the disorder makes it hard to draw conclusions. In 2000, Kaji and colleagues investigated multifocal motor neuropathy (MMN) patients for any possible changes in muscle endurance. The patients with MMN in Kaji's study presented with conduction block of the median nerve and underwent endurance testing of muscles innervated by the median nerve. During MVC's activity-dependent conduction block of the median nerve was found to occur over and above the extent of conduction block measured at rest. Additionally, a decrease in force output (muscle fatigue) was found to occur in sync with the increasing incidence of activity-dependent conduction block. This led Kaji and colleagues to conclude that activity-dependent conduction block, caused by axonal hyperpolarization of the demyelinated nerve was responsible for the reduced muscle endurance. However it is important to note the underlying causes of MMN are very different than those causing UNE and thus it is not known if the same results will be observed in patients with UNE.

2.0 INTRODUCTION

The failure of an intact axon to propagate an action potential is known as conduction block (Sears & Bostock, 1981). In the peripheral nervous system, this phenomenon is often the result of demyelination. Healthy human nerves maintain conduction with a driving current that is several times greater than necessary to reach the threshold level of stimulus needed to generate an action potential (Tasaki 1953). However, demyelination can lead to leakage of driving current out of the axon, and if the loss of driving current is so great that it falls below threshold, the propagation of the action potential will fail. It is believed that this failure to transmit nerve impulses can be responsible for many of the so-called negative, clinical deficits (muscle weakness, numbness) observed in patients with peripheral nerve injury.

In humans, demyelinative conduction block can result from many neuropathic conditions including focal peripheral neuropathies such as carpal tunnel syndrome (CTS) and ulnar neuropathy at the elbow (UNE). It is well known that individuals who are affected by these conditions may present with weakness of the muscles innervated by the injured nerve (Simpson, 2002; Schreuders *et al.* 2004; Tamburin *et al.*, 2008). Tamburin and colleagues studied 320 patients with CTS and found 113 to present with significant weakness as determined by objective manual strength testing. Kuhlman and Hennessey found weakness to be one of the most sensitive signs of carpal tunnel syndrome (sensitivity of 66%) and recommended its inclusion as part of the examination of CTS (Kuhlman and Hennessey, 1997). While it is widely accepted that muscular weakness can result from demyelinative conduction block, to date, no study has directly compared the

extent of conduction block, determined through electrophysiological measure, with an objective measurement of the extent of muscular weakness.

The effect of demyelinating peripheral neuropathy on muscular endurance or fatigue has not been investigated so thoroughly, nor the results as conclusive. In 2005, Ozcakar and colleagues studied 23 thoracic outlet syndrome (TOS) patients and found limbs affected by the syndrome to fatigue to a significantly greater extent than healthy limbs when performing isokinetic contractions. However, it is not clear how closely these findings can relate to other peripheral, focal neuropathies as the fatigue in TOS could be affected by vascular compression, and not nerve damage alone (Dorazio & Ezzel, 1979). In 2008, Bissay and colleagues described a patient suffering from chronic inflammatory demyelinating polyneuropathy (CIDP) who complained of disabling muscular fatigue. While this indicates that conduction block and increased susceptibility to muscular fatigue may be related, only one patient was described, no quantification of fatigue was used and the generalized nature of the disorder makes it difficult to draw conclusions. Garssen *et al.* (2007) examined the residual fatigue of patients with Guillain-Barré syndrome, and found patients fatigued to a significantly greater extent versus controls. However, again, the generalized nature of this syndrome makes it unsuitable for extrapolation to focal neuropathies. Studies investigating the effect of focal nerve injury on muscular fatiguability are insufficient to draw unequivocal conclusions at this time.

This study will investigate the effect of conduction block caused by ulnar neuropathy at the elbow (UNE), on the properties of the first dorsal interosseous (FDI), an intrinsic hand muscle innervated by the ulnar nerve. The aim of the present study was to objectively measure strength and fatiguability in patients presenting with conduction

block, and to compare how the extent of conduction block affected any changes in these measures versus unaffected limbs and healthy controls. We hypothesized that the FDI muscles innervated by nerves suffering from conduction block would be significantly weaker than the FDI from the unaffected contralateral limb. Additionally, we hypothesized that the extent of strength decrement in the affected limb would be directly related to the extent of conduction block in the damaged nerve. Lastly, we hypothesized that muscle innervated by a damaged peripheral nerve would fatigue more quickly at a relative force output versus its healthy counterpart, and this too would be directly related to the extent of conduction block.

3.0 METHODS

3.1 Subjects

Eight healthy control subjects with no evidence of neuromuscular or musculoskeletal disorders and nine patients with clinical and electrophysiological features of ulnar neuropathy with conduction block localized to the elbow were asked to participate in this investigation (8 males, 9 females, ages 24 years – 58 years, mean 50.4 years) (Table 1). The patients were recruited through the EMG clinic at University Hospital, London Health Sciences Centre, London, Ontario. Participants who presented with only conduction slowing across the elbow or conduction block of the ulnar nerve at sites other than across the elbow were excluded including those with features of a generalized neuropathy. Patients who presented with ulnar conduction block in both elbows (n = 1) were included in the study, but excluded from bilateral comparisons. All participants gave informed consent to take part in the protocol which was approved by the research ethics board of the University of Western Ontario.

3.2 Clinical assessment

All patients underwent routine clinical assessment to confirm the presence of ulnar neuropathy at the elbow and to identify any other focal or generalized disorder that would confound the results (e.g. upper motor neuron problems, superimposed C8 root disease).

Table 1. Participant Characteristics

Participant Group	Age (years) mean ± SD	Male : Female	Height (cm)	Weight (kg)	BMI
Control	47 ± 14	4 : 4	171 ± 9	81.6 ± 12.2	27.7 ± 5.1
Patients with UNE	53 ± 3	4 : 5	164 ± 7	77.1 ± 7.9	28.5 ± 4.6

BMI = body mass index, UNE = ulnar neuropathy at the elbow

3.3 Motor Nerve Conduction Studies

All data were collected during a single visit to the Neuromuscular Assessment Laboratory (Room B7-140, University Hospital, London, Ontario). Standard motor nerve conduction studies of the ulnar nerve were completed to provide electrophysiological evidence of conduction block localized to the across elbow segment (see Figure 1). All nerve conduction studies were performed by a qualified and experienced EMG technologist to ensure reliability and accuracy. Prior to electrode placement, the participant's skin was prepared using a 70% isopropyl alcohol solution. Disposable, self-adhering electrodes (Medical Mart, Mississauga, Ontario), cut 1 cm by 2.5 cm in size, were used for all studies. The active electrode was placed over the motor point of the first dorsal interosseous (FDI) muscle and the reference electrode was placed over the second metacarpal phalangeal joint. A full electrode, 2 cm by 2.5 cm, served as a ground and was applied to the wrist distal to the stimulation site. The recording electrodes were secured with hypoallergenic tape to minimize movement. Supramaximal stimulation was then applied to the ulnar nerve at three sites: distally at the wrist (7 cm proximal to the active electrode), below the elbow (typically 1 to 2 cm distal to the medial epicondyle) and above the elbow, typically 8 to 10 proximal to the below elbow site (Kincaid, 1988). Latencies were measured from the onset of stimulation to the first negative deflection of the muscle action potential from baseline and distances between stimulation sites with a standard tape measure.

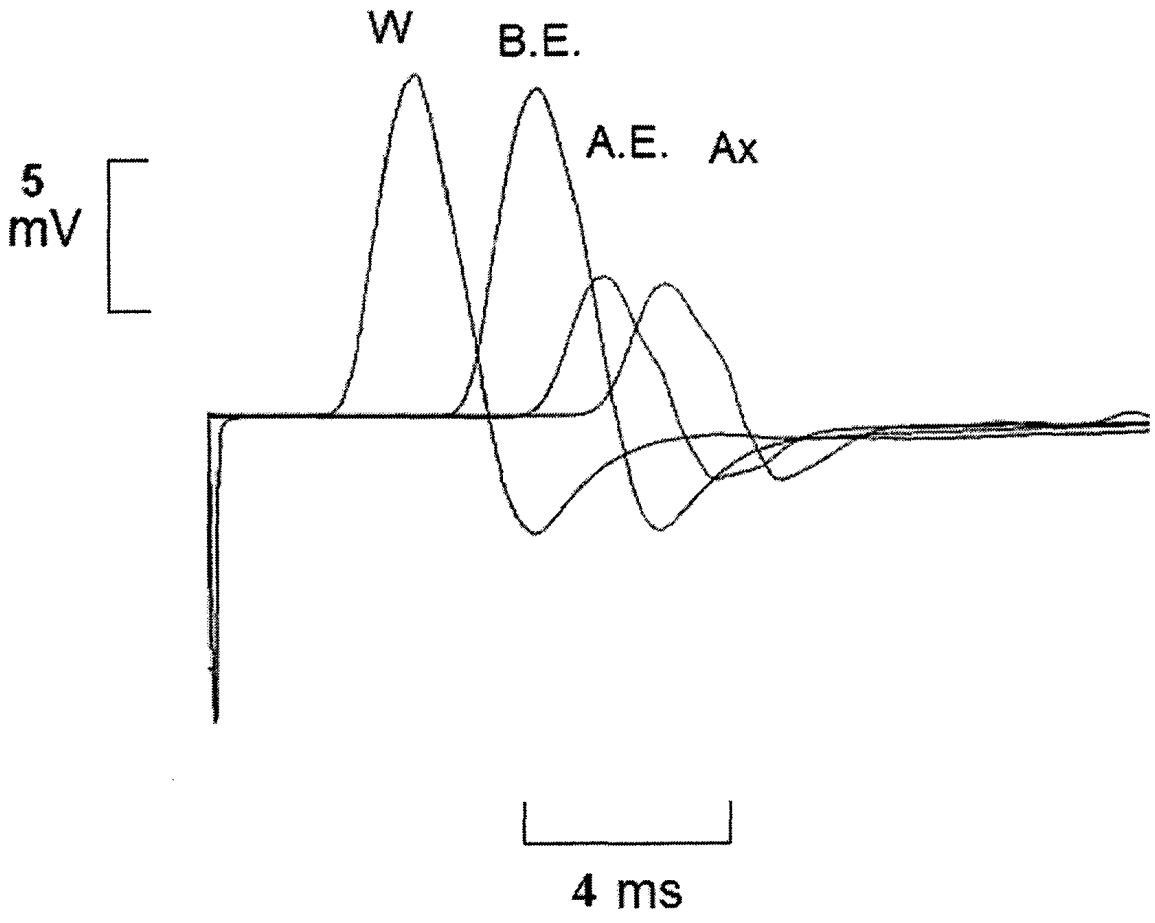


Figure 1. A standard motor nerve conduction study of the ulnar nerve as recorded from the FDI muscle. The CMAP responses elicited via electrical stimulation at standard stimulation sites are shown. Electrophysiological evidence of conduction block is present, localized to the across elbow segment, as evidenced by the greater than 20% reduction in CMAP amplitude and area from B.E. to A.E. stimulation sites. (Stimulation sites: W = wrist, B.E. = below elbow, A.E. = above elbow, Ax = axilla; units of measurement: mV = millivolts, ms = milliseconds).

Conduction velocities for the above and below elbow segments were calculated, and CMAP amplitudes and areas were recorded. Ulnar nerve conduction studies were completed for both the affected and unaffected limbs. Routine nerve conduction studies were performed for the radial and median nerves to rule out the possibility of polyneuropathy or carpal tunnel syndrome. An experienced, registered EMG technologist performed the nerve conduction studies and was blinded to the conditions of the patients' limbs.

3.4 Strength and Fatigue Testing Design

Following the motor nerve conduction studies the participant's forearm and hand were secured in a custom dynamometer designed to measure abduction of the second (index) digit. This dynamometer was designed to minimize any movement in the wrist and hand other than index finger abduction through the immobilization of the wrist, thumb and 2^{nd}, 3^{rd} and 4^{th} fingers by isolating them from the index finger, and strapping them firmly in place (Appendix A). A surface stimulator was firmly secured with hypoallergenic tape to the participant's wrist over the ulnar nerve at the same location used during the distal site of stimulation for the motor nerve conduction study, as marked by the EMG technologist. Similarly, the surface electrodes remained in the same positions as used for the nerve conduction study.

3.5 Strength and Fatigue Experimental Protocol

Once the participant was secured in the hand dynamometer, stimulation was applied to the ulnar nerve at the wrist to determine maximum twitch force of FDI in response to supramaximal stimulation. The amplitude of the M potential was monitored

as the stimulation increased until a plateau was reached, at which point the current was increased a further 15% to ensure stimulation was supramaximal. The participant was then asked to perform three isometric maximal voluntary contractions (MVC's) of index finger abduction lasting for three seconds each with three minutes of rest between each contraction. For each of these contractions force output was measured and recorded (N). Participants received strong verbal encouragement and could monitor their force output on a computer monitor. Voluntary activation of the FDI during these MVC's was measured using the interpolated twitch technique. This technique is performed by comparing the interpolated twitch amplitude elicited during an MVC (T_S) to the twitch amplitude delivered at rest, immediately after the MVC (T_R). Voluntary activation was quantified using the formula: % activation = $[1 - (T_S/T_R)] \times 100$.

Following a further three minutes of rest, the participants were asked to perform an FDI-fatigue protocol. This involved sustained isometric contraction of the FDI muscle at a force output that was approximately 60 to 70% of the participant's MVC. The participant was asked to maintain the 70% target force output for as long as possible. Strong verbal encouragement was provided, and the subject received visual feedback of their force output on a computer monitor which displayed the 70% to 60% MVC target zone. Once the subject could no longer maintain that level of force output and they dropped below the 60% MVC threshold twice, a supramaximal twitch was applied and the participant was asked to relax. The time from onset of the fatiguing protocol to the point of failure was measured. This was immediately followed by a second supramaximal twitch at rest to allow for the assessment of voluntary activation as per the interpolated twitch method.

Both the affected and unaffected hands were tested in all patients and controls to allow for side to side comparisons. Force output (N) was measured during each contraction.

3.6 Data Reduction and Analysis

All waveforms were collected, analyzed, and stored using a standard electromyography (EMG) system (Advantage Medical, London, Ontario, Canada). Negative peak amplitude (mV), negative peak area (mV.ms), and negative peak duration (ms) were measured for all individual waveforms collected. Surface EMG was collected using a D360 Model Isolated Patient Amplifier System (Digitimer Limited, Hertfordshire, United Kingdom). All force output data was amplified by a CP122 A.C./D.C. Strain Gauge Amplifier (Grass Inst., Warwick, Rhode Island). Force output data and surface EMG were sampled and analyzed online using Spike 2 software (version 5.13; Cambridge Electronic Design Ltd., Cambridge, United Kingdom).

% Conduction block was calculated by examining the % decrease in negative peak area from the site of stimulation distal to the elbow versus proximal to the elbow, % conduction block = (npArea Below Elbow – npArea Above Elbow/npArea Below Elbow) * 100. % Force decrement in patients with UNE was calculated by the formula: % force decrement = 100 – (UNE affected limb force/healthy limb force) * 100. Relative change in time to fatigue (%) was calculated by the formula: change in time to fatigue (%) = 100 – (UNE affected TTF/Healthy limb TTF) * 100.

3.7 Statistical Methods

Mean values and standard deviations (SD) are presented for all parameters. To compare differences in electrophysiological measures (negative peak area, negative peak

amplitude, sensory nerve action potential amplitude, conduction velocity) between and within groups, unpaired t-tests were used. Unpaired t-tests were also employed to compare MVC force outputs in index finger abduction and key pinch strength tests. A Mann-Whitney test was used to compare the time to fatigue results between and within groups. Pearson product-moment correlation coefficients (r) were calculated for relationships between conduction block (%) and changes in force output (%), conduction block (%) and changes in time to fatigue (%), and absolute force output (N) and time to fatigue (sec).

Data were analyzed using GraphPad Prism version 4.00 for Windows (GraphPad software, San Diego, California) and SigmaPlot version 11.0 for Windows (Systat Software Inc, San Jose, California).

4.0 RESULTS

4.1 Subject Characteristics

Subject characteristics are presented in Table 1. Subjects ranged in age from 24 to 58 years, with an average age of 50.4 years (SD = 10.15 years). According to international classification standards for body mass index (BMI), (weight (kg)/height $(m)^2$), on average both patient and control groups were overweight (BMI > 25.00). All patients had typical clinical features of ulnar neuropathy and none had any evidence of a generalized polyneuropathy.

4.2 Electrophysiological Measures

Results from the electrophysiological measures for controls and patients are summarized in Table 2. No significant differences were found when examining the CMAP negative peak amplitudes in healthy controls between dominant and non-dominant hands ($p>0.05$). Similarly, no significant differences were detected when examining the CMAP areas in healthy controls between dominant and non-dominant hands ($p>0.05$). No significant differences were found when comparing CMAP amplitudes or areas between controls and the unaffected limbs of patients with UNE ($p>0.05$).

Table 3 contains the results for the motor and sensory nerve conduction studies in the patient group. In the unaffected limb, no significant differences were detected between below-elbow and above-elbow CMAP amplitudes or areas ($p>0.05$). The unaffected limb did have a significantly slower conduction velocity (CV) across the elbow versus the forearm ($p = 0.04$). In the UNE affected limb, significant differences

were detected between below-elbow and above-elbow CMAP amplitudes, with the below-elbow CMAP significantly greater ($p = 0.001$). Also, the below-elbow CMAP area was found to be significantly greater than the above-elbow CMAP area ($p = 0.03$). In the UNE affected arm the CV across the elbow was significantly slower than the CV in the forearm ($p<0.0001$). No significant difference was detected in sensory nerve action potential (SNAP) amplitudes between UNE affected and unaffected limbs ($p>0.05$). When comparing the electrophysiological measures of the unaffected and UNE affected limbs below-elbow no significant differences were detected ($p>0.05$), while there was significantly reduced CMAP area, CMAP amplitude and CV above-elbow in UNE affected limbs versus healthy limbs ($p<0.05$). The UNE patient group presented with a mean conduction block of 42.33% of the ulnar nerve across the elbow, ranging from 18.9% to 76.07%.

4.3 Force and Endurance Measures

Results for the force measures are in Table 4. Healthy controls did not significantly differ in maximal force output in index finger abduction between non-dominant and dominant hands ($p>0.05$). Similarly, maximal force output did not differ between healthy controls and the unaffected hands of patients ($p>0.05$). However, a significant difference in maximal force output was found between the UNE affected and unaffected hands within the patient group ($p = 0.005$). No significant difference was detected between UNE affected and unaffected key pinch strength within the patient group ($p>0.05$). Manual strength testing using the Medical Research Council (MRC) 5-point scale found no weakness of the FDI muscle or abductor digiti quinti muscle (ADQM) in the patients' unaffected limbs. The UNE affected limbs of the patient group

presented with reduced muscle resistance in both FDI and ADQM as measured through manual strength testing.

Results from the endurance measures are summarized in Table 4. Healthy controls did not significantly differ in time to fatigue (TTF) in index finger abduction between non-dominant and dominant hands. Nor did TTF significantly differ between healthy controls and the unaffected hands of patients ($p>0.05$). A significant difference in TTF was found between the UNE affected and healthy unaffected hands within the patient group ($p = 0.01$).

Supramaximal stimulation of the ulnar nerve at rest produced muscle twitches with force outputs approximating 10% of MVC force output in both groups (mean twitch force = 2.4 N). No interpolated twitch was observed in controls or patients during MVC or during the fatiguing contractions.

4.4 Conduction Block-Force Output Relationships

The relationship between the % conduction block in patients with UNE and the difference in MVC performance between affected and unaffected limbs is illustrated in Figure 2. When measuring force in index finger abduction using the hand dynamometer, these two factors were found to be directly related; meaning a greater degree of conduction block was associated with a greater decrement in strength ($r = 0.74$). However, when using the key pinch test, no relationship was found between conduction block and force output ($r = 0.05$).

The relationship between the % conduction block in patients with UNE and the difference in time to fatigue between affected and unaffected limbs can be found in

Figure 3. A direct relationship between these variables was found to exist, characterized by greater decrement to endurance with greater degrees of conduction block ($r = 0.60$).

Figure 4 illustrates the differences in MVC force outputs between the UNE affected limbs and unaffected limbs within the UNE patient group. Figure 5 illustrates the differences in MVC force output between the dominant and non-dominant hands within the control group.

Figure 6 displays the relationship between MVC strength (N) and time to fatigue (sec) in all healthy controls and patients. No relationship was detected between these two variables ($r = 0.03$).

Table 2. Electrophysiological measures of controls and patients with UNE

	Electrophysiological Measure	
Controls	CMAP Amplitude (mV)	CMAP Area (mVms)
Dominant Hand	12.4 ± 2.9	29.0 ± 3.5
Non-Dominant Hand	12.2 ± 2.3	27.6 ± 2.7
Patients with UNE		
Unaffected Hand	11.6 ± 3.1	25.7 ± 6.4
UNE Affected Hand	11.1 ± 4.3	23.7 ± 9.1

Results obtained from ulnar nerve stimulation at the wrist.

CMAP = compound muscle action potential

Table 3. Motor and sensory nerve conduction studies of patients with UNE

Patients with UNE	CMAP Amplitude (mV)	CMAP Area (mVms)	Conduction Velocity (m/s)	SNAP Amplitude (μV)	Conduction Block (%)
Below-elbow Unaffected Limb	11.6 ± 3.1	25.7 ± 6.4	53.9 ± 5.2	33.7 ± 9.6	n/a
UNE Affected Limb	11.1 ± 4.3	23.7 ± 9.1	53.1 ± 5.1	30.2 ± 14.2	n/a
Above-elbow Unaffected Limb	10.6 ± 2.6	24.1 ± 6.9	48.5 ± 3.5	n/a	n/a
UNE Affected Limb	7.2 ± 3.5*†	14.5 ± 7.7*†	30.5 ± 7.1*†	n/a	42.3 ± 17.7

UNE = ulnar neuropathy at the elbow, CMAP = compound muscle action potential, SNAP = sensory nerve action potential

* denotes significant difference between limbs, † denotes significant difference between stimulation sites

Table 4. Strength and endurance measurements of isometric index finger abduction

Group	Mean MVC Force (N)	Force Range (N)	Mean TTF (sec)	TTF Range (sec)	Mean Key Pinch Force (kp)	MRC - FDI	MRC – ADQM
Control							
Dominant Limb	32.3 ± 10.6	26.4 - 62.1	116.8 ± 54.1	71.1 - 164.3	n/a	n/a	n/a
Non-Dominant Limb	27.6 ± 10.0	22.1 - 57.8	111.9 ± 36.1	70.0 - 158.0	n/a	n/a	n/a
Patient w/ UNE							
Unaffected Limb	27.9 ± 11.2	16.9 - 50.1	124.7 ± 32.2	64.7 - 256.9	6.4 ± 2.7	5	5
UNE Affected Limb	16.2 ± 8.0*‡	7.4 - 33.4	96.5 ± 33.9*‡	70.8 - 182.6	4.9 ± 2.1	4	4

MVC = maximal voluntary contraction, TTF = time to fatigue, UNE = ulnar neuropathy at the elbow

MRC = Medical Research Council, FDI = first dorsal interosseous muscle, ADQM = abductor digiti quinti muscle

* denotes significant difference between limbs, ‡ denotes significant difference between subject groups

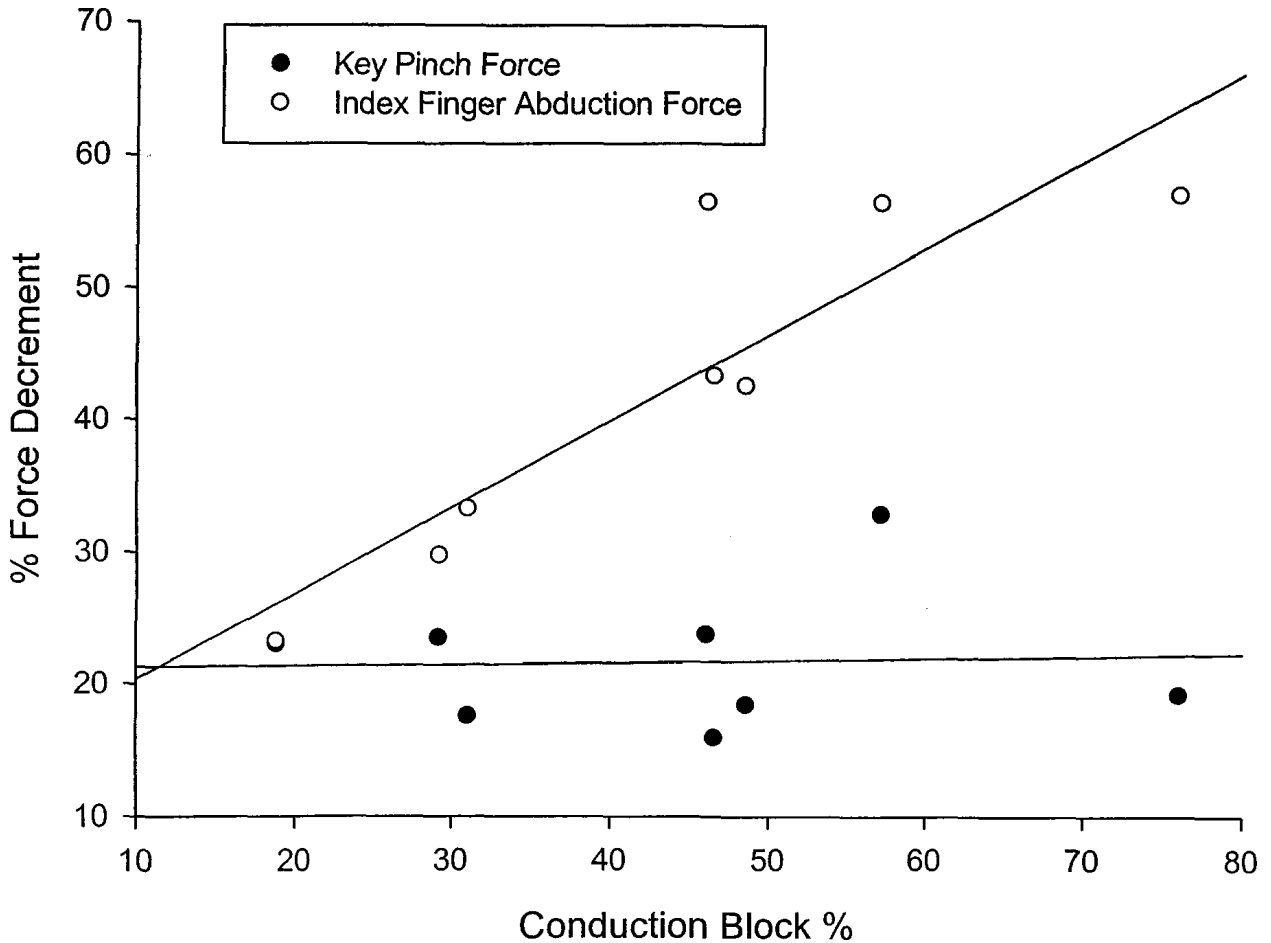


Figure 2. Relationship between conduction block and MVC force decrement as measured by index finger abduction (r = 0.74) and key pinch (r = 0.05) in patients with UNE.

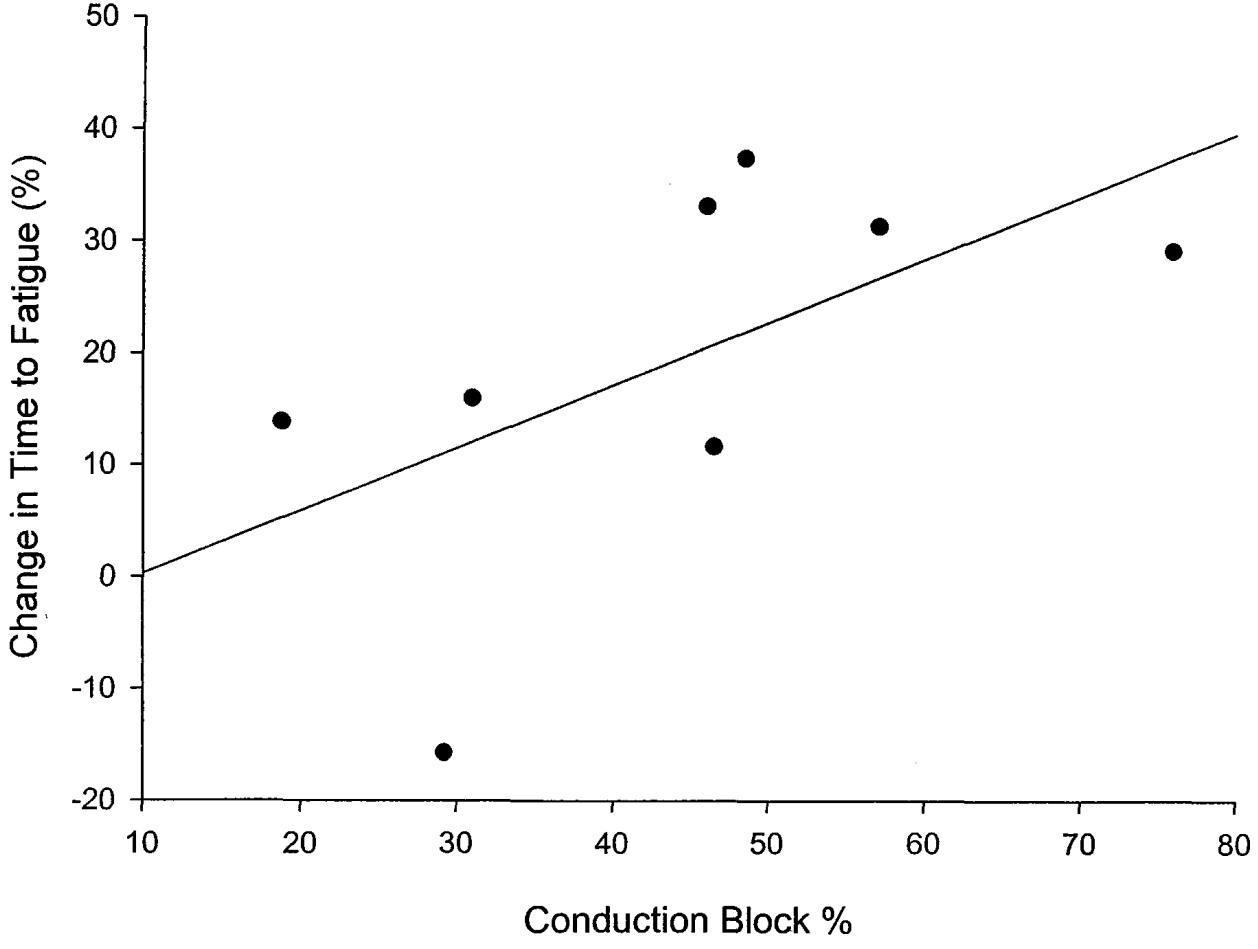


Figure 3. Relationship between conduction block and time to fatigue during 70% MVC sustained, isometric, index finger abduction (r = 0.60) in patients with UNE.

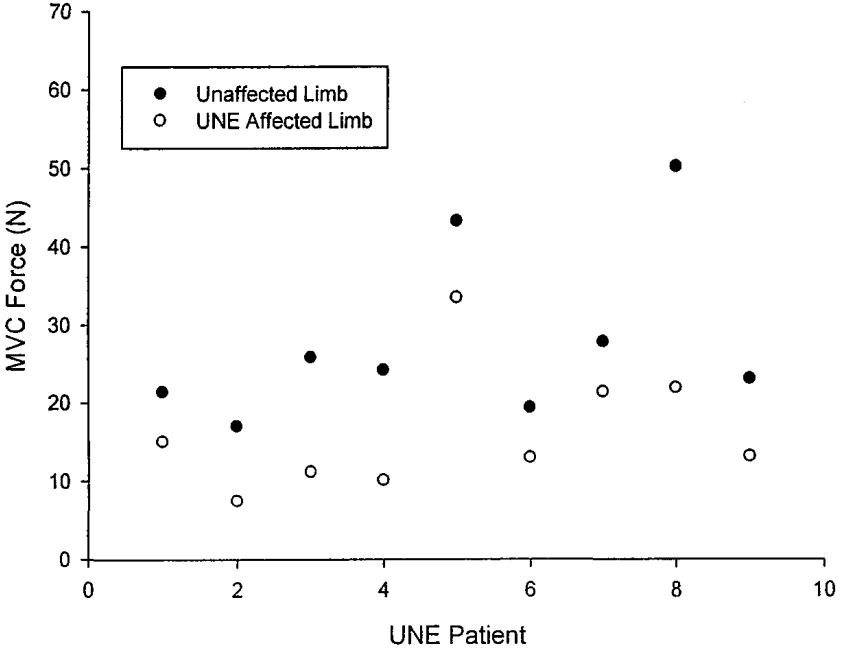


Figure 4. Difference in MVC force output between UNE affected limb and unaffected limb in patients with UNE. (MVC = maximal voluntary contraction)

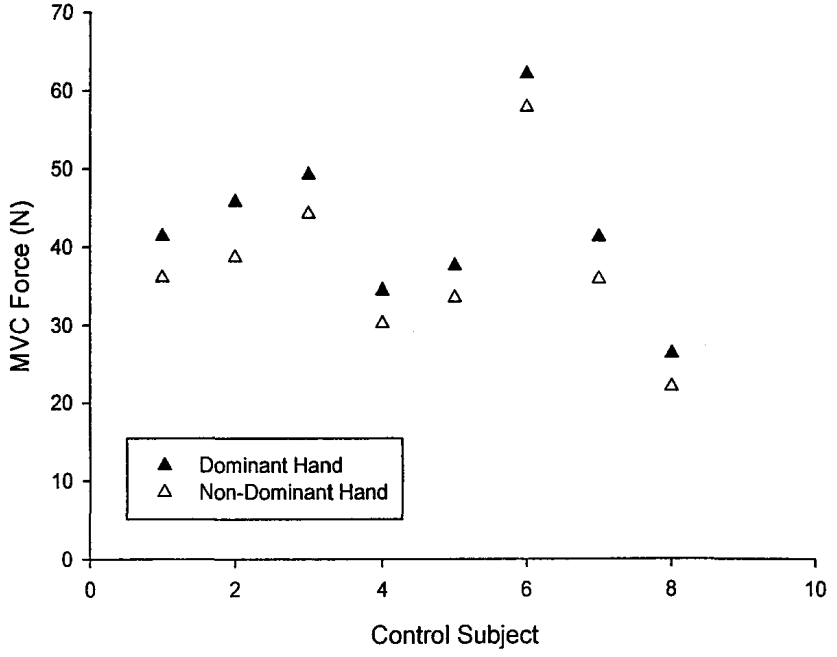


Figure 5. Difference in MVC force output between dominant and non-dominant hands in control subjects. (MVC = maximal voluntary contraction)

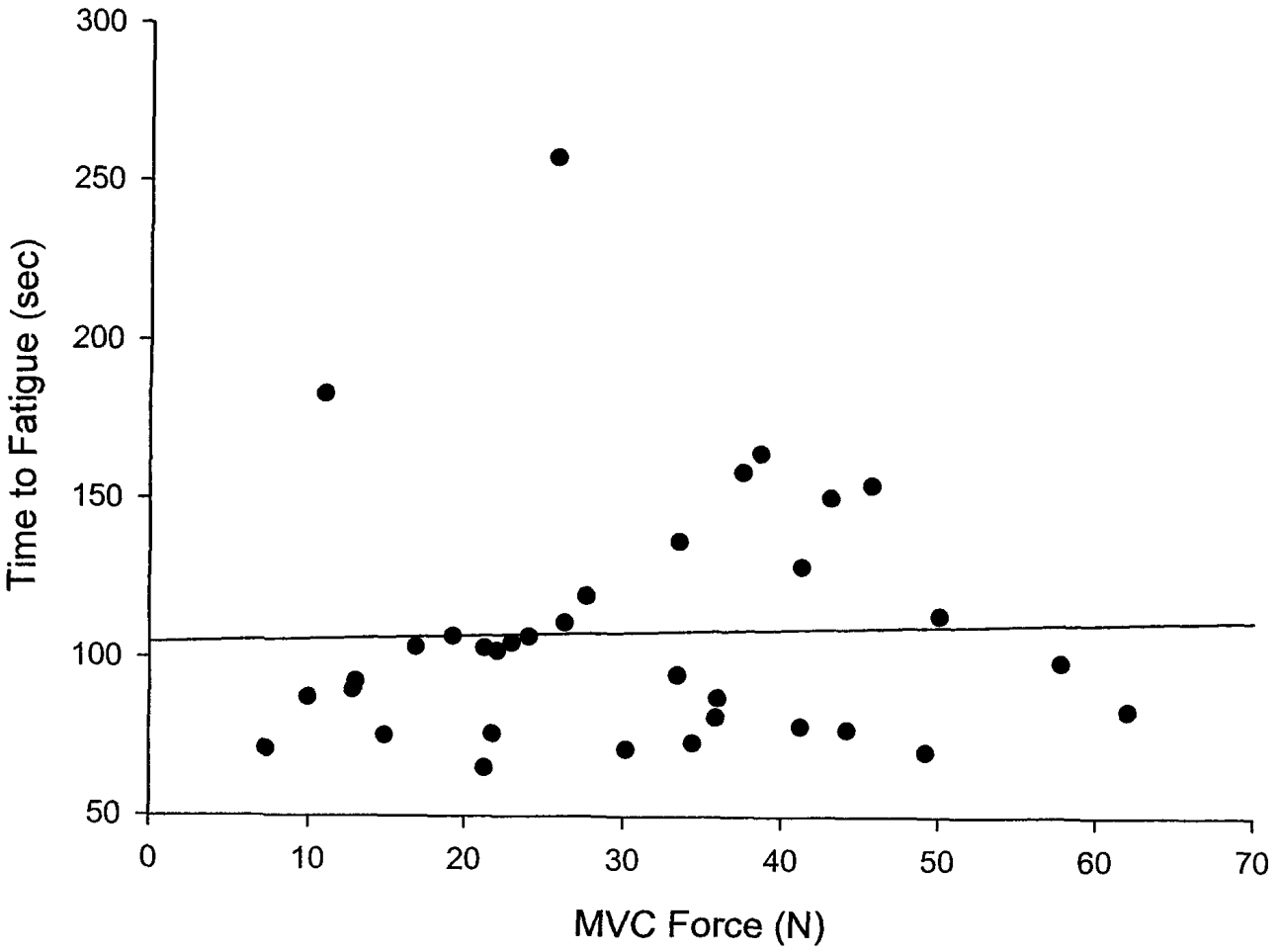


Figure 6. Relationship between MVC force output and time to fatigue in patients with UNE and healthy controls (r = 0.03)

(MVC = maximal voluntary force output, UNE = ulnar neuropathy at the elbow)

5.0 DISCUSSION

This study examined the effect of peripheral nerve conduction block on muscular strength and endurance in patients with UNE. While many studies have shown that demyelinative conduction block results in a loss of strength, to our knowledge, no study has quantified the extent of conduction block and compared it with the objective measurement of muscular strength in a focal nerve injury (Kuhlman & Hennessey, 1997; Simpson, 2002). Additionally, previous case studies have reported a decrease in muscular endurance as subjectively described by patients with focal nerve injury (Eversmann, 1993), but to our knowledge no investigation has examined changes in muscular endurance in these patients using an objective measure such as a hand dynamometer.

5.1 Major Findings

Our results demonstrate that: 1) patients with ulnar neuropathy had weaker isometric index finger abduction MVC force versus their healthy limb and control values; 2) this observed weakness was directly related to the extent of conduction block; 3) patients with UNE exhibited greater fatigue in comparison to the unaffected limb and controls; 4) this increased fatiguability was directly related to the extent of conduction block; 5) measurements acquired via strength testing using intrinsic hand muscle dynamometry relate more closely to the extent of nerve damage than key pinch dynamometry or MRC testing.

5.2 Conduction Block and Strength

Our findings indicate that patients with UNE had significantly weaker FDI muscles in their affected limb, as measured by a custom-built intrinsic hand muscle dynamometer, when compared with their unaffected limb and controls. The degree of weakness observed was strongly related to the extent of conduction block on electrophysiological testing present in the ulnar nerve. The strong correlation (Portney & Watkins, 2009) between degree of demyelinative conduction block (DCB) and force decrement suggests DCB is a factor leading to a loss of strength. When a peripheral nerve suffers from DCB some nerve fibres are unable to propagate an action potential beyond the site of demyelination, and thus their corresponding muscle fibres do not receive the signal to contract. It stands to reason that if all muscle fibres are contracting in a muscle innervated by a healthy nerve, it will be able to produce more force than a similar muscle in which some muscle fibres are unable to contract. However, it may be possible that factors other than an inability to recruit all muscle fibres could be reducing force output in patients with UNE. The relationship between nerve damage and muscle weakness found in the current study is supported by previous studies examining related neuropathic conditions. It is important to note these studies did not use conduction block itself as a measure of neural impairment.

Schreuders and colleagues (2004) examined 34 patients who had suffered ulnar, median, or combined ulnar and median nerve injury in the forearm 2 years previously and had since undergone surgical treatment to repair their injured nerve. A number of these patients also suffered muscle, tendon, bone or blood vessel injury during the event that caused the nerve damage. No electrophysiological data were provided pertaining to the

precise extent of nerve damage, but nerve impairment and the presence of conduction block was assumed. The ulnar nerve injury group had mean index finger abduction force decrement of 63% versus their non-injured side, while the combined ulnar and median nerve group had 55% decrement in index finger abduction. While the damage incurred to tissue other than the nerve itself may be a confounding factor, these results support the findings in the present study, that muscular weakness is a direct result of focal nerve injury.

Tamburin *et al.* (2008) investigated 129 carpal tunnel syndrome (CTS) patients for hand weakness and hand clumsiness. These functional evaluations of the hand were then correlated with neurophysiologic measures. Unlike the present study, Tamburin and colleagues used a 5 point scale to define the level of neural impairment (1 = minimal, 5 = extreme), and conduction block was not the main phenomenon of interest. Rather, the main neurophysiologic measures of interest included a combination of sensory nerve conduction velocity (SNCV), sensory nerve action potential (SNAP) amplitude, compound muscle action potential (CMAP) amplitude and wrist-thenar distal motor latency. Hand strength was assessed using the Medical Research Council (MRC) scale. 56% of CTS affected upper limbs were found to present with significant hand weakness, supporting the notion that focal nerve damage leads to decrement in muscle strength. However, unlike the present study, no correlation was found between thenar muscle strength and electrophysiological impairment. This result could potentially be a consequence of using a measure of strength (MRC scale) that has been found to be insensitive to small differences in force (van der Ploeg *et al.*, 1984). Additionally, while the neurophysiologic measures did include several important markers of peripheral nerve

health, conduction block was not included, which may be the most relevant measure in relation to skeletal muscle function.

Due to the lack of correlation between neurophysiologic measures and hand weakness, Tamburin suggested that pain, not neural impairment, was the preeminent factor responsible for the loss of strength. Pain has been found to disrupt performance in motor tasks (Birch *et al.*, 2000). Painful digital stimulation has been found to inhibit hand muscles, which may be part of a protective reflex meant to cause dropping a painful stimulus (Floeter *et al.*, 1998). Additionally, muscle pain is believed to cause inhibition of motor unit firing (Sohn *et al.*, 2000). These factors may have played a role in hand weakness in patients with CTS as they reported significant levels of pain during hand muscle contraction (Tamburin *et al.*, 2008). Pain has been a reported symptom in patients with UNE (Campbell, 1997), however, no specific measure of pain or discomfort was used to investigate the possibility of their presence during the study. This indicates that pain may play a role in some focal neuropathies in which it is present, but it cannot be definitively known if pain impacted the results of the present study at this time.

5.3 Conduction Block and Muscle Endurance

In the current study, ulnar nerve conduction block did result in significantly reduced endurance of the FDI muscle in isometric index finger abduction force versus the FDI muscle in the unaffected limb. In addition, the extent of conduction block was moderately correlated (Portney & Watkins, 2009) with the % decrease in time to fatigue ($r = 0.60$). To our knowledge, no previous study has quantified changes in muscle endurance in focal compressive neuropathy patients using an objective measure such as a

hand dynamometer. However, earlier investigations have found changes in fatiguability when examining other peripheral neuropathies.

In 2004, Ozcakar and colleagues examined 23 patients with thoracic outlet syndrome (TOS), a condition characterized by damage to the lower trunk of the brachial plexus. These patients were found to have significantly decreased upper limb endurance in isokinetic shoulder flexion. The authors postulated the observed changes in endurance were due to a combination of neurogenic and vascular compression at the axilla, however no measures of either form of compression were included in the study. Also, no specific aspects of neurogenic compression were put forth as the mechanism causing a reduction in muscle endurance. A case report conducted by Bissay *et al.* in 2008 found a reduction in endurance when investigating a 35 year old patient with chronic inflammatory demyelinating polyneuropathy (CIDP) who presented with conduction block in multiple nerves. Bissay postulated the prolonged refractory periods in these demyelinated nerves could have been partially responsible for changes in fatigue levels, which is a factor patients with CIDP share with the patients with UNE in this study. However, Bissay also suggested pro-inflammatory cytokines unique to inflammatory nerve diseases could have affected the patient's fatiguability, an issue unlikely to contribute to the changes in fatigue observed in patients with UNE.

In the present study, conduction block was demonstrated at rest in response to single, supramaximal stimuli, in all of the affected limbs for the patients with UNE. However, it was not known if the damage incurred to the ulnar nerve led to activity-dependent conduction block during sustained contraction in these patients. If activity-dependent conduction block was present in these patients, it is possible that it was

responsible for the decrease in time to fatigue on the UNE affected limbs of patients. In 2000, Kaji and colleagues studied multifocal motor neuropathy (MMN) patients who presented with conduction block at the median nerve. During MVC's, prolonged motor latencies were initially detected, followed by further block in conduction relative to baseline. Muscle fatigue was found to occur in parallel with the increased level of conduction block. These findings led Kaji and colleagues to conclude activity-dependent conduction block, precipitated by axonal hyperpolarization, was the main cause of fatigue in patients with MMN. While the presence of activity-dependent conduction block was not accounted for in the current study, at this time it seems the most plausible explanation for the reduced endurance in our patients with UNE.

Kiernan and colleagues (2007) described axonal changes that occur in patients' nerves that have suffered demyelination using threshold tracking techniques. In patients with multifocal motor neuropathy (MMN), Kiernan found abnormalities in excitability properties of the nerves tested just distal to the site of damage. These changes were thought to arise from reduced resting paranodal and internodal potassium conductance which was a result of increased resting membrane hyperpolarization. Similar changes were noted in patients with spinal cord injury (SCI) distally to the site of injury (Shin Yi *et al.*, 2007). These findings may relate to the patients with UNE examined in the present study, who may have similar decreases in axonal excitability distal to the site of nerve damage. These changes in axonal properties may increase the likelihood of action potential propagation failure during instances of high-frequency motor unit recruitment (as observed by Kaji *et al.*, 2000), and thus lead to the observed decrement in muscle endurance in patients with UNE as measured in this investigation.

5.4 Interpolated Twitch Technique

The interpolated twitch technique was included in the present study to assess the level of voluntary activation reached by subjects during MVC's and the fatiguing contraction. No interpolated twitches were detected during contractions in the control group. This result was expected as it has been previously demonstrated that most individuals are capable of fully activating the FDI muscle and are not susceptible to central fatigue at moderate to high intensity contraction levels (Thomas *et al.*, 1989; Kalmar & Cafarelli, 2004). Similarly, no interpolated twitch was detected during contraction in the patient group, which was not expected. Due to the nature of UNE it was predicted that interpolated twitches would be observed during MVC's and fatiguing contractions in the patient group. A possible contributing factor mitigating the FDI twitch during contraction could be antagonist action from the first palmar interosseous (FPI) muscle. The FPI muscle's main action is first finger adduction (opposing FDI) and it is also innervated by the ulnar nerve. So, as supramaximal stimulation was applied to the ulnar nerve at the wrist, both FDI and FPI would contract, possibly cancelling one another out and leaving no observable interpolated twitch. Another possible reason explaining the lack of interpolated twitch in the patient group is the intrinsic hand dynamometer used to measure force output was insensitive to the relatively small interpolated twitch force or that the twitch was undetectable behind the noise present during a high level contraction. Finally, force produced during supramaximal ulnar nerve stimulation may not have translated to perfect index finger abduction, and thus some of the force produced would not have been measured by the hand dynamometer.

5.5 Intrinsic Hand Muscle Dynamometry versus Manual Muscle Testing and Key Pinch Dynamometry

The present study allowed for the direct comparison of intrinsic hand muscle dynamometry with manual muscle testing, as graded by the MRC 0 to 5 scale. While results from the dynamometer show substantial differences in force decrement across the patient group and a direct relationship between the extent of DCB and strength loss, results from manual muscle testing did not differ from patient to patient (all patients exhibited grade 4 muscle strength in the FDI and ADQM). These results are consistent with findings from previous studies which conclude manual muscle testing is not sensitive in detecting change within grades 3 to 5 (van der Ploeg & Oosterhuis, 1984; Dvir, 1997). In 1997 Dvir found that individuals who are assessed as having grade 4 muscle strength in their elbow and knee muscles may actually demonstrate only 10% of maximal strength as measured through dynamometry. Selles and colleagues found Charcot-Marie-Tooth disease patients who were assessed with grade 4 muscle strength in their intrinsic hand muscles had overlapping force outputs with patients assessed with grade 5 muscle strength. Additionally, Selles reported a modest correlation between hand dynamometry and MRC testing of 0.65. These results indicate manual muscle strength testing is not sensitive in measuring differences in muscle strength at the upper end of the spectrum, and does not appear to be effective in differentiating between degrees of DCB. In contrast, intrinsic hand muscle dynamometry can effectively measure even small differences in muscle strength, and correlate these strength changes closely with the extent of DCB. So while manual muscle strength testing may still be a simple and useful clinical tool, especially in cases of little to no muscle resistance or changes in range of

motion, intrinsic hand dynamometry appears to be more effective in detecting small changes in strength.

In the current study we were able to compare how testing strength in patients with UNE using a custom-built hand dynamometer that measures index finger abduction differs from a key pinch dynamometer that measures the force elicited by a key pinch between the index finger and thumb. Both tests aim to measure strength primarily from skeletal muscles innervated by the ulnar nerve (Kozin *et al.*, 1999). The index finger dynamometer was designed to immobilize the wrist and all motion within the hand, while solely measuring the isometric force output of the FDI muscle as it abducts the index finger at the metacarpophalangeal joint. The key pinch dynamometer however, evaluates intrinsic and extrinsic hand muscle strength in combined action on the index finger and thumb (Selles *et al.*, 2006). Additionally, key pinch dynamometry employs significant median nerve innervated muscles (for example, flexor pollicis longus) which could further diminish its ability to effectively measure weakness in ulnar innervated hand muscles. Our results show that when using the intrinsic hand muscle dynamometer, the affected limbs of patients with UNE produce significantly less force than their healthy limbs, and there exists a close relationship between strength decrement and conduction block ($r = 0.74$). In contrast, within the same UNE patient group, no significant difference in force output was detected bilaterally when measuring force with the key pinch dynamometer. Additionally, when analyzing results from the key pinch dynamometer, no relationship was evident when examining bilateral differences in strength with corresponding levels of conduction block. That is to say, in our study while the intrinsic hand muscle dynamometer appeared to be effective in assessing the presence and severity

of nerve injury, the key pinch dynamometer was not. Notwithstanding the lack of significant difference and relationship when measuring force using the key pinch dynamometer, there was a non-significant difference of approximately 25% between UNE affected and unaffected force output in the patient group. This suggests the sample size may have been too small and thus the analysis underpowered, increasing the possibility of type two error. It is possible a greater sample size that followed a similar trend could have produced a significant difference between these measures.

Previous studies have compared pinch strength testing versus intrinsic hand muscle strength testing, in particular the Rotterdam Intrinsic Hand Myometer (RIHM), which can be employed to measure index finger abduction strength (Schreuders *et al.*, 2006). In 2006, Selles and colleagues compared strength outcome measures from pinch tests, grip tests and intrinsic hand muscle dynamometry in Charcot-Marie-Tooth (CMT) disease patients. They found that pinch strength correlated very closely (as high as 0.83) with the results from the RIHM, whereas the correlations between the RIHM and grip strength were lower (as high as 0.65). They reasoned the high correlation between RIHM and pinch measurements is a reflection of the importance intrinsic hand muscles have in pinch strength, which seems to contradict our findings. However, the high correlation found in Selles' study is most likely due to the nature of CMT, a disease that would affect both ulnar and median nerves, and thus result in a loss of strength in all intrinsic hand muscles, not just those with ulnar innervation. Additionally, it is likely that there was a wide range of clinical presentations which may have increased the chances of finding a high correlation due to high variance in the data. However, the same study also found that it is possible for patients to present with high pinch strength but little or even no intrinsic

hand muscle strength, which supports the present studies results. Selles postulated this could occur through training or compensation by extrinsic hand muscles. While Charcot-Marie-Tooth disease is not a focal neuropathy, nor is it isolated to the ulnar nerve, a similar explanation could help explain our findings.

In 2004, Schreuders and colleagues examined strength recovery in ulnar and median nerve damaged patients using the RIHM and pinch strength testing. They found that while pinch strength was found to recover to 75% of uninjured strength, a substantially more modest recovery was found in index finger abduction which recovered only to 26% of uninjured strength. Rossen found similar strength recovery results using a different intrinsic hand muscle dynamometer in ulnar neuropathy patients (Rosen, 1996). In both cases, the discrepancy in muscle strength measures was thought to arise from a compensatory mechanism causing increased activation of extrinsic, median innervated hand muscles. Although no study to date has attempted to measure any possible changes in activation pattern in these instances using EMG or other diagnostic techniques.

Therefore, perhaps the patients with UNE in the present study were able to compensate for their weakened ulnar innervated muscles by increasing activation of median nerve supplied muscles, including flexor pollicis longus, opponens pollicis, flexor digitorum superficialis. The increased activity of these median nerve innervated muscles is a possible explanation for why no force decrement was found in patients with UNE when measuring key pinch strength, despite measureable weakness in actions resulting from a purely ulnar innervated muscle (FDI).

Another technical problem associated with key pinch dynamometry involves ensuring patients are employing only the pad-to-pad pinch rather than "cheating" and using the tip-to-tip pinch. The pad-to-pad pinch primarily measures ulnar innervated muscles, whereas tip-to-tip pinching involves muscles innervated by the median nerve. It is very difficult to prevent individuals with ulnar intrinsic hand muscle weakness from resorting to tip-to-tip pinching during this test, as they are motivated to produce the maximum amount of force, and tip-to-tip pinching allows for greater force production versus pad-to-pad in this setting. This technical aspect of key pinch dynamometry use creates uncertainty in its usefulness as a measure of ulnar innervated muscles alone.

5.6 Summary and Conclusions

Conduction block of the ulnar nerve results in a reduction of FDI muscle strength due to an inability to contract all available muscle fibres, but these results do not elucidate the potential impact of pain on force output. An increase in the degree of conduction block leads to further decrement in strength. Conduction block of the ulnar nerve also leads to a reduction in FDI muscle endurance. Future studies should investigate for the presence of activity-dependent conduction block in patients with UNE to account for this change in endurance. Additionally, the intrinsic hand muscle dynamometer appears to be more sensitive in detecting changes in muscle properties caused by nerve injury than manual muscle testing or a key-pinch dynamometer due to its abilities to detect small changes in force output and to isolate a muscle innervated solely by the nerve in question.

6.0 LIMITATIONS AND FUTURE DIRECTIONS

A potential limitation in this study was the limited amount of patients with UNE that were tested. While the patients tested did range in levels of conduction block from approximately 20% to 80%, the relationships between conduction block and force decrement/changes in muscular endurance could have been made more clear with a greater sample size. This is made especially apparent as one of the patients actually had a longer time to fatigue on their injured limb, and one other patient had a time to fatigue that was nearly twice that of the next longest patient. A greater sample size would help mitigate the effect these results have on the data.

A second limitation in this study involves the questions that have arisen surrounding the interpolated twitch technique. While it was expected that interpolated twitches would be observed during contraction in the patient group (due to their inability to maximally activate the FDI muscle voluntarily) no such twitches were detected. This result leaves the investigators unable to confidently conclude whether subjects were maximally activating during the experimental protocol, or not.

Another potential limitation affecting this study was the variability in symptoms experienced by patients. While electrophysiological measures proved all patients suffered from UNE and that no significant difference was detected in SNAP amplitudes, symptoms are known to vary in patients with UNE (Campbell, 1997; Eversmann, 1993). Some patients may experience constant paraesthesia, others numbness only at night, and others none at all. Additionally, some patients may report discomfort or "unsteadiness" during sustained contractions of their UNE affected side, while others may not. No

method was used to account for differences in symptoms in this study, and it is not known how they could have impacted the subjects' performance. Future studies could group patients based on their symptoms to investigate their potential impact on results.

Using a model similar to the one employed in this study, future investigations could examine the effect, if any, of conduction slowing alone (with no conduction block present) on muscle strength and fatiguability. Conduction slowing results from the same process causing conduction block and while theoretically it may seem like slowing should have no discernible impact on skeletal muscle at natural neural firing rates, no study to date has investigated its potential affect on muscle. Also, a measure intended to test for the presence of activity-dependent conduction block should be included during the fatigue protocol. This could potentially rule out or confirm activity dependent conduction block as a factor leading to changes in muscle endurance in patients with UNE.

The results from this study concluded that the intrinsic hand muscle dynamometer was an effective tool in measuring functional changes in muscles innervated by an ulnar nerve suffering from conduction block. Future studies could use this knowledge in conducting studies designed to assess the effectiveness of the many conservative and surgical treatments currently available for treating UNE. To our knowledge, no studies have been conducted to assess or compare the effectiveness of splinting, padding, ultrasound, or lifestyle changes (e.g. no sitting with crossed arms) despite their widespread prescription. Likewise, many different surgical options exist in treating severe cases of UNE including simple decompression, submuscular, subcutaneous, or intramuscular transposition, however how these procedures differ in effectiveness

remains largely unclear. Future investigations could use a model similar to that used in this study to effectively compare how these different treatment options impact recoveries in patients with UNE.

7.0 REFERENCES

Alvine, F.G. & Schurrer, M.E. (1987). Post-operative ulnar nerve palsy: Are there predisposing factors? *J Bone Joint Surg Am*, 69:255-259.

Amadio, P.C. & Beckenbaugh, R.D. (1986). Entrapment of the ulnar nerve by the deep flexor-pronator aponeurosis. *J Hand Surg Am*, 11:83-87.

Apfelberg, D.B. & Larson, S.J. (1973). Dynamic anatomy of the ulnar nerve at the elbow. *Plast Reconstr Surg*, 51:79-81.

Birch, L., Graven-Nielsen, T., Christensen, H. & Arendt-Nielson, L. (2000). Experimental muscle pain modulates muscle activity and work performance differently during high and low precision use of a computer mouse. *Eur J Appl Physiol*, 83:492-498.

Bissay, V., Flamez, A., Schmedding, E. & Ebinger, G. (2008). Fatigue as the presenting symptom of chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve*, 38:1653-1657.

Bostock H. & Grafe, P. (1985). Activity-dependent excitability changes in normal and demyelinated rat spinal root axons. *J Physiol*, 365: 239-257.

Bostock, H. & Rothwell, J.C. (1997). Latent addition in motor and sensory fibres of human peripheral nerve. *J Physiol*, 498:277-294.

Brandsma, J.W., Schreuders, T.A., Birke J.A., Piefer, A. & Oostendorp, R. (1995). Manual muscle strength testing: intraobserver and interobserver reliabilities for the intrinsic muscles of the hand. *J Hand Ther*, 8(3):185-190.

Brown, W.F. & Feasby, T.E. (1984). Conduction block and denervation in Guillain-Barre polyneuropathy. *Brain,* 107: 219-239.

Brown, W.F. & Watson, B.V. (2002). Pathophysiology of conduction in peripheral neuropathies. In: Brown, W.F., Bolton, C.F. & Aminoff, M.J., editors. Neuromuscular function and disease: basic, clinical, and electrodiagnostic aspects. Philadelphia: W.B. Saunders; p 56-94.

Campbell, W. W. (2000). Ulnar neuropathy at the elbow. *Muscle Nerve*, 23:450-452.

Campbell, W.W. (1997). Diagnosis and management of common compression and entrapment neuropathies. *Neurol Clin*, 15:549-67.

Campbell, W.W., Carol, D.J., Greenberg, M.K., *et al.* (1999). Practice parameter for electrodiagnostic studies in ulnar neuropathy at the elbow: summary statement. *Muscle Nerve*, 22:408-411.

Cappelen-Smith, C., Kuwabara, S., Lin, C.S., Mogyoros, I. & Burke, D. (2000). Activity-dependent hyperpolarization and conduction block in chronic inflammatory demyelinating polyneuropathy. *Ann Neurol*, 48:826-832.

Carpentier, A., Duchateau, J. & Hainaut, K. (2001). Motor unit behaviour and contractile changes during fatigue in human first dorsal intersosseus. *J. Physiol,* 534(3):903-912.

Craven, P.R. & Green, D.P. (1980). Cubital tunnel syndrome: Treatment by medial epicondylectomy. *J Bone Joint Surg*, 62:986-989.

Daube, J.R. (1985). Electrophysiologic studies in the diagnosis and prognosis of motor neuron diseases. *Neurol Clin*, 3:473-493.

Dorazio, R.A. & Ezzel, F. (1979). Arterial complications of the thoracic outlet syndrome. *Am J Surg*, 138:175-182.

Dvir, Z. (1997). Grade 4 manual muscle testing: the problem with submaximal strength assessment. *Clin Rehabil*, 11(1): 36-41.

Eichelberger, T.D. & Bilodeau, M. (2007). Central fatigue of the first dorsal interosseous muscle during low-force and high-force sustained submaximal contractions. *Clin Physiol Funct Imaging*, 27(5): 298-304.

Elhassan, B. & Steinmann, S.P. (2007). Entrapment Neuropathy of the Ulnar Nerve. *J Am Acad Orthop Surg*, 15:627-681.

Etheredge, S., Wilber, B. & Stoney, R.J. (1979) Thoracic outlet syndrome. *Am J Surg*, 138:175-182.

Eversmann, W.W. Jr. (1993). Entrapment and compressive neuropathies, in Green DP (ed): *Operative Hand Surgery,* ed 3. New York, NY: Churchill Livingston, p 1341-1389.

Feasby, T.E., Brown, W.F., Gilbert, J.J. & Hahn A.F. (1985). The pathological basis of conduction block in human neuropathies. *J Neurol Neuosurg Psyciatry*, 48:239-244.

Floeter, M.K., Gerloff, C., Kouri, J. & Hallett, M. (1998). Cutaneous withdrawal reflexes of the upper extremity. *Muscle Nerve*, 21:591-598.

Folberg, C.R., Weiss, A.P. & Akelman, E. (1994) Cubital tunnel syndrome. Part I Presentation and diagnosis. *Orthop Rev*, 23:136-144.

Garssen, M.P., Schillings, M.L., Van Doorn, P.A., Van Engelen, B.G. & Zwarts, M.J. (2007). Contribution of central and peripheral factors to residual fatigue in Guillain-Barre syndrome. *Muscle Nerve*, 36(1):93-99.

Geere, J., Chester, R., Kale, S. & Jerosch-Herold, C. (2007). Power grip, pinch grip, manual muscle testing or thenar atrophy – which should be assessed as a motor outcome after carpal tunnel decompression. *BMC Musculoskelet Disord,* 20(8):114-123.

Haig, A.J., Huey-Ming, T. & Belongia LeBreck, D. (1999). The value of electrodiagnostic consultation for patients with upper extremity nerve complaints: a prospective comparison with the history and physical examination. *Arch Phys Med*, 80:1273-1281.

Inglis, J.T., Leeper, J.B., Wilson, L.R., Gandevia, S.C. & Burke, D. (1998). The development of conduction block in single human axons following a focal nerve injury. *J Physiol*, 513:127-133.

Kaji, R. (2003). Physiology of conduction block in multifocal motor neuropathy and other demyelinating neuropathies. *Muscle Nerve*, 27:285-296.

Kalmar, J.M. & Cafarelli, E. (2004). Central fatigue and transcranial magnetic stimulation: effect of caffeine and the confound of peripheral transmission failure. *J Neurosci Methods*, 138:15-26.

Shin-Yi, L., Macefield, V.G., Elam, M., Wallin, B.G., Engel, S. & Kiernan, M.C. (2007). Axonal changes in spinal cord injured patients distal to the site of injury, *Brain*, 130:985-994.

Kiernan, M., Guglielmi, J.M., Kaji, R., Murray, N.M.F. & Bostock, H. (2002). Evidence for axonal membrane hyperpolarization in multifocal motor neuropathy with conduction block. *Brain,* 125: 664-675.

Kincaid, J.C. (1988) AAEE minimonograph #31: the electrodiagnosis of ulnar neuropathy at the elbow. *Muscle Nerve*, 11:1005-1015.

Kuhlman, K.A. & Hennessey, W.J. (1997) Sensitivity and specificity of carpal tunnel syndrome signs. *Am J Phys Med Rehabil*, 76(6):451-457

Latinovic, R., Gulliford, M.C. & Hughes, R.A. (2006). Incidence of compressive neuropathies in primary care. *J Neurol Neurosurg Psychiatry*, 77(2):263-265.

Loewy, J. (2001). Ultrasonography and magnetic resonance imaging of abnormalities of the peripheral nerves. *Can Assoc Radiol J*, 52(5):292-301.

Lundborg, G. & Dahlin, L.B. (1992). The pathophysiology of nerve compression. *Hand Clin*, 8(2):215-227.

Miller, R. (1979). The cubital tunnel syndrome: diagnosis and precise localization. *Ann Neurol*, 6:56-59.

Nodera, M.D., Bostock, H. Izumi, Y. Nakamura, K., Urushihara, R., Sakamoto, T. Murase, N., Shimazu, H. Kusunoki, S. & Kaji, R. (2006). Activity-dependent conduction block in multifocal motor neuropathy. *Neurology,* 67: 280-287.

Mondelli, M., Giannini, F., Ballerini, M., Ginanneschi, F. & Martorelli, E. (2005). Incidence of ulnar neuropathy at the elbow in the province of Siena (Italy). *J Neurol Sci*, 234:5-10.

Ogata, K. & Naito, M. (1986). Blood flow of peripheral nerve effects of dissection, stretching and compression. *J Hand Surg Br,* 11(1): 10-14.

Olney, R.K. & Miller, R.G. (1984). Conduction block in compression neuropathy: recognition and quantification. *Muscle Nerve*, 7(8):662-667.

Osborne, G. (1970). Compression neuritis of the ulnar nerve at the elbow. *Hand*, 2:10-13.

Ozcakar, L., Inanici, F., Kaymak, B., Abali, G., Cetin, A. & Hascelik, Z. (2005). Quantification of the weakness and fatigue in thoracic outlet syndrome with isokinetic measurements. *Br J Sports Med*, 39:178-181.

Payan, J. (1969). Electrophysiological localization of ulnar nerve lesions. *J Neurol Neurosurg Psychiatry*, 32:208-20.

Piligian, G., Herbert, R., Hearns, M., Dropkin, J., Landsbergis, P. & Cherniak, M. (2000). Evaluation and management of chronic work-related muscloskeletal disorders of the disal upper extremity. *Am J Ind Med*, 37:75-93.

Portney, L.G. & Watkins, M.P. (2009). Foundations of Clinical Research: Applications to Practice. Upper Saddle Hill, New Jersey: Pearson Prentice Hall, p 525.

Posner, M.A. (1998). Compressive ulnar neuropathies at the elbow: I. Etiology and diagnosis. *J Am Acad Orthop Surg*, 6:282-288.

Raynor, E.M., Shefner, J.M., Preston, D.C. & Logigian, E.L. (1994). Sensory and mixed nerve conduction studies in the evaluation of ulnar neuropathy at the elbow. *Muscle Nerve*, 17:785-792.

Rhee, E.K., England, J.D. & Sumner, A.J. (1990). A computer simulation of conduction block: effects produced by actual block versus interphase cancellation. *Ann Neurol*, 28:146-156.

Robertson, C. & Saratsiotis, J. (2005). A review of compressive ulnar neuropathy at the elbow. *J Manipulative Physiol Ther,* 28(5): 345

Schreuders, T.A., Roebroeck, M.E., Jaquet, J.B., Hovius, S.E. & Stam, H.J. (2004). Long-term outcome of muscle strength in ulnar and median nerve injury:

comparing manual muscle strength testing, grip and pinch strength dynamometers and a new intrinsic muscle strength dynamometer. *J Rehabil Med*, 36(6):273-278.

Sears, T.A. & Bostock, H. (1981). Conduction failure in demyelination: is it inevitable? In: Waxman, S.G. & Ritchie, J.E. (1981). Demyelinating Diseases. Basis and Clinical Electrophysiology. New York: Raven Press, 357-376.

Selles, R.W., van Ginneken, B.T., Schreuders, T.A., Janssen. W.G. & Stam, H.G. (2006). Dynamometry of intrinsic hand muscles in patients with Charcot-Marie-Tooth disease. *Neurology,* 67(11): 2022-2027.

Sherrat, R.M., Bostock, H. & Sears, T.A. (1980). Effects of 4-aminopyridine on normal and demyelinated mammalian nerve fibres. *Nature*, 283(5747):570-572.

Simpson, C.S. (2002). Hand Assessment. A Clinical Guide for Therapists. Salisbury, APS Publishing.

Smith, K.J., Felts, P.A. & John, G.R. (2000). Effects of 4-aminopyridine on demyelinated axons, synapses and muscle tension. *Brain*, 123:171-184.

Sohn, M.K., Graven-Nielsen, T., Arendt-Nielsen, L. & Svensson, P. (2000). Inhibition of motor unit firing during experimental muscle pain in humans. *Muscle Nerve*, 23:1219-1226.

Sohn, M.K., Graven-Nielsen, T., Arendt-Nielson, L. & Svensson, P. (2000). Inhibition of motor unit firing during experimental muscle pain in humans. *Muscle Nerve*, 23:1219-1226.

Spinner, M. & Kaplan, E.B. (1976). The relationship of the ulnar nerve to the intermuscular septum in the arm and its clinical significance. *Hand*, 8:239-242.

Stewart, J. D. (1987). The variable clinical manifestations of ulnar neuropathies at the elbow. *J Neurol Neurosurg Psychiatry* 50:252-258

Tamburin, S., Cacciatori, C., Marani, S. & Zanette, G. (2008). Pain and motor function in carpal tunnel syndrome: A clinical, neurophysiological and psychophysical study. *J Neurol*, 255:1636-1643.

Tasaki, R. (1953). Nervous transmission. Springfield: Charles C. Thomas.

Taylor, A.M., Christou, E.A. & Enoka, R.M. (2003). Multiple features of motor-unit activity influence force fluctuations during isometric contractions. *J Neurophysiol*, 90:1350-1361.

Thomas, C.K., Woods, J.J., & Bigland-Ritchie, B. (1989). Impulse propagation and muscle activation in long maximal voluntary contractions. *J. Appl. Physiol*, 67(5): 1835-1842.

van der Ploeg, R.J., Oosterhuis, H.J. & Reuvekamp, J. (1984). Measuring muscle strength. *J Neurol*, 231:200-203.

Vanderpool, D.W., Chalmer, J. & Lamb, D.W. (1968). Peripheral compression lesions of the ulnar nerve. *J Bone Joint Surg Br*, 50:792-803.

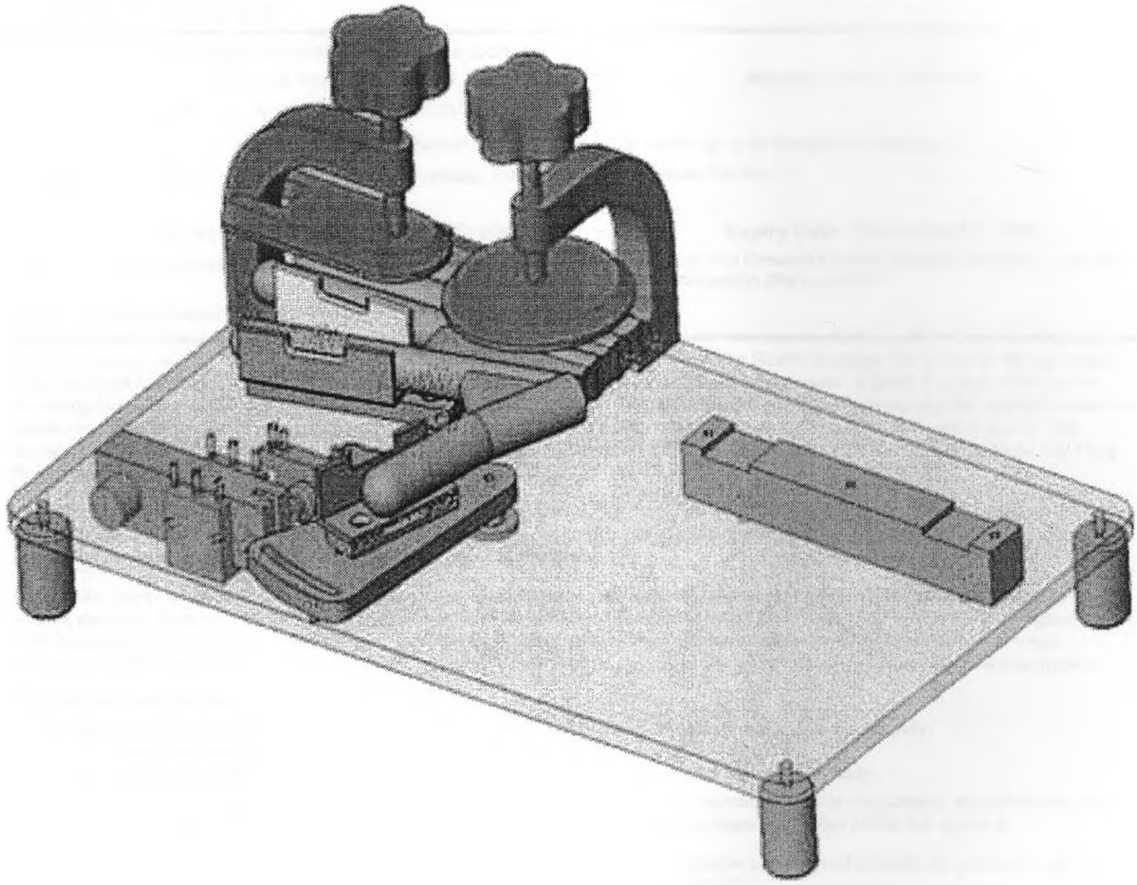
Waxman, S.G. & Brill, M.H. (1978). Conduction through demyelinated plaques in multiple sclerosis: computer simulations of facilitation by short internodes. *J Neurol Neurosurg Psyciatry,* 41:408-416.

Weber, F. (1997). Conduction block and abnormal temporal dispersion: diagnostic criteria. *Electromyogr Clin Neurophysiol*, 37(5):305-309.

Werner, C.O., Ohlin, P. & Elmqvist, D. (1985). Pressures recorded in ulnar neuropathy. *Acta Orthop Scand*, 56:404-406.

Zijdewind, I. & Kornell, D. (1994). Index finger position and force of the human first dorsal interosseous and its ulnar nerve antagonist. *J. Appl. Physiol,* 77(2):987-997.

APPENDIX A



Custom-built hand dynamometer used to measure finger abduction force.

APPENDIX B

Office of Research Ethics

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

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. T.J. Doherty
Review Number: 14086 **Review Level:** Full Board
Review Date: March 11, 2008
Protocol Title: Effect of demyelinating ulnar nerve injury on strength and fatigue
Department and Institution: Neurology, London Health Sciences Centre
Sponsor:
Ethics Approval Date: April 10, 2008 **Expiry Date:** December 31, 2008
Documents Reviewed and Approved: UWO Protocol, Letter of Information and Consent-Control Subjects version 1, Letter of Information and Consent-Ulnar Conduction Block version 1
Documents Received for Information:

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

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

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

Investigators must promptly also report to the HSREB:

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

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

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

Chair of HSREB: Dr. John W. McDonald

Ethics Officer to Contact for Further Information

☐ Janice Sutherland ☑ Jennifer McEwen ☐ Grace Kelly ☐ Denise Grafton

This is an official document. Please retain the original in your files.

cc: ORE File (HR: