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Frequency-Dependent Conduction Block In Demyelinating Focal Neuropathies

Brad V. Watson
The University of Western Ontario

Supervisor
Dr. Timothy Doherty
The University of Western Ontario

Graduate Program in Kinesiology
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy
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**FREQUENCY-DEPENDENT CONDUCTION BLOCK IN
DEMYELINATING FOCAL NEUROPATHIES**

(Spine Title: Frequency Dependent Conduction Block)

(Thesis format: Integrated-Article)

by

Bradley V. Watson

Graduate Program
In
Kinesiology

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

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

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THE UNIVERSITY OF WESTERN ONTARIO
SCHOOL OF GRADUATE AND POSTDOCTORAL STUDIES

CERTIFICATE OF EXAMINATION

Supervisor

Dr. Timothy Doherty

Supervisory Committee

Dr. Charles Rice

Dr. Michael Nicolle

Examiners

Dr. Charles Rice

Dr. Anthony Vandervoort

Dr. Thomas Miller

Dr. Richard Lewis

The thesis by
Bradley V. Watson

entitled:

FREQUENCY-DEPENDENT CONDUCTION BLOCK IN DEMYELINATING FOCAL
NEUROPATHIES

is accepted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

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ABSTRACT

It is the objective of this thesis to demonstrate conduction block across regions of focal demyelination by utilizing a conventional electrophysiological technique used frequently in the diagnosis of peripheral nerve disease. Specifically, patients with moderate to severe carpal tunnel syndrome (CTS), but, with no evidence of conduction block via conventional motor nerve conduction study techniques, were assessed in the initial studies of this thesis for evidence of frequency-dependent conduction block (FDB) by way of high-frequency nerve stimulation (HFNS) applied across the region of entrapment. The final studies examined whether FDB could be demonstrated along the median motor fibers in mild cases of CTS, despite the presence of normal motor nerve conduction studies and lastly, whether other focal entrapment or compressive neuropathies behaved similar to the results obtained from CTS patients.

The application of HFNS (30-Hz, 20 stimuli) was successful in demonstrating FDB in the median motor fibers across the region of the carpal tunnel (CT), in moderate to severe CTS patients (experiment 1). FDB was shown to be rate dependent and was more demonstrable using higher stimulus frequencies in cases with greater prolonged distal motor latencies. Unlike previous studies, these results suggest that demyelination plays a role in the pathophysiology and focal conduction slowing in CTS patients and that FDB may be responsible for the grip weakness and fatigue often described by these patients, particularly in the absence of conduction block.

FDB was successfully demonstrated again across the region of the CT, similar to experiment 1, but was also observed more distally across the distal margins of the palmar

aponeurosis and motor terminal axon (experiment 2). These results suggest that demyelination may occur distal to the lesion in CTS, supporting previous morphological and histological observations. Further, these data also suggests that the safety margin for impulse transmission can be impaired distal to the presumed site of injury in CTS and that this region should be considered as a potential site of injury, particularly in patients who fail to respond to more proximal steroid injection or surgical treatment.

Mild cases of CTS with complaints of hand weakness, but, with normal motor nerve conduction studies were then examined to determine if FDB could be demonstrated using physiological rates of HFNS (experiment 3). The results indeed demonstrated evidence of FDB (albeit mild) in patients with mild CTS that were significantly different than what was observed in controls, despite having similar conventional motor nerve conduction study results. This suggests that the FDB (also referred as activity-dependent block) may be partially responsible for the hand weakness or the difficulties with normal everyday tasks often described by patients with mild CTS. Further, this provides evidence that conventional motor nerve conduction studies, which use stimulation rates well below physiological rates of motor unit activation, fail at times to demonstrate the extent of the underlying pathophysiology affecting the motor fibers.

Lastly, the relationship between focal entrapment neuropathies with respect to the degree of FDB was examined in patients with relatively acute ulnar neuropathy localized to the elbow (UNE) and compared to previous results obtained in CTS patients from experiments 1 and 2 (experiment 4). Surprisingly, the results failed to demonstrate FDB in the remaining ulnar motor fibers across the elbow, despite evidence of severe demyelination as demonstrated by the significant conduction slowing and conduction block

observed through conventional motor nerve testing. This suggests that the margin of safety for ulnar nerve transmission is intact at physiological rates of 30-Hz in the remaining ulnar motor fibers, despite the evidence of significant conduction slowing, and that there may be a separate mechanism involved in acute focal UNE that differs from the more chronic entrapment of CTS.

KEYWORDS: frequency-dependent conduction block, activity-dependent conduction block, demyelination, high-frequency nerve stimulation, carpal tunnel syndrome, ulnar neuropathy, thenar, hypothenar

CO-AUTHORSHIP

This thesis contains material from published (Chapters 2, 3 & 5) and unpublished manuscripts (Chapter 4). The first author on all manuscripts was Bradley V. Watson. All manuscripts were co-authored by Timothy J. Doherty and William F. Brown was co-author of manuscript 1 (Chapter 2). All experimental data presented in this thesis was collected, analysed and interpreted by Bradley V. Watson.

ACKNOWLEDGEMENTS

There a number of close friends and colleagues that deserve sincere acknowledgement for contributing in many ways to the wonderful and memorable journey I've had in completing this chapter of my life. First I would like to thank Tim Doherty who has been my supervisor and mentor throughout this academic endeavour. More importantly, however, he has been more of a close friend with remarkable patience allowing me to complete this work autonomously, but, knowing when to intervene and challenge my progress and when to share his experience and wisdom. Your advanced knowledge in motor nerve physiology and wonderful sense of humour and belief in me was invaluable; thank you for this!

Secondly, I would like to thank Charles Rice and Mike Nicolle who both acted as committee members during my time as a graduate student at Western. Charles, you have that rare ability to always seem to ask the right questions that force us all to think beyond our textbooks and your help in preparing me for my written and oral examinations was greatly appreciated. And Mike, our friendship, including your advice, guidance and support over the years has been very special, thank you.

I would also like to acknowledge and thank Stephen Sims who spent a number of evenings with me reviewing in greater detail the “ins and outs” of ions and the action potential. I can only hope one day to know even a fraction of what you know on this topic.

There are a number of University Hospital staff members that played a significant role in helping me complete my thesis. Firstly, Sharon Beck, who was my director at the beginning, allowed me to pursue this goal, including taking time away from the lab to complete my course work. Secondly, Mike Nicolle, Tim Doherty, Shannon Venance,

Christen Shoesmith and Mike Strong who were always so patient with me when I wasn't around to manage the lab. Your consideration for me and your support and friendship has not gone unnoticed, thank you. Thirdly, it would be remiss of me not to thank all the EMG technologists at University Hospital who helped me during the patient recruitment phase of my work. In particular, special thanks must be given to Beata Engler for her considerable contribution and her sincere willingness in helping me collect my data.

My interest for clinical neurophysiology may have begun as an undergraduate, but, my I owe the root of my passion for this wonderful science and technology to Bill Brown. I thank you Bill for teaching me the skills of electromyography, including the ability to sort out what's important and what's not, to always go back to the fundamentals and to always be critical of my work. The countless board sessions to residents and fellows helped pave the way for what I love to do best, teach. Thank you for this and for inspiring me to start this journey at a time when I thought this discipline could offer me no more.

Rarely, does someone come into your life, well beyond your university years and put an arm around you to help guide you through some of the challenges life can throw at you. I will always be indebted to John Davidson Brown for always being there for me and my family, for teaching me the value of a close family and for letting me into his private life and allowing me to watch him live this life based on sound principles, morals and ethics. This and his close attention to quality and detail have made me not only a better researcher, but, more importantly a better person. I miss you dearly.

I'd also like to thank my parents. Regardless of the ups and downs we have all encountered, you both have always been there to support me in all my endeavours. You

have given me the foundation that was necessary for me to achieve my goals and succeed in life. I love you for this.

Lastly, and most importantly, I want to thank my beautiful wife Julie and my wonderful twins, Spencer and Matthew. Your unconditional love and support for me during this journey cannot be expressed in words. You have done more for me than what I could ever give back to you in a lifetime. I love you all and look forward with excitement in sharing the rest of my journeys with the three of you.

DEDICATION

This journey of mine is dedicated to my mother, Kathy, who left us way too early. She was the strength of our family and never once gave up on me throughout her life, regardless of the situation. I think of you every day and miss you terribly. Your love will never be forgotten.

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LIST OF ABBREVIATIONS

ADB – activity-dependent conduction block
ADM – abductor digiti minimi
AE – above elbow
ANOVA – analysis of variance
APB – abductor pollicis brevis
Ax – axilla
BE – below elbow
CIDP – chronic inflammatory demyelinating polyneuropathy
CMAP – compound muscle action potential
CT – carpal tunnel
CTS – carpal tunnel syndrome
EMG – electromyography
FDB – frequency-dependent conduction block
HFNS – high-frequency nerve stimulation
Hz – hertz
I – current
ILC – internal longitudinal current
LEMS – Lambert Eaton myasthenic syndrome
MG – myasthenia gravis
MMN – multifocal motor conduction block neuropathy
ms – milliseconds
MTL – motor terminal latency
mV – millivolts
MVC – maximal voluntary contraction
mVms – millivolt milliseconds
npAmp – negative peak amplitude
npArea – negative peak area
npDur – negative peak duration
R – resistance
RNS – repetitive nerve stimulation
s – seconds
μV – microvolts
V – voltage
W – wrist

GLOSSARY OF TERMS

Carpal tunnel syndrome (CTS) – the most frequently occurring focal peripheral neuropathy involving compression of the median nerve localized within the carpal tunnel region, beneath the flexor retinaculum. Conventional nerve conduction study techniques usually demonstrate slow conduction velocities in the sensory fibers in mild CTS and increased distal motor terminal latencies in the moderate to severe cases, suggesting demyelination

Conduction block – failure of nerve transmission or the internal longitudinal current to continue down the axon often as a result of demyelination, or pathological injury to the nodes of Ranvier

Conduction velocity – the measure of how fast the action potential travels along the nerve or muscle fiber, usually measured in meters per second (m/s). The conduction velocity of a nerve trunk or branch represents its fastest fibers and is often termed the maximum conduction velocity

Decrement – a decline in the maximum compound motor action potential during repetitive motor nerve stimulation

Demyelination – loss of the myelin sheath that insulates the larger peripheral motor and sensory axons and is responsible for the fast impulse transmission along the larger myelinated nerve fibers. Mild demyelination may produce slow nerve conduction velocities, whereas more severe demyelination may cause complete nerve transmission failure or conduction block

Frequency or activity-dependent conduction block (FDB/ADB) – the failure of high-frequency nerve transmission across sites of impaired safety margin often due to demyelination or focal nerve injury. FDB/ADB can occur during repetitive nerve stimulation or voluntary contraction which can generate significant axonal hyperpolarization resulting in conduction block across these sites of injury

High-frequency nerve stimulation (HFNS) – the electrophysiological technique of repeated supramaximal stimulation of a peripheral motor or sensory nerve using high frequency levels of stimulation (e.g. 30-Hz) while recording the compound motor or sensory nerve action potential, respectively

Internal longitudinal current (ILC) – the internal current available, following a depolarizing stimulus current, for continued membrane depolarization down the core of the axon. In myelinated axons, the ILC depolarizes the membrane at the nodes of Ranvier

Maximum compound motor action potential (CMAP) – the surface recorded electrical summation of all motor units, within a muscle or muscle group, following supramaximal stimulation of the innervating motor nerve either directly or indirectly

Motor terminal latency (MTL) – the interval (recorded in milliseconds) between the onset of motor nerve stimulation and the onset of the resultant compound motor action potential as determined by the fastest conducting motor nerve fibers

Motor Unit – the most fundamental peripheral motor nervous system structure consisting of a motor neuron cell, its motor axon and the numerous muscle fibers that are innervated by this axon

Neuromuscular junction (NMJ) – the region or junction where the motor axon terminal synapses with the motor end-plate of a muscle fiber. It is here where the nerve impulse is transmitted to the highly-excitabile region of a muscle fiber for continued depolarization along the muscle membrane

Repetitive nerve stimulation (RNS) – the electrophysiological technique of repeated supramaximal nerve stimulation while recording the compound motor action potential from the muscle innervated by the stimulated nerve. The pre-determined train of stimulation can vary regarding the number of stimulations and the stimulus frequency

Safety factor (for nerve transmission) – represents the ratio of available internal depolarizing longitudinal current and the current required to depolarize the next axonal membrane unit or node of Ranvier. In healthy myelinated axons, this ratio is usually greater than 5:1

Saltatory conduction – the perceived “leaping” or “jumping” of the action potential between the nodes of Ranvier in myelinated axons. This physiological phenomenon is responsible for the high conduction velocities between 50 to 70+ meters per second as measured using conventional nerve conduction study techniques

Supramaximal stimulation – electrical stimulation of a peripheral nerve usually 10 to 20% above the amount of current required to maximally stimulate the nerve

Ulnar neuropathy (localized to the elbow) – injury to the ulnar nerve usually as a result of compression, entrapment or trauma. Slow conduction velocities and/or conduction block, suggesting demyelination, are often recorded when stimulating across the elbow using conventional nerve conduction study techniques

CHAPTER 1

NERVE TRANSMISSION, DEMYELINATION AND FREQUENCY-DEPENDENT

CONDUCTION BLOCK

1.0 GENERAL INTRODUCTION

1.0.1 The Motor Unit

The motor unit is the most fundamental, functional component of the peripheral nervous system and when activated regulates our motor responses. A single motor unit consists of three primary components; a motor neuron, a motor axon and the numerous muscle fibers that are innervated by that axon. Each muscle typically contains hundreds of these motor units, the number which varies between individual muscle groups¹. Whether the activation of the motor nerve is generated within the motor cortex, supraspinal segments, at the level of the motor neuron or even more distally along the motor axon, the impulse that is conducted along the peripheral motor axon is translated into an impulse along the muscle fiber via the neuromuscular junction and action of a single neurotransmitter, acetylcholine (ACh). When this pathway is working efficiently, the result is contraction of the muscle and the ensuing production of the desired force. For the purposes of this introduction, nerve transmission along the larger myelinated motor axons will be reviewed as it relates to normal healthy motor conduction velocity versus pathological conditions where conduction slowing and conduction block are observed.

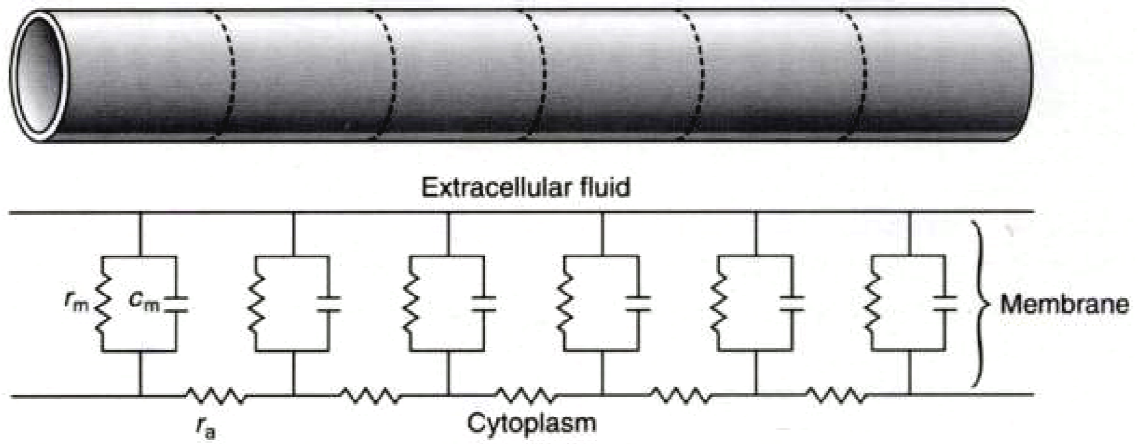
The diameter range for motor axons is bi-modal and can vary between 2 μm and 14 μm in size³. Fibers with large diameters in the order of 7 μm to 14 μm correspond to the larger alpha motor neurons which conduct their impulses between 30 and 68 m/s,

determined from numerous physiological and computer techniques⁴⁻¹⁰. The relationship between the size of the motor axon and its conduction velocity is reasonably direct, but, it is also related to their myelin sheaths, which are the lipid coverings that surround the axon and aid in the fast propagation of the motor nerve action potential. As will be discussed, alterations in myelin properties can cause significant conduction slowing leading to transmission failure and in severe cases, complete conduction block.

1.0.2 Nerve Transmission In Myelinated and Unmyelinated Axons

Nerve transmission across myelinated nerve fibers occurs as a result of saltatory conduction, better recognized as the ability for the nerve impulse to “leap” or “jump” across segments of the nerve resulting in fast conduction velocities. But, to understand more completely the propagation of the action potential along these larger nerve fibers, nerve transmission along smaller, unmyelinated nerve fibers needs to be appreciated.

An unmyelinated axon can be arbitrarily divided into small unit lengths, with each unit representing an equivalent electrical circuit². Each unit length therefore, consists of its own membrane resistance and capacitance, with each of these circuits (units) being connected together by resistors representing the segments of cytoplasm which is responsible for axial resistance (Figure 1.1). When a local current is applied or injected into an unmyelinated axon, the injected current flows out across each of these numerous current pathways (units), with most of the current flowing across the membrane nearest the injection site (Figure 1.2); this occurs as a result of the current taking the path of least resistance, which is greatest immediately adjacent to the injection site. The membrane in an unmyelinated nerve fiber has a very large capacitance; therefore, a large charge must be deposited initially on the inside of the membrane in order to change the membrane



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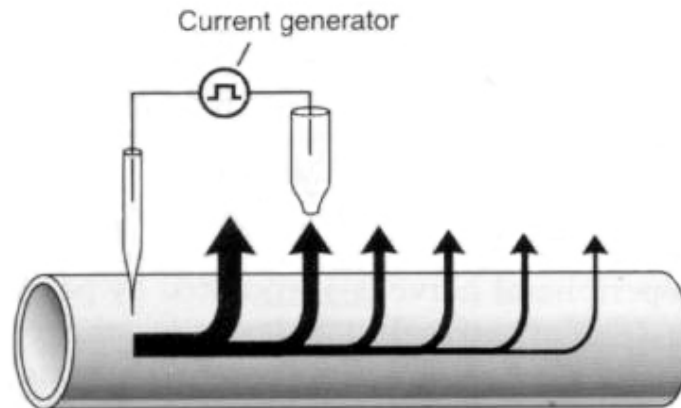
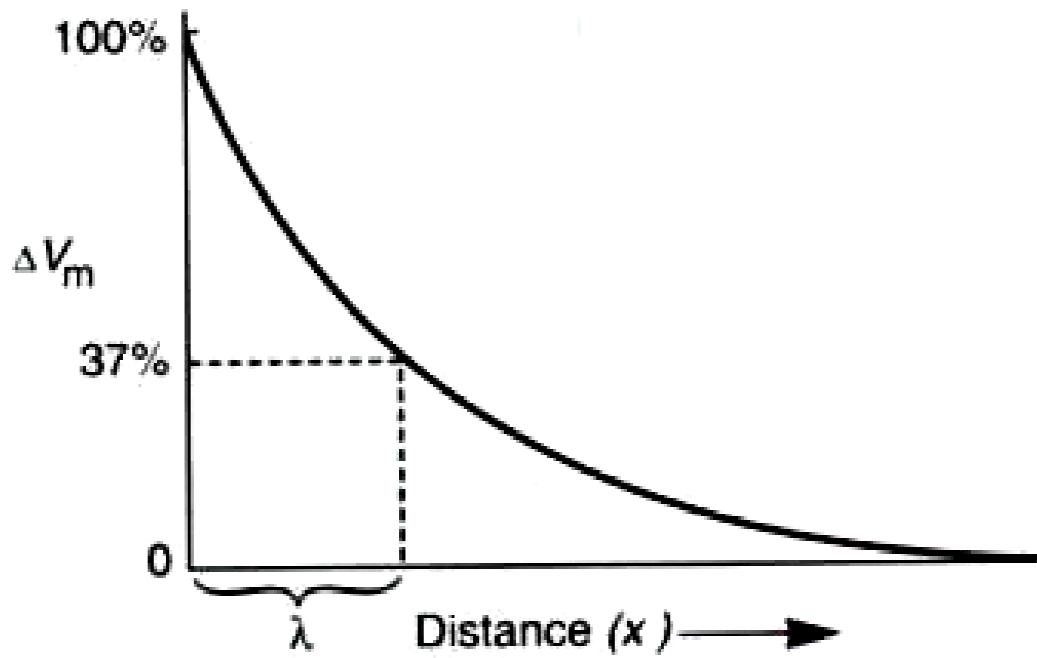


Figure 1.2. Current flow in an unmyelinated axon. The majority of current injected into a neuronal process by a microelectrode follows the path of least resistance to the return electrode in the extracellular fluid (thicker arrows). Multiple arrows indicate how the current flows out across the membrane by several pathways along the length of the neuronal process. The total axial resistance increases with the distance from the injection site causing the change in membrane potential to become smaller and smaller as the current flows down the process (thinner arrows). (Adapted from Kandel ER, Schwartz JH, Thomas MJ: Principles of Neural Science. New York, Elsevier, 1991; p 99).²

potential. The remaining internal longitudinal current (ILC) or driving current continues down the unmyelinated axon to depolarize the next membrane unit, however, as the distance increases from the current injection site, so does the axial resistance. Thus, it takes longer and longer to depolarize each successive unit, particularly when the current available has decreased each time following each membrane depolarization. Therefore, the change in voltage across the membrane decreases exponentially with the distance along the axon (Figure 1.3).

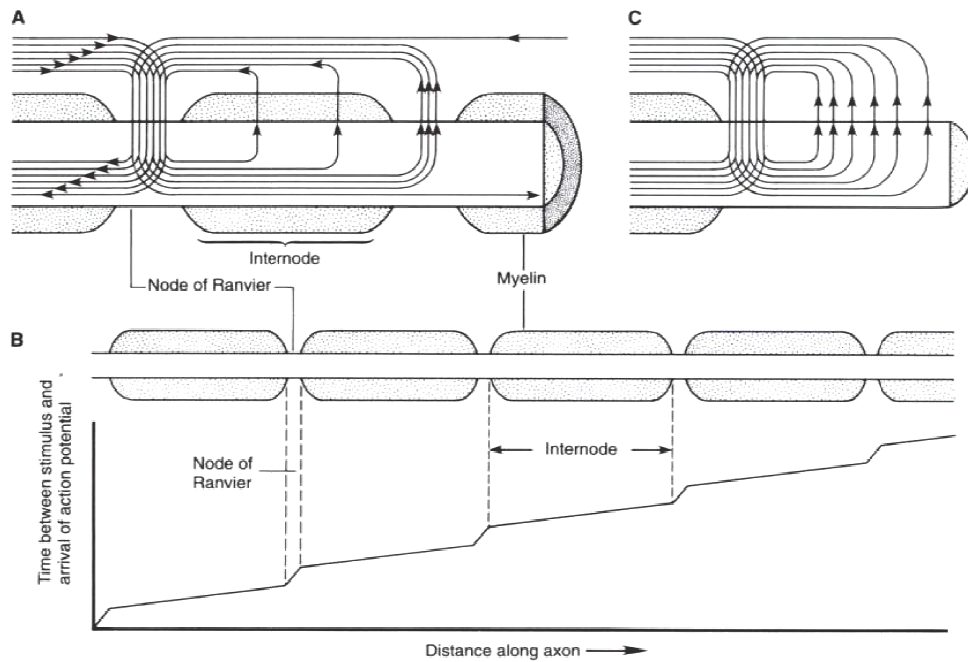
In general, the time required for depolarization to occur is directly related to the axial resistance (cytoplasm) and the capacitance per unit length of the axon, which is precisely why in small unmyelinated nerve fibers, with increased axial resistance and large membrane capacitance throughout the length of the nerve, the ability to transmit their impulses occurs at very slow rates of conduction (≤ 10 m/s). This can also be explained through Ohm's Law, which from its formula, current (I) = voltage (V) / resistance (R) ($I=V/R$) illustrates that with increased resistance there is a decrease in current and with a decrease in current flow around each unit's circuit loop, the longer it takes to change the charge on the adjacent membrane for depolarization².

The differences in conduction between unmyelinated and myelinated nerve fibers can be further illustrated with respect to their length constants, which affect the efficiency of the passage of current down the axon. Membranes with no insulation (i.e. lacking myelin) have shorter length constants, which cause more current to leak across the membrane as it charges large areas of membrane capacitance, versus longer length constants (i.e. myelin internodes) which prevent current leakage, thus providing more current to spread further down the axon².



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Nerve transmission in larger myelinated peripheral motor axons occurs very quickly with normal conduction velocities approaching 70 m/s, measured by conventional nerve conduction study techniques. These faster conduction velocities occur as a result of a very important lipid/protein insulating layer which winds itself around the axon to form what is called the myelin sheath. Numerous sections of myelin are distributed along the entire main axon producing internodes which are between 1-2 mm in length and are separated by approximately 2 μm of bare axon membrane (nodes of Ranvier). The myelin internode is a region of high resistance and low capacitance (limited current flow), while each node of Ranvier is an area of low resistance and high capacitance (current flow). As a result, the passive Na^+ current is “pushed” past each high resistant internode to the less resistant nodes of Ranvier, thus requiring less time and current to depolarize these small regions of the axonal membrane while at the same time avoiding having to charge the larger membrane surface beneath each internode. This combined, with a high density of voltage-gated Na^+ channels found at each node, which generate significant depolarizing inward Na^+ currents (500-fold increase in sodium permeability)¹¹ and provides a boost of passive current to the adjacent nodes downstream, is why conduction is much faster in the myelinated versus unmyelinated axon. Thus, unlike unmyelinated nerve fibers, which conduct their nerve impulses very slowly down the axon as continuous conduction (described above), myelinated nerve fibers conduct their impulses by “leaping” from node to node, better defined as saltatory conduction (Figure 1.4). Lastly, although the myelin sheath has traditionally been considered a region of perfect insulation, there is evidence that there are many pathways available for current to pass around or penetrate the layer of myelin and therefore polarizing the internodes¹². The physiological or functional role for a



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leaky myelin sheath in saltatory conduction may be to limit or reduce the amount of nodal capacitance thereby depolarizing the node more quickly¹³

When using surface stimulation to depolarize a peripheral motor nerve (e.g. median nerve), the depolarizing end of the stimulator (negative pole) attracts the extracellular positive cations (cathodal depolarization), thereby allowing negative charges to accumulate directly outside the axon membrane. This in turn makes the inside of the axon relatively more positive and with 10 to 30 mV¹¹ of depolarizing current, the membrane potential ultimately reaches its critical threshold, voltage-gated Na⁺ channels open, Na⁺ ions enter and the all-or-nothing action potential is generated. In general, this occurs as a result of an intracellular toggle from the potassium equilibrium (resting potential) to the sodium equilibrium (action potential). The speed at which depolarized nodes of Ranvier return to their resting transmembrane potential and their availability for the next wave of current is due to two important membrane properties, namely the inactivation of the voltage-gated Na⁺ channels and the delayed opening of the voltage-gated slow K⁺ channels, located in high density at the node^{14, 15}.

In summary, the Na⁺ and K⁺ ionic mechanisms associated with impulse conduction in myelinated nerve fibers include, in order, *depolarization* (opening of voltage-dependent Na⁺ channels), *repolarization* (largely current leak), *refractory periods* (inactivation of Na⁺ conductance), *supernormal period* (passive discharge of current stored in internodal membrane, limited in size by paranodal fast K⁺ channels), *late subnormal period* (activation of nodal slow K⁺ channels), *post-tetanic subexcitability following short impulse trains - H₁ or P₁* (activation of nodal slow K⁺ channels), *post-tetanic subexcitability following long impulse trains - H₂ or P₂* (activation of the electrogenic Na⁺/K⁺ ion pump)¹⁶.

1.0.3 Nerve Transmission In Demyelinated And Remyelinated Axons

When large myelinated nerve fibers undergo paranodal or segmental demyelination, the biophysical properties of the paranodal and/or internodal regions change causing a delay in saltatory conduction or in extreme cases, continuous conduction can occur^{17, 18}. Exposure of the paranodal or internodal regions from demyelination increases the capacitance and reduces the transverse resistance within these segments (current leakage), which subsequently increases the load on the available but finite ILC generated by the preceding “active” node of Ranvier. If there is significant drain on the ILC as a result of leakage current, then insufficient current will only be available to depolarize the next “inactive” node. The inability to depolarize the next node of Ranvier results in conduction block and continued transmission along the nerve ceases. In cases where demyelination has not been severe enough to cause conduction block, conduction along the nerve will continue, but at a very slow rate as a result of the time required to charge the larger region of membrane capacitance.

Retraction of the myelin sheath in the paranodal region is critical for three reasons. Firstly, the available nodal membrane region increases thus diluting the available depolarizing ILC current over a much larger membrane surface¹⁷⁻¹⁹. Secondly, potassium channels located in the paranodal region become exposed and reduce the safety factor for nerve transmission by hyperpolarizing the membrane²⁰⁻²². Thirdly, Na⁺/K⁺ pump activity in the increased nodal region will attempt to drive the membrane toward the K⁺ equilibrium, further increasing the load on the available driving current²³.

Restoring nerve transmission across a previously demyelinated internode can occur with only a few additional wraps of myelin^{19, 24}. Remyelination in the paranodal region is

particularly important for restoring nerve conduction as it reduces the exposure of K^+ channels, which when exposed, reduces the available ILC for depolarizing the node. This has been shown by applying 4-aminopyridine, 3-4 diaminopyridine or tetra-ethyl-ammonium to experimentally demyelinated nerve fibers, blocking the outward K^+ currents, and resulting in restoration of conduction in previously blocked fibers²⁵.

Proliferation of Schwann cells leads to newer shorter length internodes within the demyelinated region²³. This shortening of the internodal distance between each node may indeed increase the safety factor for nerve transmission in the affected nerve fibers, however, paradoxically conduction velocities across these numerous smaller internodes may be slowed because of the increased time required to depolarize the increased number of nodes of Ranvier created during the regeneration process.

1.0.4 Focal Entrapment Neuropathies (Median and Ulnar Neuropathy)

Among the many types, causes and locations of focal individual peripheral neuropathies, the two most commonly seen in electrodiagnostic labs are the median and ulnar neuropathies localized to the wrist and elbow, respectively. Compression of the median nerve within the carpal tunnel, giving rise to symptoms of nocturnal and daytime hand paresthesias, wrist pain, dropping objects or clumsiness of the hand, is better known as carpal tunnel syndrome (CTS)²⁶. Nerve conduction studies typically demonstrate slow median sensory nerve conduction to the 1st, 2nd, 3rd and 4th digits and when the condition worsens, median motor nerve studies to the thenar eminence show prolonged distal motor terminal latencies following stimulation at the wrist. In CTS patients where median motor nerve conduction studies demonstrate conduction slowing with very little evidence of axonal loss (i.e. normal thenar compound motor action potential), the pathophysiology is

presumably demyelination, although studies have challenged this interpretation due to the lack of findings of frequency-dependent conduction block across the carpal tunnel²⁷⁻²⁹.

The pathophysiology of CTS may vary depending on the length and severity of compression; however, in most cases, CTS is considered a chronic focal neuropathy with the earliest changes seen in the myelin sheath which begins to retract from the nodes of Ranvier. Identical histological studies showing thinning and retraction of the myelin sheath at one end and bulbous myelin swellings at the other end were observed in both the guinea pig, a model for chronic focal neuropathy, and in human nerves from common sites of entrapment³⁰⁻³⁵. These early changes of paranodal retraction and myelin thinning in chronic compression differ from acute compressive neuropathies where instead there is myelin invagination from one side of the node of Ranvier into the myelin sheath located at the other side of the node²⁶.

Ulnar neuropathy localized to the elbow (UNE) characteristically presents with sensory symptoms along the ulnar innervated region of the hand, plus or minus hand weakness and discomfort along the medial border of the elbow, depending on the severity of injury²⁶. This focal neuropathy can occur as a result of many factors, both chronically and acutely, from habitual elbow leaning or with certain sleep positions to symptoms developing acutely from resting the elbow on hard surfaces while driving or during surgery. Nerve conduction studies in the ulnar nerve are somewhat similar to the median nerve across the wrist in CTS in that they demonstrate conduction slowing across the site of compression. Although sensory nerve conduction studies across the elbow are potentially more sensitive than motor nerve conduction studies recording from either the hypothenar eminence or first dorsal interosseous muscle, technical challenges coupled

with small sensory potentials can make it difficult to obtain accurate segmental sensory conduction velocity results³⁶⁻³⁸; therefore, ulnar motor nerve conduction studies are routinely used when attempting to demonstrate conduction slowing across the elbow.

One recognizable difference between CTS and UNE is that UNE can often be associated with conduction block when presenting acutely, an observation that is typically not seen in the more chronic CTS. The pathophysiology or mechanism of injury may also differ between these two separate presentations. Indeed, as noted earlier, there are differences between the acute and chronic forms of focal nerve compression in how the myelin is interrupted²⁶; it has also been recognized that in most acute nerve injuries there are variable degrees of damage to the fascicles and their nerve fibers^{39, 40}.

1.0.5 High-Frequency Nerve Stimulation

Higher rates of nerve stimulation (3 to 50-Hz) to the larger myelinated motor axons is a common electrophysiological technique often used to assess the integrity of the neuromuscular junction for pre-synaptic diseases such as Lambert-Eaton Myasthenic Syndrome (LEMS) or botulism and for post-synaptic diseases such as myasthenia gravis (MG). Results from 3-Hz stimulation (6 to 10 stimuli) typically show a decrementing or decreasing pattern in the CMAP in LEMS and in MG (i.e. greater than 10% decrease) and an incrementing or increasing pattern (often exceeding 200 percent of the baseline CMAP value) in LEMS patients, when stimulating at higher frequencies such as 20 to 50-Hz¹¹. In these cases, the pathophysiology lies within the region of the neuromuscular junction with the main trunk or branch of the axon being intact; in other words, nerve conduction velocity study results are usually within normal limits, suggesting that the main axon and its myelin sheath are unaffected.

In normal healthy subjects, lower-frequency nerve stimulation (e.g. 3-Hz) reveals little change in the surface recorded CMAPs (less than 10% change in negative peak amplitude when compared to the stimulus train's first CMAP)¹¹, whereas higher-frequency nerve stimulation (e.g. 30-Hz) typically produces an increase in the same CMAP^{41, 42}. This CMAP phenomenon, known as "potentiation," occurs as a result of increased muscle fiber hyperpolarization due to enhanced Na⁺/K⁺ pump activity as well as the increase in muscle fiber conduction velocities resulting in more synchronized action potentials during higher-frequency nerve stimulation^{42, 43}. This phenomenon appears to be present within healthy subjects regardless of the peripheral motor nerve that is being stimulated or the location of stimulation^{41, 42}. Optimum recording position for the G1 or recording electrode is imperative, as improper placement of this electrode may contribute to decreases in the CMAP in healthy individuals⁴².

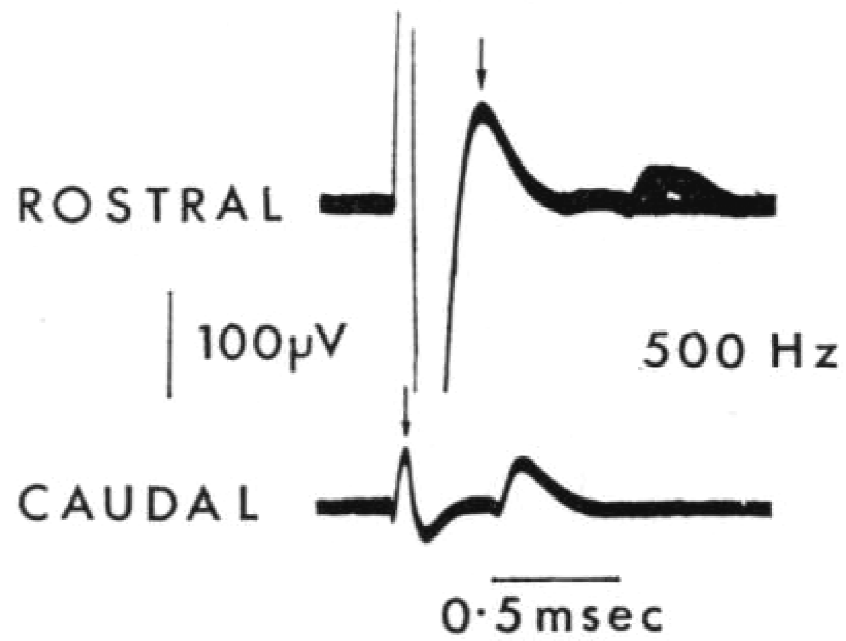
1.0.6 Frequency-Dependent Conduction Block

Frequency-dependent conduction block (FDB) or activity-dependent conduction block (ADB) is a phenomenon in which nerve impulses are blocked across sites of demyelination as a result of increased axonal hyperpolarization (axonal hypoexcitability). Although axonal hyperpolarization occurs normally in healthy axons during the transmission of a train of impulses, the safety margin for conduction prevents FDB or ADB from occurring. The safety margin or "safety factor" for the transmission of a nerve impulse is defined as the ratio between the current available within the driving or internal longitudinal current and the threshold current required to excite a node⁴⁴. In normal healthy nerve, this ratio is normally 5:1 or greater. However, when this margin of safety is critically impaired to near unity (1:1) as a result of demyelination, the driving current may

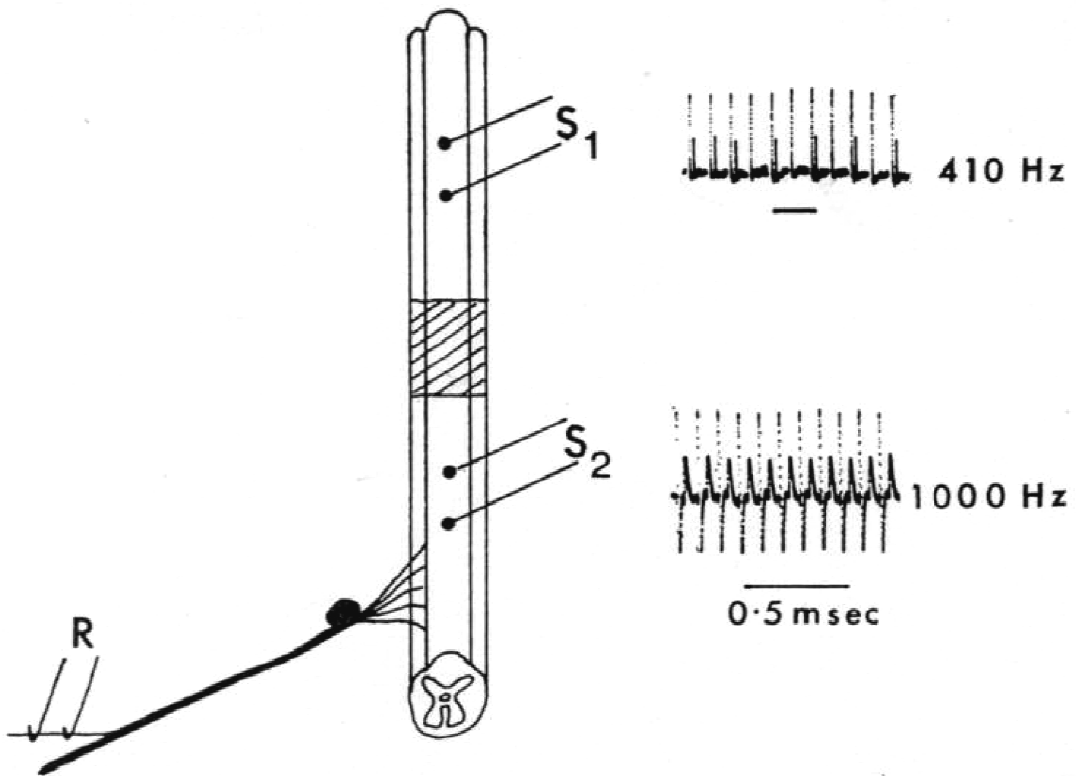
fail to meet the increased nodal threshold current (due to current leakage and increased nodal capacitance), resulting in the failure of this transmission and subsequent conduction block.

The reduced ability for demyelinated axons to conduct trains of nerve impulse was first shown in experimentally induced demyelination in both the central and peripheral nervous systems^{17, 45-52}. Stimulus frequencies even as low as 10-Hz were capable of producing conduction block across demyelinated segments in the rat spinal root axons⁵². The delay or complete failure of transmission can be seen in Figures 1.5 and 1.6 through a T₉ demyelinating lesion with HFNS of 500-Hz and 410-Hz, respectively⁵¹. Figure 1.6 also demonstrates how the margin of safety is still preserved distal to the lesion, even at stimulus frequencies of 1000-Hz.

Later, attempts to demonstrate FDB/ADB using HFNS or maximal voluntary contraction in human subjects was explored in normal cutaneous axons⁵³, across regions of focal entrapment²⁷⁻²⁹ and in patients with multifocal motor conduction block neuropathy (MMN)⁵⁴ and chronic inflammatory demyelinating polyneuropathy (CIDP)⁵⁵. Activity-dependent hyperpolarization and conduction block was successfully demonstrated in both the MMN and CIDP patients, however, in CTS patients with mild to moderate focal median sensory nerve conduction slowing at the wrist, FDB could not be demonstrated in the compound median sensory action potentials due to the effects of temporal dispersion, despite greater depressions in the compound sensory action potential amplitude relative to healthy subjects²⁷. As well, in a study examining the effects of MVC in CTS patients, ADB failed to occur following 60 s of voluntary contraction, even though the degree of axonal hyperpolarization recorded in these patients was sufficient to produce conduction block in



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CIDP patients²⁸. These latter results in CTS patients suggest that FDB/ADB and demyelination may play little role in the pathophysiology and the conduction slowing in CTS patients, despite in one of the studies, patients had mean sensory conduction velocities and motor terminal latencies well outside normal values (35.3 m/s and 5.5 ms, respectively)²⁸. However, the effects of temporal dispersion²⁷ and the possibility of submaximal efforts due to deafferentation, particularly during 60 s of contraction²⁸ are two important factors that need to be considered for the lack of ADB in these studies.

Although previous studies failed to demonstrate FDB in median sensory fibers in CTS^{27, 29}, there is a discrepancy between sensory and motor fibers in that the degree of axonal hyperpolarization is greater in motor axons than in cutaneous afferents, for similar discharge rates^{56, 57}. Therefore, the median motor fibers in CTS are more likely susceptible to conduction block during higher-frequency impulse conduction than median sensory fibers, particularly across focal sites (wrist) of demyelination.

The first study to show that FDB/ADB, within a peripheral nerve trunk, plays a role in causing muscle fatigue examined patients with MMN and provided evidence that axonal hyperpolarization was responsible for the conduction block and that this conduction block occurred in parallel with muscle fatigue⁵⁴. Earlier studies in animal models of central demyelination suggested as well that FDB/ADB may be responsible for the central fatigue experienced in multiple sclerosis patients^{47, 51}. Although many studies have recently explored nerve excitability in different diseases, few have attempted to directly explore the relationship between FDB/ADB and fatigue in peripheral nerve disease.

1.0.7 Mechanisms Associated with Axonal Hyperpolarization

In healthy myelinated axons, axonal hyperpolarization (axonal hypoexcitability) or an activity-dependent depression in excitability occurs as a result of a train of impulses and is associated with two after-potential positive waves, P₁ and P₂⁵⁸. The mechanisms associated with the P₁ and P₂ waves include the activation of slow K⁺ conductance produced by a brief train of impulses^{14, 16, 53, 59-61} and the activation of the Na⁺/K⁺ pump during longer stimulus trains^{12, 16, 52, 62-68}, respectively. Na⁺-activated K⁺ channels (K+Na channel) localized to the nodal region is also a likely contributory mechanism regarding the P₂ wave⁶⁹.

Evidence to support the influence of the Na⁺/K⁺ pump on axonal hyperpolarization during longer stimulus trains showed that by inhibiting this electrogenic pump with ouabain, a short-acting cardiac glycoside, rate-dependent conduction block could be reversed in the demyelinated rat axon⁴⁶. Earlier experiments provided additional support for Na⁺/K⁺ pump involvement by demonstrating complete block of membrane hyperpolarization in normal rat nerve fibers during intermittent tetanization (300-Hz for 400 ms/s)⁵². This was achieved by replacing extracellular NaCl by LiCl. Li⁺ is capable of substituting for Na⁺ as the charge carrier for inward current, however, it does not stimulate the electrogenic Na⁺/K⁺ pump.

The size of the positive after-potential is cumulative and increases with increasing stimulus duration and frequency. For example, in the sciatic nerve of the green frog, with a stimulus frequency of 180-Hz, the size of the after-positive potential continues to increase between 20 to 40 seconds of stimulation, after which it then begins to plateau⁵⁸. Similarly, the amplitude of the positive potential increases sharply from 0 to approximately 300-Hz

stimulation and then plateaus, at a stimulus duration of 2.5 s⁵⁸. The positive after-potential was shown to attain an amplitude height equaling 40 per cent of the spike-height⁵⁸. The P₁ wave follows short stimulus trains between 10 to 20 impulses^{14, 16, 53, 60}, while the P₂ wave follows more prolonged trains⁵³.

1.1 OVERVIEW OF THESIS CHAPTERS

It is the objective of this thesis to examine the physiological concept of frequency-dependent conduction block (FDB) by applying high-frequency nerve stimulation (HFNS) directly across regions of focal demyelination in patients with clinical and electrophysiological evidence of entrapment neuropathy. Secondary objectives are to provide further evidence regarding the pathophysiology of these entrapments, to determine whether similar FDB results can be observed between different peripheral motor nerves that are entrapped or compressed and whether FDB in motor fibers contributes to the weakness and or fatigue often associated with entrapment neuropathies. These objectives have been approached in a number of ways, including the establishment of normative data (experiments 1, 2, 3 and 4) and the comparison of these results in patients with carpal tunnel syndrome (CTS) to examine whether FDB can actually be demonstrated for the first time in this condition (experiment 1); whether the results from experiment 1 can be further localized to the region within the carpal tunnel (CT) or possibly beyond its boundaries (experiment 2); and whether FDB contributes to the weakness in mild CTS patients with normal conventional motor nerve conduction studies (experiment 3). Lastly, the relationship between two separate entrapment neuropathies was examined to determine whether similar degrees of FDB are observed when identical protocols of HFNS are applied (experiment 4).

1.1.1 Experiment 1

Objective: To determine whether FDB occurs across an area of focal nerve injury in response to brief, HFNS stimulation. To increase the probability of demonstrating FDB

across the CT, patients with CTS demonstrating moderate to severe conduction slowing in the median motor fibers across the wrist will be studied. In addition to collecting and reporting control data, which will be used as the necessary background data to which HFNS in CTS patients will be compared, the magnitude of FDB as it relates to the extent of demyelination, as determined by the degree of distal motor slowing, will also be assessed.

Rationale: Previous studies have been unsuccessful in their attempts to demonstrate FDB in median sensory nerve fibers in CTS despite studying patients with sufficient evidence of median nerve conduction slowing^{27, 29} and changes in motor nerve threshold similar to other demyelinating diseases²⁸. To address this, HFNS (30-Hz, 20 stimuli) was applied to the median motor nerves in CTS patients, which have been shown to have greater degrees of hyperpolarization (hypoexcitability) than cutaneous nerves^{56, 57}. Direct stimulation of the median motor nerve also by-passes any limitations attributable to voluntary contraction which has been unsuccessful in demonstrating FDB in previous studies of CTS²⁸.

1.1.2 Experiment 2

Objective: This study was undertaken to determine whether FDB in patients with CTS occurs only across the region of the CT or, in addition, more distally across the margins of the palmar aponeurosis, within the motor terminal branches. As in experiment 1, the probability of demonstrating FDB across both locations was increased by studying CTS patients with moderate to severe conduction slowing in the median motor fibers across the wrist.

Rationale: Given that FDB was observed across the CT in CTS patients in experiment 1, the question was raised whether FDB also occurs beyond the region of the CT as a result of known differences in excitability properties distally within the motor terminal branches when compared to the more proximal portions of the nerve⁷⁰⁻⁷³. Studies have also shown that demyelination can occur distal to the lesion in CTS³¹⁻³³, which would reduce the safety factor for nerve transmission, particularly during higher physiological rates of stimulation. Results of this experiment may provide additional support for compression distal to the CT⁷⁴⁻⁷⁶, particularly in patients who fail to respond to more proximal steroid injection or surgical treatment.

1.1.3 Experiment 3

Objective: To determine whether FDB can be demonstrated in patients with milder forms of CTS using HFNS following maximal voluntary contraction (MVC). Specifically, the presence of FDB pre- and post-exercise (60 s MVC) in mild CTS patients, when stimulating the median motor nerve at a physiological rate of 30-Hz, will be assessed. Additionally, the degree of FDB in more severe cases of CTS, following exercise, will be compared to controls and to the mild CTS group. Lastly, as it has already been established that there are significant differences between controls and moderate to severe CTS subjects in response to HFNS^{77,78}, the differences between mild CTS and moderate to severe CTS subjects will also be compared.

Rationale: Conventional motor nerve conduction studies (NCS) are often performed using non-physiological rates of stimulation (≤ 1 -Hz), thereby potentially failing to demonstrate the full extent of the patient's clinical complaints, particularly when the motor system is

involved. In order to test this potential shortcoming, mild CTS patients with clinical complaints of hand weakness and/or fatigue, but with normal motor NCSs, were assessed using physiological rates of stimulation (30-Hz, 20 stimuli) in combination with exercise and compared to controls with similar normal conventional motor NCS results. Results from this study (i.e. evidence of FDB in the mild CTS group) may provide support that the motor system is partially responsible for the hand weakness that is often described by mild CTS patients whose only electrophysiological change is conduction slowing in the median sensory nerve fibers.

1.1.4 Experiment 4

Objective: To determine whether FDB can be demonstrated in a second common entrapment neuropathy causing demyelination. In contrast to the previous two studies (experiments 1 and 2), which examined CTS patients with chronic symptoms (12 weeks to 33 years) and with no evidence of conduction block, this study will examine ulnar neuropathy patients with shorter duration onset (2-16 weeks) coupled with significant conduction block across the elbow.

Rationale: It has been shown that there are differences between individual nerves in terms of their degree of axonal hypoexcitability during trains of electrical stimuli or during voluntary contraction⁷⁹⁻⁸². Therefore, whether differences occur between the two most common entrapment neuropathies, axonal hypoexcitability in the ulnar nerve was explored using the same method of stimulation (30-Hz, 20 stimuli) used in experiment 1. Results from this study may show that changes in nerve threshold are dissimilar for two

distinct forms of focal nerve entrapment and that the mechanism for injury may also be different.

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CHAPTER 2

FREQUENCY-DEPENDENT CONDUCTION BLOCK IN CARPAL TUNNEL

SYNDROME

2.0 INTRODUCTION

Frequency-dependent conduction block (FDB), described also as “activity”- or “rate”-dependent conduction block has been demonstrated in the peripheral and central nervous systems across regions of demyelination with high-frequency nerve stimulation and during maximal voluntary contraction¹⁻⁹. In most instances, despite the presence of axonal hyperpolarization (axonal hypoexcitability), which occurs normally in healthy axons as a result of the transmission of a train of impulses, the safety margin for conduction prevents the occurrence of FDB. However, when this margin of safety is critically impaired, for example, from the effects of demyelination, the driving or internal longitudinal current may fail to meet the increased nodal threshold current (due to increased nodal capacitance) resulting in a failure of transmission and subsequent conduction block¹⁰.

Experimentally, FDB has been successfully demonstrated in animals^{1,5-7,9} and more recently in humans with multifocal motor neuropathy⁴ or chronic inflammatory demyelinating polyneuropathy¹¹. However, studies involving patients with entrapment neuropathies, such as carpal tunnel syndrome (CTS), resulting in conduction slowing from presumed myelin injury^{12,13}, have failed to demonstrate this phenomenon despite stimulating the median nerve at frequencies in the order of 200 Hz^{14,15}. Similar results have been observed in the thenar motor nerve fibers following voluntary contraction¹⁶.

A version of this chapter has been published.

Watson BV, Brown WF, Doherty TJ. Frequency-dependent conduction block in carpal tunnel syndrome. *Muscle & Nerve* 2006; 33:619-626.

Reasons for this are unclear, but, the fact that median sensory nerve action potentials in CTS undergo greater phase cancellation than the compound muscle action potential (CMAP), because of increased temporal dispersion, makes it difficult to attribute any reduction in the compound sensory nerve action potential to FDB alone. With regard to the motor fibers, the “stress” produced from voluntary contraction necessary to produce FDB may be limited due to the reduced impulse load as a result of deafferentation or submaximal efforts¹⁶. Alternatively, high-frequency nerve stimulation of the median motor nerve in patients with carpal tunnel syndrome is achievable, but has yet to be examined for the purpose of demonstrating FDB, presumably because of discomfort.

The present study was undertaken to determine whether FDB occurs across a focal nerve lesion in response to brief, high-frequency repetitive nerve stimulation, thus bypassing the potential limitations attributable to voluntary contraction. We attempted to increase the probability of demonstrating FDB in CTS by studying patients with moderate to severe focal conduction slowing in the median motor fibers across the wrist, with no evidence of axonal loss. Our goal was to determine whether the magnitude of FDB was related to the extent of demyelination as determined by the degree of distal motor slowing.

2.1 METHODS

2.1.1 Subjects

Fifteen healthy control subjects with normal median sensory and motor distal latencies (12 men and 3 women; age, 37.5 ± 12.3 years; age range, 21 to 66 years) and 17 patients (7 men, 10 women; age, 57.2 ± 10.3 ; age, range, 43 to 79 years) with clinical and electrophysiological evidence of moderate to severe carpal tunnel syndrome (as defined

below by the distal motor terminal latency) were asked to participate in this study. Subjects with clinical or electrophysiological evidence of a generalized peripheral neuropathy or with evidence of focal conduction block across the wrist were excluded. All subjects gave informed consent to the experimental protocol, which was approved by the Research Ethics Board of the University of Western Ontario.

2.1.2 Electrophysiological Data Collection

Controls: For this study, it was necessary to establish the response to 30-Hz repetitive nerve stimulation in controls, as this was the background data to which median nerve stimulation in CTS patients was compared. Control studies using high-frequency nerve stimulation were performed by applying 20 stimuli at a rate of 30-Hz (total time of stimulation, 0.667 s) to the median nerve at the wrist, while recording over the motor point of the thenar eminence (G1) with the reference electrode (G2) placed over the first metacarpophalangeal joint.

Patients: Routine median motor nerve conduction studies were performed separately to ensure that all inclusion criteria were met (distal motor terminal latency across the wrist ≥ 5.0 ms; distal compound muscle action potential obtained from wrist stimulation ≥ 6.0 mV; no evidence of conduction block across the wrist segment). These criteria were chosen to represent moderate to severe conduction slowing across the carpal tunnel with no or very little evidence of motor axonal involvement. Palmar stimulation was performed in all cases to exclude conduction block across the wrist. In six patients, needle EMG studies of the abductor pollicis brevis muscle were performed to assess the degree of axonal involvement in terms of spontaneous activity or motor unit remodeling.

Repetitive nerve stimulation (20 stimuli) of the median nerve at the wrist (7 cm proximal to the G1 electrode), at frequencies of 3, 5, 10, 20, and 30-Hz was then performed in 14 cases while recording over the thenar eminence. Stimulation at 30-Hz alone was also performed in 3 additional cases of CTS. In one case, a bilateral study was performed. This resulted in a total of 18 limbs studied. Lower-frequency stimulation was performed to examine the relationship, if any, between the different stimulation frequencies and the degree of FDB. All studies (3, 5, 10, 20, and 30-Hz) were completed within 30 to 60 seconds of one another.

In all studies, surface disposable recording electrodes (Ag/AgCl Mactrode Electrodes; GE Medical Systems, Milwaukee, Wisconsin) were used and secured with tape to prevent displacement, particularly during higher frequency levels of stimulation. In an attempt to minimize hand movement during the procedure, the hand was secured firmly, but comfortably within a modified wrist splint and the thumb was held in place by a laboratory staff member. Supramaximal stimulation (15 - 20% greater than maximal stimulation) was used in all cases. Limb temperature was maintained at $\geq 32^{\circ}$ C with the aid of a portable heat lamp. The skin was prepared using 70% isopropyl alcohol and when necessary in subjects with rough, oily or greasy skin, One-Step Skin Prep (3M, London, Ontario, Canada) was used to mildly abrade the skin to reduce impedance. All waveforms were collected, analyzed and stored using a standard EMG machine (Advantage Medical, London, Ontario, Canada). Negative peak amplitude (mV), negative peak area (mVms), and negative peak duration (ms) were measured for all individual waveforms collected.

2.1.3 Calculations and Statistics

Calculations. In order to determine whether negative peak amplitude (npAmp) or negative peak area (npArea) should be used to assess FDB, calculations were made in controls to determine the percent increase or decrease for each of these parameters in response to a train of impulses. Each individual waveform collected during 30-Hz stimulation was compared relative to the first waveform collected (i.e., $\text{npAmp}_{2\text{nd}} / \text{npAmp}_{1\text{st}} \times 100$, $\text{npAmp}_{3\text{rd}} / \text{npAmp}_{1\text{st}} \times 100$...).

To calculate the overall percent change in amplitude for each train, the npAmp (chosen as a result of the above assessment) from the 20th waveform was compared relative to the 1st waveform ($\text{npAmp}_{20\text{th}} / \text{npAmp}_{1\text{st}} \times 100$).

Conduction block was considered present across the wrist if there was a greater than 20% decrease¹⁷ in npArea between the responses obtained from palmar and wrist stimulations [$(\text{npArea}_{\text{palm}} - \text{npArea}_{\text{wrist}}) / \text{npArea}_{\text{palm}} \times 100$].

Statistics. Range of values, their means and standard deviations are presented throughout. Mean values were examined between and within groups with the Student's *t*-test statistic. Correlations were examined with the Pearson product moment statistic and 1st thenar CMAP comparisons between stimulation protocols (3, 5, 10, 20 and 30-Hz) were examined with the repeated measures analysis of variance (ANOVA) and Tukey's multiple comparison test statistic.

2.2 Results

2.2.1 Control Subjects and CMAP Analysis

Relative to the 1st CMAP waveform (100%), there was considerably less change in npAmp than npArea during RNS at 30 Hz (Fig. 2.1). Twelve of 15 controls (80%) showed an overall increase in npAmp (mean increase, +10.9%; range, +1.7 to +33%) whereas the remaining 3 subjects showed only a minimal decrease in npAmp (all $\leq -7\%$). Conversely, npArea was markedly reduced in all 15 control subjects (mean reduction, -37.5%; range, -24.4 to -50.1%). From these results, we concluded that npAmp would serve as the best parameter to demonstrate FDB as a result of the lower mean percent difference relative to the first response.

2.2.2 CTS Subjects and Nerve Conduction Studies and EMG

Routine motor nerve conduction studies revealed normal thenar distal compound muscle action potentials (mean, 8.4 mV; range, 6.1 to 13.2 mV) but, increased distal median motor terminal latencies (mean, 6.7 ms; range, 5.0 to 9.4 ms). The mean CMAP negative peak duration was 7.0 ± 0.8 ms (range, 5.4 to 9.8 ms) and there was no significant difference when compared to controls ($P > 0.05$). No case showed evidence of conduction block across the wrist. Needle electromyography (EMG) in 2 of 6 patients examined revealed only mild evidence of chronic motor unit remodeling with no signs of spontaneous activity; the remaining cases were normal.

2.2.3 Repetitive Nerve Stimulation

Figure 2.2 illustrates the overall relationship between the control group and CTS group in terms of the degree of FDB during 30-Hz stimulation. The control group's mean change from the 1st to 20th npAmp response was +7.9% (107.9%), whereas the CTS

group's mean change was -11.2% (88.8%); this represented a mean difference between the groups of 19.1% . Only 2 of the 18 limbs (11%) studied in the CTS group demonstrated a pattern consistent with the control subjects, although the 20th response in one of these cases still fell below our mean control data. Figure 2.3 represents a typical study seen from a control subject and one of the CTS subjects during 30-Hz stimulation.

2.2.4 CTS Subjects and Stimulation Frequencies

Mean percent changes in npAmp (1st – 20th) at 3, 5, 10, 20, and 30-Hz in the CTS subjects were -2.4% (range, 0 to -5.1%), -3.3% (range, -1.2 to -6.3%), -4.6% (range, $+2.4$ to -17.5%), -7.7% (range, $+6.5$ to -20.5%), and -11.3% (range, $+7.0$ to -25.8%), respectively. In all cases there was an overall decrease in the npAmp during the train of responses, but, it was less evident during lower frequency stimulation (3, 5, and 10-Hz). According to Student's t-test, there were significant differences ($P < 0.05$) between 30-Hz stimulation and the lower frequencies (3, 5, and 10-Hz). Conversely, there was no significant difference between the two higher stimulation frequencies (30 and 20-Hz) or between 3, 5, and 10-Hz.

2.2.5 CTS Subjects and Motor Terminal Latency

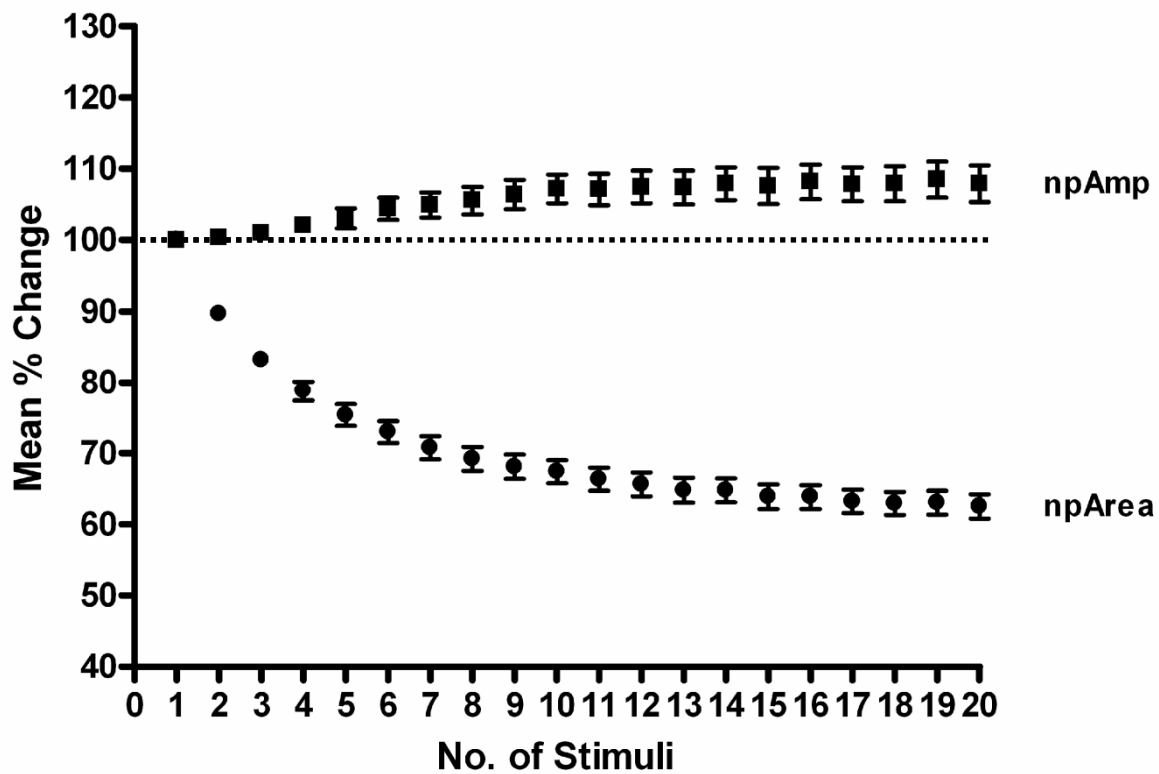
Figures 2.4 and 2.5 illustrate the relationship between the percent change in npAmp (1st – 20th response) and the distal motor terminal latency studied at frequencies of 3, 5, 10, 20, and 30-Hz in the CTS group. At 3, 5, and 10-Hz the correlations were weak and not significant ($R < -0.5$, $P > 0.05$), whereas, at 20 and 30-Hz the relationships were moderately strong and were significant at $R = -0.53$, $P < 0.05$ and $R = -0.63$, $P < 0.05$, respectively.

2.2.6 CTS Subjects and Negative Peak Duration

Additional comparisons were made to assess whether negative peak duration was associated with and could account for the increased probability of FDB occurring with longer distal motor terminal latencies. In other words, was it possible for phase cancellation to contribute to the FDB observed in this study as a result of changes in negative peak duration? To address this, we divided our CTS subjects into two groups of ascending distal motor terminal latencies (group 1, 5.0 to 6.9 ms and group 2, 7.1 to 9.4 ms) and statistically compared: (1). their associated thenar CMAP negative peak duration (npDur) values and, (2). the percent change in npDur across the carpal tunnel. Student's *t*-test was non-significant for both comparisons ($P > 0.05$).

2.2.7 CTS Subjects and the First CMAP Response in each Train

A repeated-measures ANOVA, comparing the amplitude of the initial CMAP for each was not significant ($P = 0.74$). In other words, there was no statistical evidence suggesting that previous trains of repetitive nerve stimulation influenced subsequent studies. Tukey's multiple comparison test between each stimulation protocol (3, 5, 10, 20, and 30-Hz) was also non-significant ($P > 0.05$).



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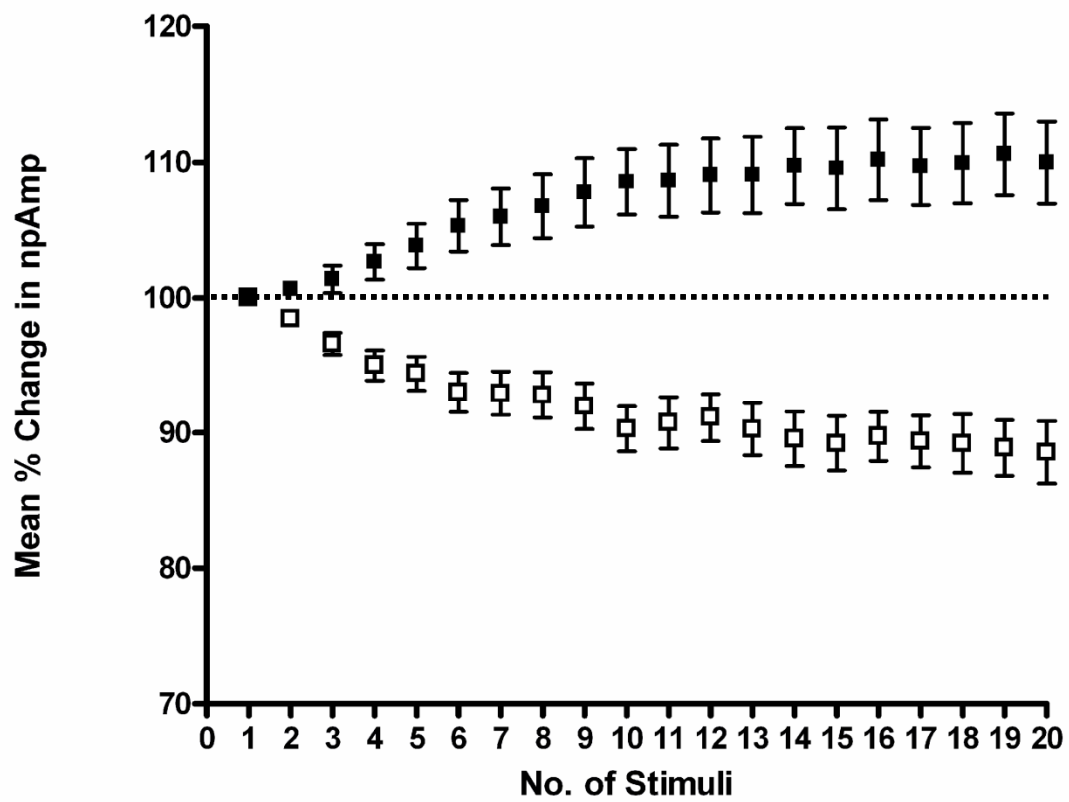
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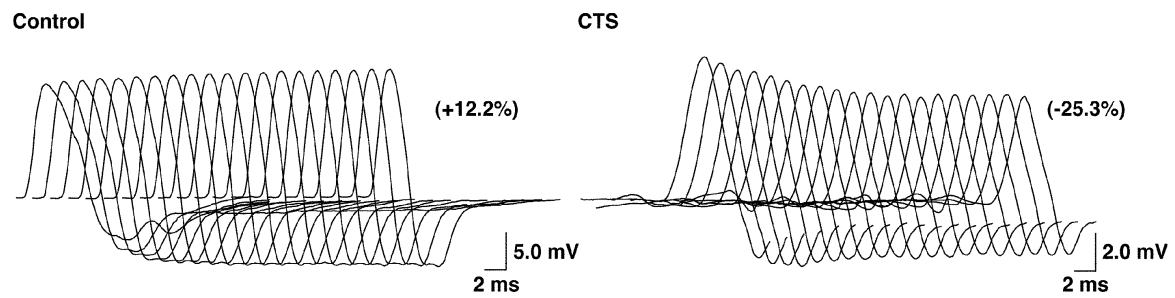


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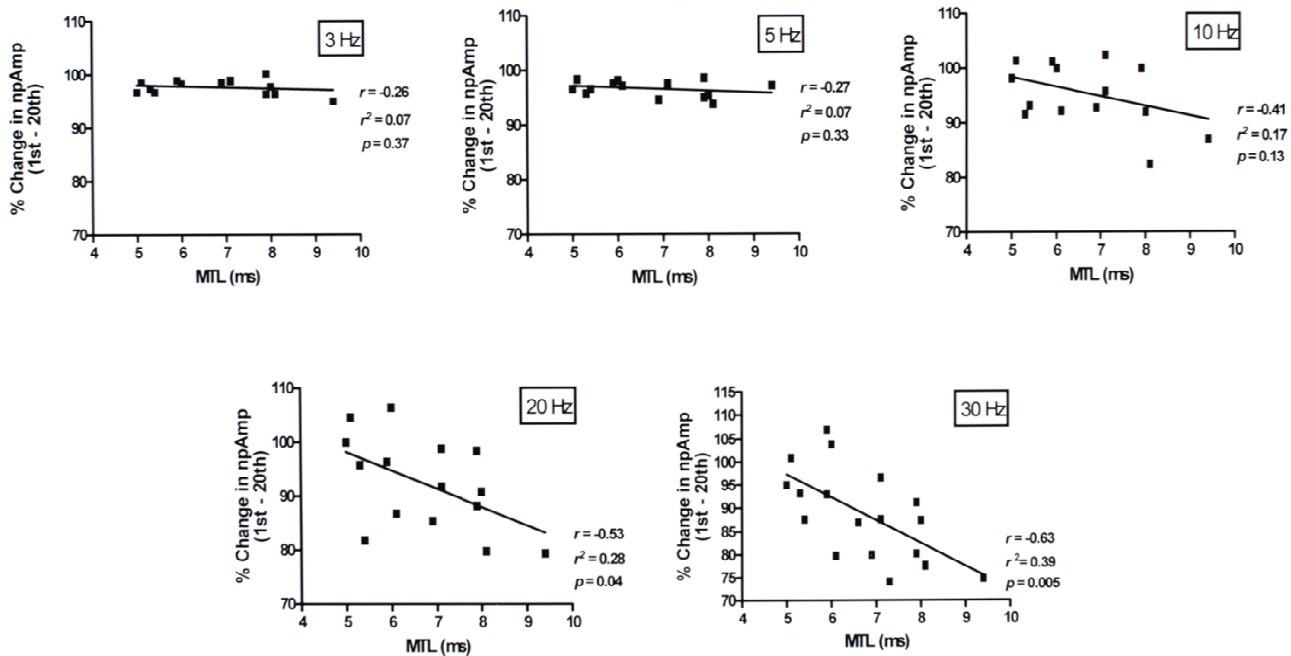
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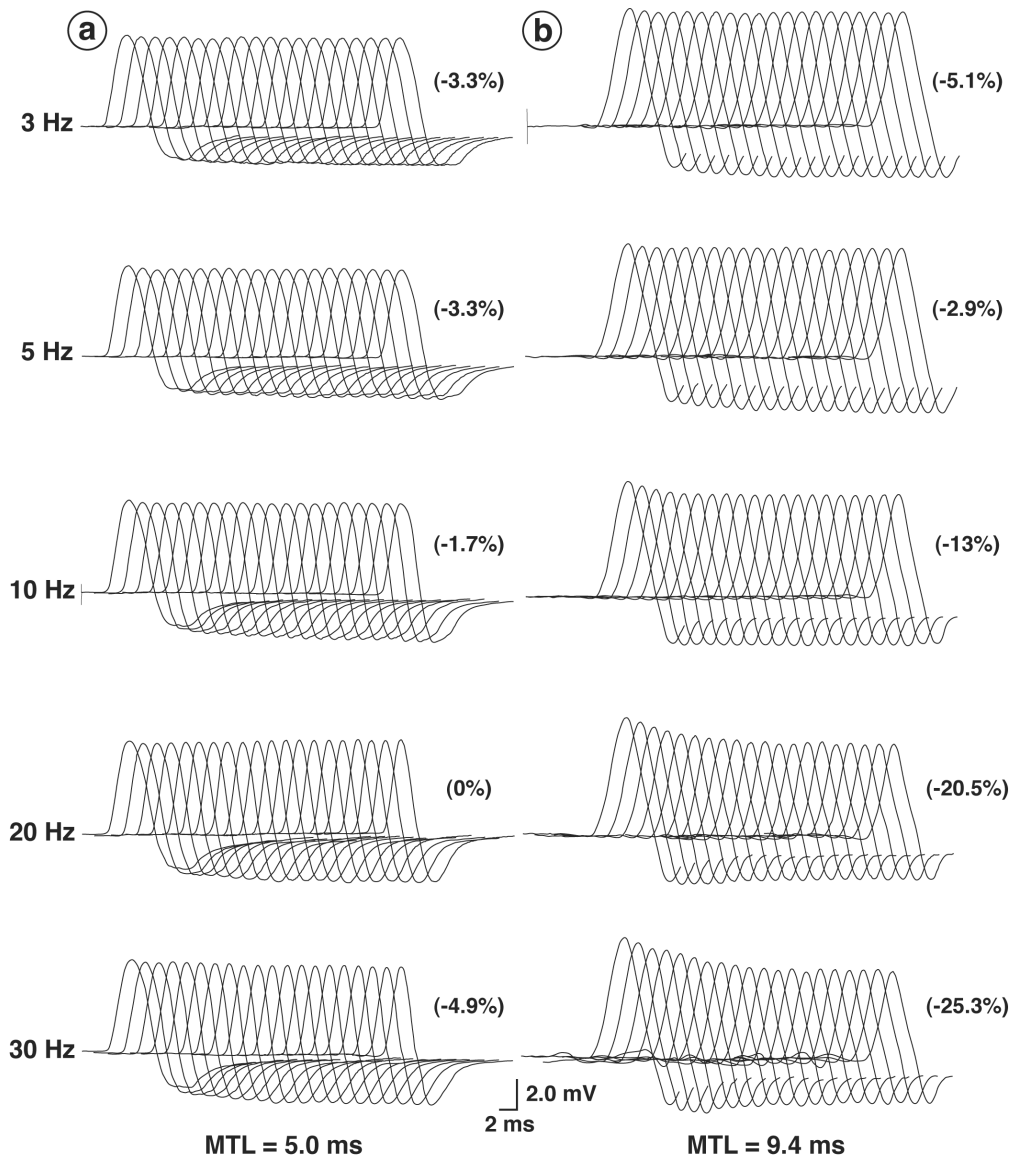


Figure 2.5. Comparison of the thenar motor response in two CTS subjects from both ends of the distal motor terminal latency spectrum. **(a)** Note there is very little change in npAmp (close to control values) with 30-Hz stimulation (-4.9%) with the moderate increase in MTL compared to **(b)** the hand with the more severe increase in MTL, which shows a percent change in npAmp of -25.3%. In this particular case, significant changes began to occur at 10-Hz (-13%) (CTS = carpal tunnel syndrome, Hz = hertz, mV = millivolts, ms = milliseconds, MTL = motor terminal latency, npAmp = negative peak amplitude).

2.3 DISCUSSION

This study has demonstrated FDB in patients with moderate to severe carpal tunnel syndrome. Additionally, we have shown that the degree of FDB was greater when distal motor latency was more prolonged and that FDB was more pronounced at higher stimulation frequencies (20 and 30-Hz).

Maximum physiological rates of motor unit firing vary among muscle groups and experimentally have been shown to occur, on average, at frequencies close to 30-Hz^{18, 19}. Interestingly, while maximally contracting isolated muscle groups^{20, 21} or stimulating healthy peripheral motor nerves at these frequencies,^{22, 23} an increase in size of the CMAP has been observed. This phenomenon, known as “potentiation,” occurs as a result of increased muscle fiber hyperpolarization due to enhanced Na⁺/ K⁺ pump activity²⁰. In our controls, 80% of cases showed such an increase in the thenar CMAP npAmp when the median nerve was stimulated at a frequency of 30-Hz. Conversely, as a result of FDB, 89% of limbs studied in the CTS group showed a decreasing response in the CMAP. Also, although there was a slight increase in amplitude size in the remaining limbs (11%), only one of these two cases fell within the 95% confidence interval of controls. These two subjects also had distal motor latencies that were not as prolonged (< 6 ms), so it was not surprising to see only minimal changes in the npAmp relative to that observed in subjects whose latencies exceeded 7 ms. Overall, 94% of CTS limbs studied (17 of 18) fell outside our range of control data in terms of npAmp change during 30-Hz stimulation.

Previous studies have been unable to demonstrate FDB or activity-dependent conduction block (ADB) in patients with CTS, despite showing greater (but not significant) reductions in sensory response amplitudes compared to controls^{14, 15} and sufficient

degrees of axonal hyperpolarization that would otherwise produce conduction block¹⁶, such as that observed in patients with chronic inflammatory demyelinating polyneuropathy^{2, 11}. One possible explanation for our positive results is that motor fibers appear to be more susceptible to axonal hyperpolarization than sensory fibers^{24, 25}. In addition, we purposely set out to increase the probability of demonstrating FDB by studying patients with moderate to severe CTS based on their distal motor terminal latency, whereas previous studies examined patients with only mild to moderate evidence of CTS, and then only in terms of their sensory nerve responses¹⁴⁻¹⁶.

When examining the relationship between the degree of demyelination and the probability of occurrence of FDB, it would be prudent to predict that the greater the degree of motor slowing, the greater is the likelihood of demonstrating FDB. Our results reflect this in that the percentage of FDB was greater as distal motor latencies increased. This suggests that there must be a considerable degree of demyelination present causing focal conduction slowing in patients with CTS. This, of course, assumes that the increase in latency is not due to other possible factors associated with axonal loss such as a loss of the larger myelinated motor nerve fibers, axonal tapering, or even remyelination. Careful attempts were made in this study to eliminate the possibility of secondary distal axonal loss as a contributor to the increase in latency and even to the degree of FDB produced by only including patients with distal CMAPs that were within our normal laboratory limits (> 6.0 mV). Needle studies were also performed in six subjects and were normal with the exception of an occasional large motor unit seen in two cases. Therefore, the probability of axonal loss as the causative factor for these prolonged distal motor terminal latencies or for FDB (due to impaired function of the neuromuscular junction resulting from immature,

reinnervating axonal sprouts) is unlikely. Furthermore, our results from studies performed at lower frequencies, routinely used to demonstrate decrement in diseases of the neuromuscular junction, were well within normal limits²⁶.

Because the refractory periods are increased in demyelinated nerve fibers^{27, 28}, increasing the stimulation rate should increase the probability of transmission failure or FDB, particularly across segments of severe demyelination. This trend was observed in the CTS group when at 3, 5, and 10-Hz, the mean decrease in npAmp (1st to 20th responses) was less than 5%. However, as the stimulation rate increased from 10 to 20-Hz, the mean change or degree of FDB nearly doubled, and then nearly tripled at 30-Hz stimulation. Similar results have been observed in sensory fibers in which increases in threshold current were recorded as stimulation rates increased from 8 to 30-Hz²⁵. It is important to note, however, that despite a relatively strong trend between stimulation frequency and FDB, not all our CTS subjects followed this expected relationship. For example, two of eight more severe cases with distal motor latencies greater than 7.0 ms had less than 10% reduction between the 1st to 20th responses. Although there was still evidence of FDB, it is quite possible that over time substantial remyelination occurred, accounting for most of the conduction slowing across the carpal tunnel. Indeed, the clinical symptoms for these patients exceeded 3 and 25 years, respectively.

Could our findings be influenced by technical factors? The results from our control data suggest otherwise. As mentioned previously, 30-Hz stimulation in 12 of 15 control subjects showed an increase in the npAmp, and only a minimal decrease in the remaining 3 cases, whereas all but one case of CTS fell well outside our control range of values. Also, to avoid excessive movement during stimulation (a potential cause for technical error), all

hands were secured firmly and the thumb was held in place by another examiner. In the remote chance that the slightest repositioning of the recording dipole (due to changes in muscle length and position of the contracting muscle during the first few stimulations) could produce “technically” related changes in the CMAP, these changes would presumably cease when the muscle finally shortened to its new length²⁰. This, however, was not the case, as changes in npAmp continued well into the train of recorded responses.

Phase cancellation, as a result of increased negative peak duration causing temporal dispersion, is another non-physiological cause for reduction in the CMAP or sensory nerve action potential waveforms. This occurs more so in healthy peripheral sensory nerve fibers than in motor fibers, even across short distances such as the carpal tunnel^{14, 29}.

Importantly in our study, there was no significant difference in the thenar CMAP negative peak duration (wrist stimulation) between the control and CTS groups. Furthermore, when dividing the CTS subjects into two groups representing ascending distal motor latencies and their associated negative peak durations (group 1, 5.0 to 6.9 ms; group 2, 7.1 to 9.4 ms), there was no significant difference between the group npDur means either when comparing the absolute negative peak duration following stimulation at the wrist or the percent change in duration across the carpal tunnel. Based on this analysis, the increase in the extent of FDB observed with increasing distal motor terminal latencies, at 30-Hz stimulation, is not associated with changes in negative peak duration. Therefore, based on this information and similar values seen in controls, it is unlikely that the degree of FDB observed in our cases was the result of changes in negative peak duration across the carpal tunnel. Additionally, both the current study and previous work²² have shown that with increasing stimulation frequencies, the CMAP’s duration shortens, thus providing

further evidence that the observed reduction in negative peak amplitude is unlikely the result of phase cancellation.

When attempting to demonstrate ADB or FDB in peripheral motor nerve fibers, presumably both maximal voluntary contraction and high-frequency nerve stimulation “stress” the nerve at similar firing rates of approximately 30-Hz. Why this was not observed in a previous study while examining the median motor fibers¹⁶ is unclear, despite the sufficient degree of axonal hyperpolarization realized. Possibly, it was related to their sample group of mild to moderate CTS (mean distal motor latency, 5.5 ms; range, 3.8 to 7.4 ms) whereas, we set out to examine subjects with moderate to severe focal conduction slowing (mean distal motor terminal latency, 6.6 ms; range, 5.0 to 9.4 ms). Lack of patient effort may have also accounted for the inability to demonstrate ADB. For example, it has been shown that deafferentation can affect one’s ability to sustain maximal motor contraction³⁰⁻³². Therefore, our decision to use high-frequency nerve stimulation presumably by-passed these limitations associated with voluntary contraction.

In healthy myelinated axons, axonal hyperpolarization occurs as a result of a train of impulses and is associated with two positive after-potentials, P_1 and P_2 ³³. The two mechanisms responsible for these two peaks of hyperpolarization are the activation of slow K^+ conductance produced by a brief train of impulses^{29, 34-37} and the activation of the Na^+/K^+ electrogenic pump produced by longer trains of impulses^{1, 36, 38-45}, P_1 and P_2 respectively. In most instances, the margin of safety in myelinated nerve fibers is high enough to prevent conduction block from occurring during these trains of impulses, despite these periods of axonal hypoexcitability. However, this safety factor is reduced in demyelinating conditions as a result of increased nodal capacitance, which causes the

driving current available to fall short of meeting these higher nodal thresholds. FDB occurs as a result of the failure to maintain saltatory conduction through these demyelinated segments, particularly during higher-frequency trains of impulses. In this study, FDB was demonstrated using only a brief train of impulses (20 stimuli at 30-Hz) lasting less than 1 second. This implies that the margin of safety in a number of motor fibers must have been reduced to near unity as a result of demyelination⁴⁶ and that activation of the slow K⁺ conductances presumably played a contributing role in the FDB observed in this study. It is important to recognize, however, that further decreases in npAmp may have occurred with longer trains of stimulation or higher stimulation frequencies. Unfortunately, the discomfort experienced with these higher levels of stimulation precludes the use of such techniques in the conscious patient.

In conclusion, we have demonstrated FDB in the median motor fibers of CTS patients with moderate to severe prolonged distal motor latencies. FDB appears to be rate dependent and is more demonstrable when using high-frequency nerve stimulation in those cases with significantly prolonged distal motor latencies. Our results suggest that demyelination plays a role in focal conduction slowing in carpal tunnel syndrome and that FDB may be responsible for the grip weakness often described by these patients. We have also demonstrated that the safety margin for impulse transmission is impaired in the motor axons of the median nerve in CTS patients. It remains unknown whether these results can be extrapolated to other entrapment neuropathies.

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CHAPTER 3

LOCALIZATION OF FREQUENCY-DEPENDENT CONDUCTION BLOCK IN CARPAL TUNNEL SYNDROME

3.0 INTRODUCTION

Short duration, high-frequency repetitive nerve stimulation (30-Hz) characteristically produces an increase in the compound muscle action potential (CMAP) in normal healthy subjects^{1,2,3}. This occurs despite evidence of axonal hypoexcitability during this physiological rate of activation⁴. Fortunately, the safety margin for impulse transmission during the periods of hypoexcitability is sufficient in healthy nerves to prevent transmission failure from occurring. However this safety factor can be reduced to near unity during conditions of demyelination⁵ resulting in transmission failure and conduction block. This has been observed experimentally in animals^{6,7,8,9,10} and in human demyelinating conditions^{11,12}. It has been termed frequency-dependent conduction block (FDB) or activity- or rate-dependent conduction block, depending on the method used to demonstrate this phenomenon.

More recently, FDB has been demonstrated in the motor fibers of the median nerve in patients with clinical and electrophysiological evidence of carpal tunnel syndrome (CTS)³. Based on the presumed mechanism of injury in CTS, it might be assumed that FDB occurs directly within the region of the carpal tunnel (CT). However, caution should be taken regarding this inference, as it is equally possible, given the methods used in our first study, that all or a portion of the observed block in transmission may have occurred more

A version of this chapter has been published.

Watson BV, Doherty TJ. Localization of frequency-dependent conduction block in carpal tunnel syndrome. *Muscle & Nerve* 2010; 42:120-126.

distally within the higher-threshold unmyelinated axon terminals that are significantly devoid of sodium channels^{13,14,15} or even at the neuromuscular junction. If FDB occurs beyond the region of the carpal tunnel then it might suggest that secondary effects from the site of injury occur more distally. This could produce a reduced margin of safety and transmission failure or there may be extensive compression beyond the carpal tunnel, within the boundaries of the palmar aponeurosis.

Taking those possibilities into consideration, this study was undertaken to determine whether FDB in subjects with CTS occurs specifically across the region of the CT or more distally across the distal margins of the palmar aponeurosis, within the motor axon terminals, or possibly at all sites. We increased the probability of demonstrating FDB across both locations by studying CTS patients with moderate to severe conduction slowing in the median motor fibers across the wrist. We attempted to exclude subjects with any evidence of axonal loss.

We hypothesized that when FDB is observed, the majority of this phenomenon will occur across the region of the CT, but, in some cases a portion of FDB may occur more distally as a result of “downstream” influences from nerve injury beneath the CT affecting the distal or terminal portion of the nerve.

3.1 METHODS

3.1.1 Subjects

Fourteen healthy control subjects with normal median motor and sensory nerve conduction studies across the CT (7 men and 7 women; age, 49.5 ± 13.6 years; range, 22 to 68 years) and 10 patient subjects (4 men, 6 women; age, 58.3 ± 11.5 ; range, 45 to 78 years)

with clinical and electrophysiological evidence of moderate to severe CTS (as defined below by the distal motor terminal latency) were asked to participate in this study. Subjects with clinical or electrophysiological evidence of a generalized peripheral neuropathy or evidence of focal conduction block were excluded. One subject with CTS was diabetic. All subjects gave informed consent to the experimental protocol, which was approved by the Health Sciences Research Ethics Board of The University of Western Ontario.

3.1.2 Electrophysiological Data Collection

Controls. Consistent with our previous study³, it was necessary to establish the response to 30-Hz repetitive nerve stimulation (RNS) in controls for both the palm and wrist sites of stimulation, as this was the background to which the CTS patients were compared. Control studies using high-frequency nerve stimulation (HFNS) were performed on the non-dominant hand by applying 20 stimuli at a rate of 30-Hz (total time of stimulation, 0.667 s) to the median nerve in the palm (distal to the flexor retinaculum, near the motor point along the medial margin of the thenar eminence, approximately 2 to 3 cm distal to the distal wrist crease and 1 to 2 cm medial to the G1 strip recording electrode, depending on the size of the hand), and at the wrist, approximately 7 cm proximal to the active electrode. Whenever necessary, slight rotation of the stimulating anode, either medially or laterally and/or minimal repositioning of the stimulating electrode further away from the recording electrode was done to eliminate the contaminating effects of the stimulus artifact on the thenar CMAP; this was successful in all cases. The active recording electrode was placed over the motor point of the thenar eminence, perpendicular to its

muscle fiber orientation, and the reference electrode was placed over the first metacarpophalangeal joint.

CTS Patients. Routine median motor nerve conduction studies were performed separately to ensure that all inclusion criteria were met: distal motor terminal latency (MTL) across the wrist ≥ 5.0 ms; distal CMAP obtained from wrist stimulation ≥ 6.0 mV (lower limit of normal for controls in our laboratory); and no evidence of conduction block in comparing stimulation at the wrist and palm. These criteria were chosen to represent moderate to severe conduction slowing across the carpal tunnel with no or very little evidence of motor axonal involvement.

RNS (30-Hz, 20 stimuli) of the median nerve in the palm and wrist was then performed in all 10 CTS subjects while recording over the thenar eminence. In two cases, bilateral studies were performed. This resulted in a total of 12 limbs studied. Additional studies were also performed in all CTS subjects using lower stimulation frequencies (3 and 10-Hz). This was not done for the purpose of analysis but to ensure that the stimulating and recording set-up for 30-Hz stimulation was secure and void of any movement or stimulus artifact.

Possible patterns (scenarios) while stimulating at 30-Hz in our patient group were as follows:

1. Both palm and wrist stimulation behave similarly to controls, and therefore no evidence of FDB is observed.
2. Palm stimulation behaves similarly to controls, while wrist stimulation produces FDB, suggesting impaired conduction across the carpal tunnel.

3. Palm stimulation produces a similar degree of FDB as the wrist stimulation, suggesting impaired conduction distal to the CT somewhere between the distal margins of the palmar aponeurosis and motor terminal branches.
4. Both palm and wrist stimulation produces FDB, but wrist stimulation generates a greater degree of FDB, suggesting two sites of impaired conduction with greater impairment across the CT.
5. Palm stimulation produces a greater degree of FDB than wrist stimulation does, suggesting a technical error with palmar stimulation.

In all studies, surface, disposable recording electrodes (Ag/AgCl Mactrode Electrodes; GE Medical Systems, Milwaukee, Wisconsin) were used and secured with tape to prevent displacement, particularly during higher frequency stimulation. The skin was prepared using 70% isopropyl alcohol and when necessary in subjects with rough, oily or greasy skin, One-Step Skin Prep (3M, London, Ontario, Canada) was used to mildly abrade the skin to reduce impedance. The active electrode was moved a minimum of three times and placed over the location which elicited the maximum thenar CMAP negative peak amplitude. In an attempt to minimize hand movement during stimulation, it was secured firmly, but comfortably within a wrist splint, and the thumb was manually held in place. Supramaximal stimulation, 15 - 20% greater than maximal stimulation, was used in all cases. Limb temperature was maintained at $\geq 32^{\circ}$ C with the aid of a portable heat lamp, when necessary. All waveforms were collected, analyzed and stored using a standard EMG machine (Advantage Medical, London, Ontario, Canada). Negative peak amplitude (mV), negative peak area (mVms) and negative peak duration (ms) were measured for all individual waveforms collected.

3.1.3 Calculations and Statistics

Calculations. To calculate the overall percent difference in amplitude for each train, the negative peak amplitude (npAmp) from the 20th waveform was compared relative to the 1st waveform ($\text{npAmp}_{20^{\text{th}}} / \text{npAmp}_{1^{\text{st}}} \times 100$). During the routine nerve conduction studies, conduction block was considered present across the wrist if there was a greater than 20% decrease in negative peak area (npArea) between the responses obtained from palm and wrist stimulations $[(\text{npArea}_{\text{palm}} - \text{npArea}_{\text{wrist}}) / \text{npArea}_{\text{palm}} \times 100]$; temporal dispersion was considered to be present if there was a 15% increase in npDur between these similar responses $[(\text{npDur}_{\text{palm}} - \text{npDur}_{\text{wrist}}) / \text{npDur}_{\text{palm}} \times 100]$ ¹⁶.

Statistics. Range of values, their means and standard deviations are presented throughout. Significant differences in the 1st thenar CMAP amplitude, between stimulation protocols, were examined via a within-subjects repeated measures analysis of variance (ANOVA). One and two-way ANOVAs were used to assess whether there were main effect when comparing stimulation sites (palm and wrist) within and between groups (1st, 10th and 20th responses were used for each comparison). Mean values were compared within groups with the Student's *t*-test statistic. The relationship between age and changes in the 20th thenar CMAP was examined within groups using the Spearman rank correlation statistic.

3.2 RESULTS

3.2.1 Control Subjects and Nerve Conduction Studies

Routine motor nerve conduction studies revealed normal distal thenar CMAPs (mean, 11.8 ± 2.2 mV; range, 8.5-15.7 mV) and normal motor terminal latencies (mean, 3.1

± 0.4 ms; range, 2.5-4.1 ms) following wrist stimulation. Palm stimulation elicited similar results for the thenar CMAP (mean, 11.7 ± 2.3 mV; range, 7.6-15.3 mV) with less than 1 mV difference between these two sites of stimulation in 9 of 10 cases ($P > 0.05$).

3.2.2 Control Subjects and RNS (30-Hz, 20 stimuli)

Relative to the first thenar CMAP waveform (100%), there was a mean increase in the 20th response of +6.3% (range, -4.5 to +21.1%) for the control group when stimulating in the palm. Similarly, when stimulating at the wrist, there was a mean increase in the 20th response of +8.2% (range, -3.4 to +23.6%).

Overall, only 2/14 control subjects showed a decrease in the 20th response relative to the 1st response, when stimulating in the palm and at the wrist (1st subject, 96.7% and 96.6%; 2nd subject, 95.1% and 97.1%, respectively). Based on these results, the greatest individual decrease in the 20th response from palm (-4.9% or 95.1% of the 1st response) and wrist (-3.4% or 96.6% of the 1st response) stimulation were used as the lower range of normal when comparing results from the CTS subject group.

To demonstrate further consistency within controls, similar percent changes in the 20th thenar response were observed when comparing their individual palm and wrist stimulation results together. Specifically, there was less than 6.5% difference between these two stimulation sites, in 12/14 controls. Further, when comparing the 1st, 10th and 20th responses (30-Hz stimulation) between the palm and wrist stimulation sites, a two-way ANOVA revealed no main effect ($P > 0.05$).

3.2.3 CTS Subjects and Nerve Conduction Studies

The mean duration of symptoms in the CTS subject group was 4.3 years (range, 0.6-10 years). Routine motor nerve conduction studies revealed normal thenar distal CMAP

amplitudes (mean, 8.0 ± 1.4 mV; range, 6.2-10.5 mV) but increased distal median motor terminal latencies (mean, 6.9 ± 0.9 ms; range, 5.5-8.9 ms) following stimulation at the wrist. Palm stimulation elicited similar sized thenar CMAPs (mean, 8.7 ± 1.6 mV; range, 6.7-11.8 mV) ($P > 0.05$). Individually, there was no evidence of conduction block across the CT.

3.2.4 CTS Subjects and RNS (30-Hz, 20 stimuli)

Relative to the 1st thenar CMAP, there was an overall mean decrease in the 20th response of -4.9% (range, -28.2 to +7.7 %) for the CTS group when stimulating in the palm. Within the 10 subjects tested (12 studies in total), 7/12 studies (58%) either showed an increase in the 20th response, or there were minor decreases that were within the lower range of normals; 5/12 (42%) studies showed decreases in this response outside control values, with four having marked decreases of 13.1, 14.8, 17.3 and 28.2% when compared to the 1st response.

In contrast to palm stimulation and contrary to what was observed in most controls for wrist stimulation, all 10 CTS subjects (12 studies) showed a decreased 20th thenar CMAP when stimulating at the wrist, just proximal to the CT. Only 1/12 studies fell within the lower limit of controls (96.9%). The overall group mean decrease was -12.0% with an individual range between -3.1% and -28.1%.

Figure 3.1 represents a typical study recorded from a control subject and two distinct patterns recorded from CTS subjects during 30-Hz stimulation. Overall, four out of a possible five patterns emerged within the CTS group following stimulation at both sites: (1) 1/12 (8.3%) studies produced results similar to controls. (2) 6/12 (50%) studies produced a decrease in the 20th thenar response (relative to the 1st response) following wrist stimulation, whereas palm stimulation produced an increase similar to controls.

(3) 4/12 (33.3%) studies produced similar percent decreases (within 5%) for both sites of stimulation. (4) 1/12 (8.3%) studies, despite producing a decrease when stimulating at both sites, showed a greater decrease when stimulating at the wrist (Fig. 3.2). The first pattern suggests that there is no evidence of FDB; the second pattern suggests that FDB occurs across the CT; the third pattern suggests that FDB occurs somewhere across the distal portion of the palmar aponeurosis and the motor terminal branches; the fourth pattern suggests FDB occurs at both sites, more so across the wrist. Importantly, there was no case that showed a markedly greater percentage of FDB occurring more distally than what was observed across the CT (fifth pattern/scenario).

Figure 3.3 illustrates the overall relationship between the controls and CTS subjects when stimulating at 30-Hz. Within groups, the overall mean difference at 30-Hz between the wrist and palm sites of stimulation was much larger for the CTS group (7.1%) than controls (1.9%). Between groups, there was a difference of 11.2% when comparing the palm sites of stimulation and a much greater difference of 20.2% when comparing stimulation at the wrist. When comparing the two stimulation sites (palm and wrist) within groups, a two-way ANOVA (using the thenar CMAP npAmp values) revealed a stronger main effect ($P < 0.05$, $P = 0.001$) in the CTS group at 30-Hz stimulation, whereas in the control group there was no significant difference ($P > 0.05$, $P = 0.482$) between stimulation sites using 30-Hz stimulation. When comparing the relationship between the study groups and sites of stimulation, there was a significant difference (effect) when stimulating at 30-Hz in the palm ($P = 0.0001$) and at the wrist ($P < 0.0001$).

3.2.5 CTS Subjects and Negative Peak Duration.

Additional comparisons were made to assess whether npDur was associated with and could account for the increased probability of FDB occurring with more prolonged distal motor terminal latencies. In other words, was it possible for phase cancellation to contribute to the FDB observed in this study as a result of changes in npDur? To address this, we divided our CTS subjects into two groups of ascending distal motor terminal latencies since there was a trend for increased MTLs to show greater levels of FDB (group 1, 5.5-6.9 ms and group 2, 7.0-8.9 ms). We did statistical comparisons of their respective thenar CMAP npDur values recorded following palm and wrist stimulation. All comparisons were non-significant ($P > 0.05$). Individually, there were only 2/10 CTS subjects (two studies) with a greater than 15% change in npDur across the CT, however both cases also demonstrated FDB distal to the CT following palm stimulation.

3.2.6 CTS Subjects and the First CMAP Response in each Train

A repeated measures ANOVA, comparing the first CMAP response (npAmp) from each train, with palm and wrist stimulation, was not significant ($P > 0.05$). Specifically, there was no statistical evidence that suggested previous trains of repetitive nerve stimulation influenced subsequent studies.

3.2.7 CTS and Control Subjects and the influence of age on FDB

There was no relationship between age and the degree of FDB (percent of 20th CMAP relative to the 1st CMAP) either with palm or wrist stimulation for the CTS group (palm, $P = 0.658$, $r = 0.14$; wrist, $P = 0.766$, $r = 0.10$) or in a comparison of age with the change in the 20th CMAP in the control group (palm, $P = 0.453$, $r = -0.22$; wrist, $P = 0.336$, $r = -0.28$).

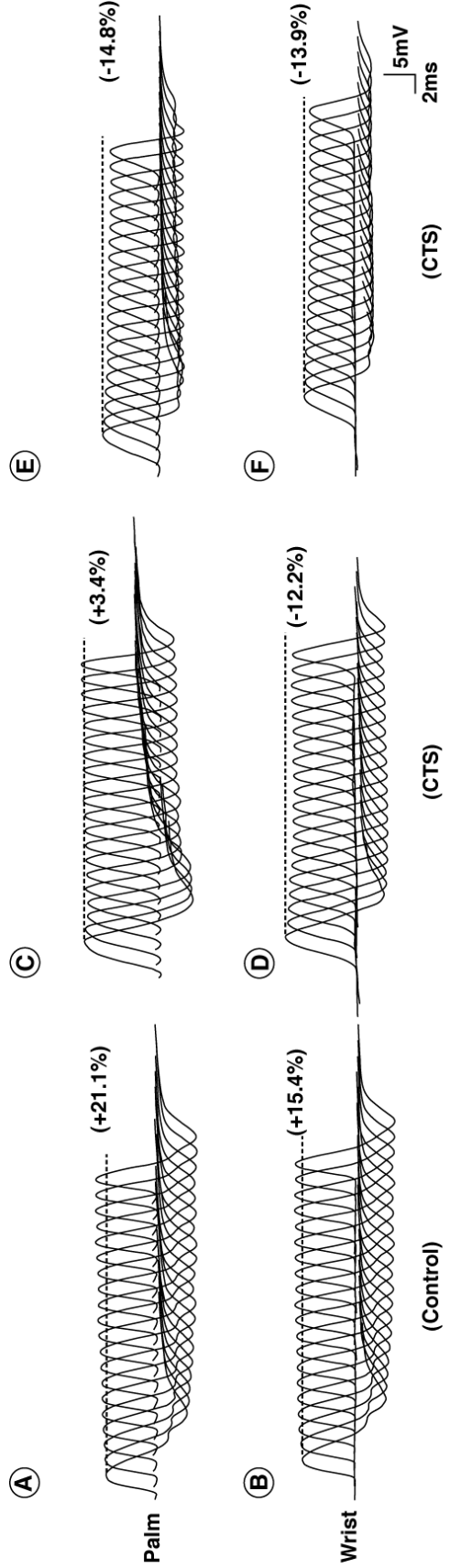


Figure 3.1. Typical thenar motor recordings following stimulation (30-Hz, 20 stimuli) of the median nerve (palm and wrist)

from a control subject **(A,B)** and two CTS subjects **(C-F)**. Note that in the two CTS examples, two different patterns emerge;

(1) **(C,D)**, palmar stimulation produced an increasing amplitude pattern similar to controls, whereas wrist stimulation

produced a decreasing pattern (this suggests that in these examples the FDB observed is occurring across one site within the

CT region). (2) **(E,F)**, palmar stimulation elicits the opposite pattern to (C) where the amplitude decreases, similar to what

is typically observed when stimulating CTS subjects at the wrist (this suggests that it is possible that the degree of FDB

observed in these examples can be attributed to the region distal to the CT, across the distal region of the palmar aponeurosis

and axon terminals or as a result of more distal influences from compression beneath the CT). Dashed lines indicate the peak

of 1st response (100%) (Hz = hertz, CTS = carpal tunnel syndrome, mV = millivolts, ms = milliseconds, FDB = frequency-

dependent conduction block, CT = carpal tunnel).

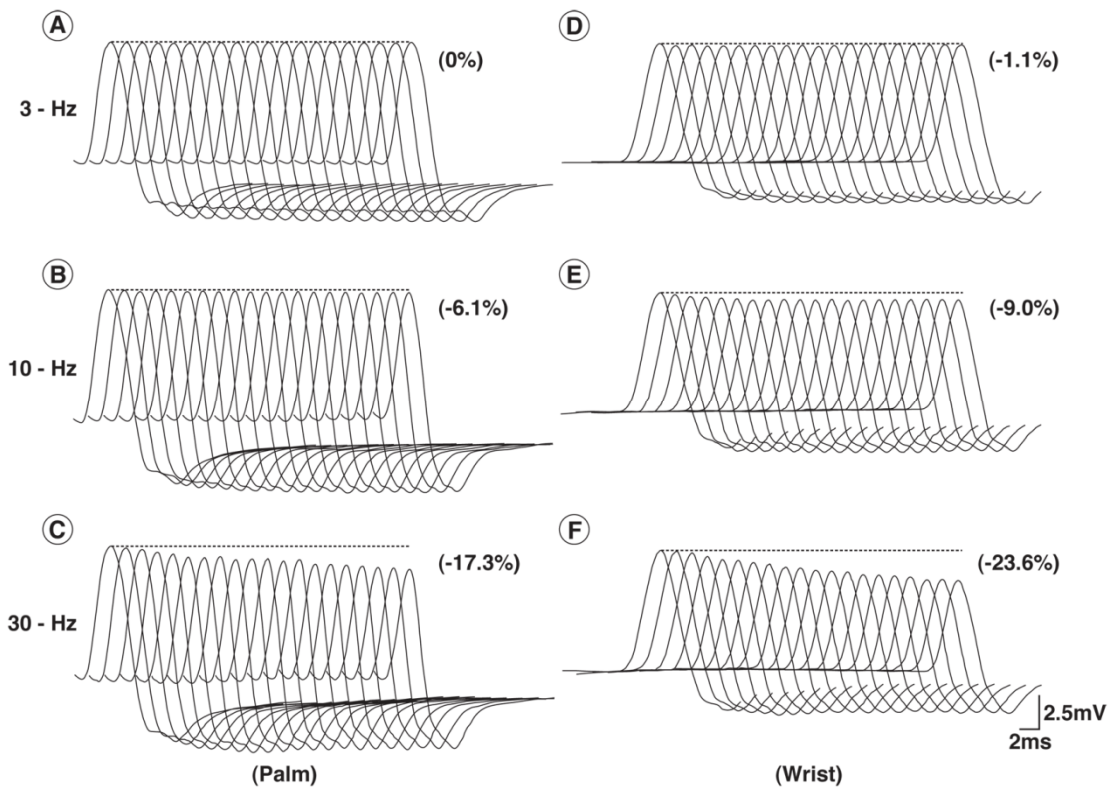


Figure 3.2. Results from one CTS subject showing the relationship between three frequency levels of stimulation (3-Hz, 10-Hz, and 30-Hz) when stimulating in the palm (traces **A-C**) and at the wrist (traces **D-F**). Note that FDB was seen at both sites, particularly at 30-Hz, but more so across the wrist (traces **C,F**). Percentages in parentheses represent the change in the 20th response npAmp relative to the 1st response (higher negative percentages, outside the lower limits of controls, indicate evidence of FDB). Lower limits of normal for the palm and wrist (30-Hz) are -4.9% (95.1% of 1st response) and -3.4% (96.6% of 1st response), respectively. Dashed lines indicate the peak of 1st response (100%) (mV = millivolts, ms = milliseconds, CTS = carpal tunnel syndrome, Hz = hertz, FDB = frequency-dependent conduction block, npAmp = negative peak amplitude).

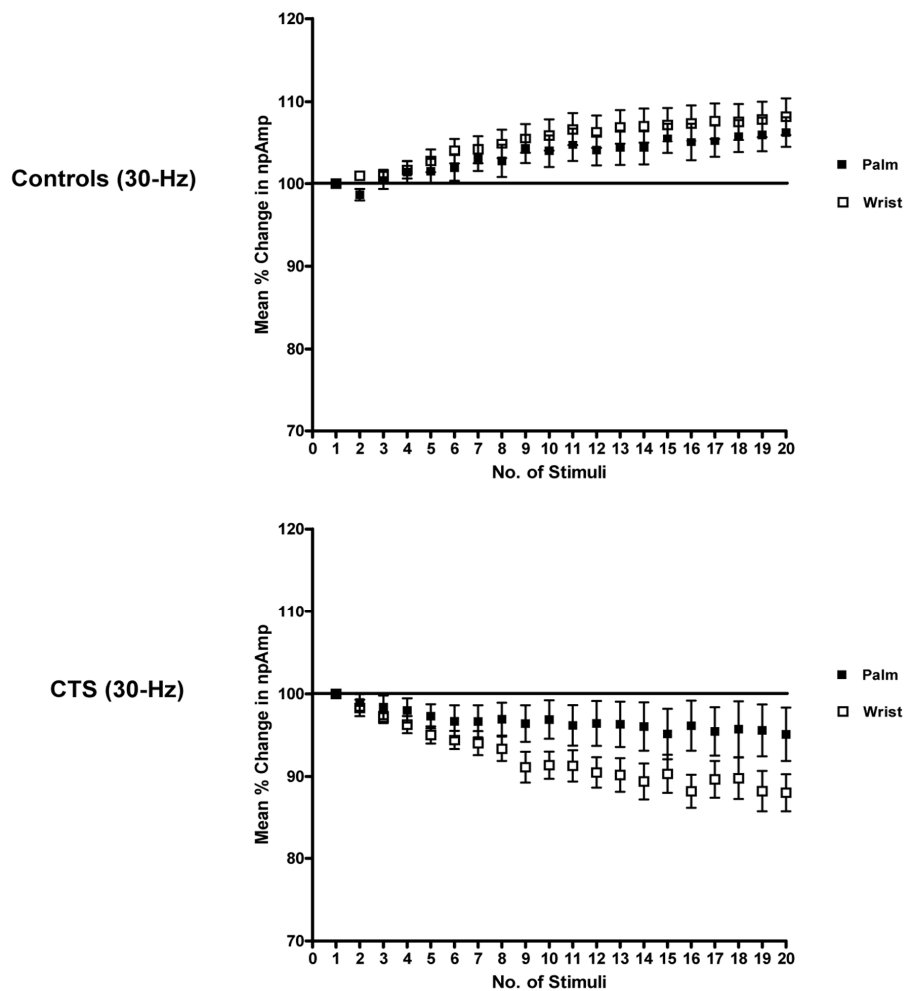


Figure 3.3. Relationship between the group mean percent changes in npAmp in 14 studies from 14 control subjects (top trace) and in 12 studies from 10 CTS subjects (bottom trace), while stimulating the median nerve (30-Hz, 20 stimuli) and recording over the thenar eminence. All responses were compared to the first response (100%). Note, FDB is clearly evident here in CTS subjects, both with palm and wrist stimulation (compare with controls, which typically demonstrate an increasing pattern: top trace). Solid lines represent 1st CMAP response at 100% (npAmp = negative peak amplitude, CTS = carpal tunnel syndrome, Hz = hertz).

3.3 DISCUSSION

The results of this study compare favorably with our previous results from high-frequency stimulation of the median nerve proximal to the CT in patients with CTS³. The purpose of this study, however, was to further investigate whether FDB occurred specifically across the region of the carpal tunnel or more distally within more distal terminal branches of the median nerve. Our results showed that FDB occurred across the CT in 11/12 studies in severe CTS patients, defined by their median nerve distal MTL, and specifically across the distal region of the palmar aponeurosis or motor terminal axon in 5 of these studies. These results suggest that in some cases of CTS, FDB could occur as a result of either primary injury distal to the CT but within the boundaries of the palmar aponeurosis, or alternatively, the primary injury beneath the CT influenced the transmission properties of the nerve more distally.

Recently it was shown that FDB occurs in CTS patients with prolonged distal motor latencies and that the greater the latency prolongation, the greater the degree of FDB across the carpal tunnel³. However, what was uncertain was whether a portion or all of the FDB observed occurred more distally beyond the CT, the presumed site of nerve compression and myelin injury. Our results from this study revealed that in $\approx 92\%$ of the CTS subjects FDB occurred in response to stimulation proximal to the CT, and in approximately $\approx 42\%$ of studies, FDB occurred with stimulation distal to the CT. Conversely, only 2/14 control studies showed any evidence of a decrease in the thenar CMAP in response to 30-Hz stimulation, and in those cases the results were negligible. Importantly, from a technical and physiological point of view, there was not a single CTS

case that demonstrated a greater degree of FDB distal to the CT than what was observed with stimulation proximal to the CT.

Although it is reasonable to predict that FDB might occur across anatomical regions of compression or entrapment that cause demyelination, the explanation for its occurrence distal to the carpal tunnel in some CTS subjects remains speculative and less clear. It is possible in these cases that the lesion is less focal and more extensive throughout the palm^{17,18,19} or that the presumed focal median nerve injury beneath the CT may be severe enough to produce myelin changes in the nerve distal to the actual site of entrapment^{20,21}. Similar changes have been observed in humans where altered median nerve internodes were observed up to 2 cm distal to the lesion in the form of bulbous myelin swellings at one end and myelin retraction and thinning at the other²². Such abnormalities 2 cm distal to the CT would certainly relate to the site of palm stimulation used in this study.

Despite our conclusions, it is still important to consider “immature” neuromuscular junctions as potential sites for FDB (as a result of denervation/ reinnervation). Attempts were made to control for motor axonal loss by only including patients who had distal thenar CMAPs above normal laboratory values (≥ 6.0 mV), although this does not necessarily exclude axonal injury. Further, results from lower stimulation frequencies, routinely used to demonstrate decrement in diseases of the neuromuscular junction, were well within normal limits²³.

As in our previous paper³, the control studies provided the necessary template from which to compare the results obtained from our patient population. Importantly, the results from controls were remarkably consistent between the two studies, with very

similar increases between the 1st and 20th thenar CMAP in response to 30-Hz stimulation. However, could our results obtained with palm stimulation (a less frequent site of stimulation) be influenced by technical error? Again, as in previous results³, our control data would suggest otherwise. In 12/14 control cases, palm stimulation at 30-Hz produced a characteristic and expected increase in the 20th response in comparison to the 1st. Lastly, phase cancellation, as a result of temporal dispersion due to increases in npDur, could be a non-physiological cause for CMAP reductions. Importantly, in the only two CTS cases in which npDur increased by greater than 15% across the CT, the majority of FDB that was observed occurred distal to the CT and not across the wrist.

One potential mechanism that has been described to explain the degree of FDB observed in our study, is the activation of slow K⁺ conductance produced by a brief train of impulses^{24,25,26,27,28}. This produces axonal hyperpolarization (axonal hypoexcitability) and is associated with a positive after-potential, P₁ wave⁴. The trains of impulses that produced FDB in this study were brief with 20 stimulations at 30-Hz, lasting less than 1 s. It is possible that further decreases in the npAmp may have occurred with longer trains of stimulation, but the potential discomfort experienced at supramaximal levels of stimulation precluded testing train durations beyond our current protocol.

In conclusion, the primary purpose of this article, to determine if FDB occurred distal to the CT, has been met. Our results have demonstrated that in patients with moderate to severe conduction slowing associated with CTS, FDB occurs in median motor fibers, not only across the region of the carpal tunnel (previously demonstrated³) but, also more distally across the distal margins of the palmar aponeurosis and motor terminal axon (Fig. 3.3). Although, the design of this study was not to establish the pathophysiology or

mechanism responsible for our findings, this suggests that demyelination may occur distal to the lesion in CTS, and supports morphological and histochemical observations recorded in both animal and human studies^{20,21,22}. Our data also suggests that the safety margin for impulse transmission is impaired distally in the motor axons of the median nerve in moderate to severe CTS patients and that this region should be considered to be a potential site of injury, particularly in patients who fail to respond to more proximal steroid injection or surgical treatment. Whether FDB is a significant contributor to the intermittent weakness often described by these patients remains unknown. Further studies that combine HFNS with a fatiguing exercise protocol may be helpful to determine whether the motor or sensory system is truly responsible for this weakness, particularly in milder cases of CTS.

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CHAPTER 4

FREQUENCY-DEPENDENT CONDUCTION BLOCK IN MILD CARPAL TUNNEL SYNDROME WITH NORMAL MOTOR NERVE CONDUCTION STUDIES

4.0 INTRODUCTION

Patients with clinical and electrophysiological evidence of mild carpal tunnel syndrome (CTS) may complain of hand weakness, clumsiness or decreased hand dexterity despite having normal median motor nerve studies with absence of slowing or conduction block across the wrist, and normal motor amplitudes. It is commonly assumed that in these milder forms of CTS, the apparent weakness or loss of dexterity is due to decreased sensory input rather than direct median motor nerve dysfunction. However, conventional motor nerve conduction studies are performed with non-physiological rates of stimulation, with most labs using stimulus frequencies less than or equal to 1-Hz. Therefore, it's conceivable that deficits in the median motor nerve may be contributing to weakness or fatigue in these mild forms of CTS but, conventional conduction studies at non-physiological rates of stimulation are insensitive to these potential deficits in conduction. Recently, in subjects with moderate to severe CTS, higher rates of stimulation (30-Hz), reflecting physiological rates of motor unit recruitment³, have demonstrated frequency-dependent conduction block (FDB) within the median motor fibers across the carpal tunnel (CT)¹ and in some cases, FDB more distally along the terminal branches of the median nerve².

FDB or activity-dependent conduction block (ADB) occurs across regions of demyelination when nodal capacitance increases to a level resulting in a reduction in the safety margin for nerve transmission. When this margin of safety is critically impaired,

there is failure of transmission across these nodes of Ranvier, resulting in conduction block. This phenomenon has been demonstrated previously in animals⁴⁻⁸ and in humans with multifocal motor neuropathy⁹ and chronic inflammatory demyelinating polyneuropathy (CIDP)¹⁰. However, previous attempts to demonstrate FDB/ADB in mild to moderate forms of CTS following exercise have been unsuccessful, despite the presence of prolonged median motor terminal latencies and evidence of sufficient degrees of axonal hyperpolarization that would otherwise have produced conduction block in other demyelinating conditions^{10, 11}.

The present study was undertaken to determine whether FDB can be demonstrated in patients with milder forms of CTS, using high frequency nerve stimulation (HFNS) following exercise. Specifically, we examined patients with symptomatic CTS with normal routine motor nerve conduction studies, but, who complain of hand weakness. Our goals were to determine if: 1) there is any pre-exercise evidence of FDB when stimulating the median motor nerve at a physiological rate of 30-Hz?, and 2) 60 s of maximal voluntary contraction (MVC) increase the median motor nerve's threshold to a point where FDB is either observed post-exercise or to a greater degree than what was observed pre-exercise? Further, 3) does the degree of FDB increase in more severe cases of CTS, following exercise, when compared to controls and the mild CTS group? Lastly, since it has already been established that there are significant changes in the thenar compound muscle action potential (CMAP) between controls and moderate to severe CTS subjects in response to HFNS^{1, 2}) are there also significant differences in the CMAP between mild CTS and moderate to severe CTS subjects?

4.1 METHODS

4.1.1 Subjects

Fifteen healthy control subjects with normal median motor and sensory nerve conduction studies across the CT (five men and ten women; age, 41.5 ± 11.4 years; age range, 24-60 years), twelve patients (three men, nine women; age, 40.8 ± 11.3 years; age range, 23-53 years) with clinical and mild electrophysiological evidence of CTS (as defined below) and an additional fifteen patients (six men, nine women; age, 49.5 ± 9.6 years; age range, 36-66 years) with clinical and electrophysiological evidence of moderate to severe carpal tunnel syndrome (as defined below by the distal motor terminal latency) were asked to participate in this study. Subjects with clinical or electrophysiological evidence of a generalized peripheral neuropathy or with evidence of focal conduction block across the CT were excluded. All subjects gave informed consent to the experimental protocol, which was approved by the Health Sciences Research Ethics Board of The University of Western Ontario.

4.1.2 Electrophysiological Data Collection

Controls. Consistent with our previous studies^{1, 2, 12}, it was necessary to establish the response to 30-Hz repetitive nerve stimulation in controls, as this was the background data to which median nerve stimulation in CTS patients was compared. Control studies using HFNS were performed on the non-dominant hand (15 subjects, 15 limbs), before and after short-term exercise, by applying 20 stimuli at a rate of 30-Hz (total time of stimulation, 0.667 s) to the median nerve and at the wrist, approximately 7 cm proximal to the active electrode. The active electrode was placed over the motor point of the thenar eminence with the reference electrode placed over the first metacarpophalangeal joint.

Exercise Protocol. With audio feedback of the EMG signal and strong verbal encouragement, control subjects performed 60 s of isometric maximal voluntary contraction (MVC) of the abductor pollicis brevis muscle with the thumb fixed and against resistance.

CTS Patients (mild). Routine median motor nerve conduction studies were performed separately on 12 subjects (3 subjects studied bilaterally totaling 15 limbs) to ensure that all electrophysiological and clinical inclusion criteria were met: discrete 3rd-digit median sensory nerve conduction velocity < 48.0 m/s or ≥ 0.4 ms difference between 4th-digit median and ulnar sensory latencies in very mild, but symptomatic cases; distal motor terminal latency (MTL) across the wrist < 4.2 ms; distal compound muscle action potential obtained from wrist stimulation ≥ 6.0 mV; and no evidence of conduction block across the CT. All criteria values above represent the upper or lower limits of normal from our own laboratory control data. These criteria were chosen to represent nerve conduction study abnormalities only in the median nerve sensory fibers in combination with clinical signs and symptoms of CTS.

CTS Patients (severe). Routine median motor nerve conduction studies were performed separately on 15 subjects (4 subjects studied bilaterally totaling 19 limbs) to ensure that all electrophysiological and clinical inclusion criteria were met: discrete 3rd-digit median sensory nerve conduction velocity ≤ 48.0 m/s or absent; distal motor terminal latency (MTL) across the wrist ≥ 5.0 ms; distal compound muscle action potential obtained from wrist stimulation ≥ 6.0 mV; and no evidence of conduction block across the CT. Palmar stimulation was performed in all cases to exclude conduction block across the wrist. These criteria were chosen to represent moderate to severe nerve conduction study

abnormalities in the median nerve with little or no motor axonal involvement in combination with clinical signs and symptoms of CTS.

Pre- and post-exercise (60 s MVC) studies of HFNS were performed in both CTS subject groups in an identical manner to controls.

For all studies, surface, disposable recording electrodes (Ag/AgCl Mactrode Electrodes; GE Medical Systems, Milwaukee, Wisconsin) were used and secured with tape to prevent displacement. The skin was prepared using 70% isopropyl alcohol and when necessary in subjects with rough, oily or greasy skin, One-Step Skin Prep (3M, London, Ontario, Canada) was used to mildly abrade the skin to reduce impedance. The active electrode was moved a minimum of three times and placed over the location, which elicited the maximum thenar compound muscle action potential (CMAP). The stimulating electrode (13L36; Alpine Biomed; Fountain Valley, CA) was positioned and held firmly over the median nerve at the wrist during the entire stimulating and exercise protocol. The stimulating pads were kept moist during the period of testing by saturating them in water prior to stimulation. In an attempt to minimize hand movement during stimulation, the hand and thumb were secured firmly, but comfortably, within a modified wrist splint. Further immobilization of the thumb was carried out by manually holding the thumb in place during stimulation to eliminate movement artifact and to minimize dipole changes between the recording and reference electrodes. Supramaximal stimulation, 15 - 20% greater than maximal stimulation, was used in the pre-exercise stimulus train, but, was not adjusted thereafter for the post-exercise train so that changes in nerve threshold could be measured, using the maximum thenar negative peak amplitude (npAmp). All waveforms were collected, analyzed and stored using a standard EMG machine (Advantage Medical,

London, Ontario, Canada). Negative peak amplitude (mV), negative peak area (mVms) and negative peak duration (ms) were measured for all individual waveforms collected.

Negative peak amplitude was used specifically to measure the degree of FDB or potentiation¹³⁻¹⁷. Limb temperature was maintained at $\geq 32^{\circ}$ C with the aid of a portable heat lamp, when necessary.

4.1.3 Symptom and Functional Severity

Although the Levine Symptom Severity and Functional Status scales were designed to assess the outcomes of treatment for carpal tunnel syndrome, all CTS subjects were asked to fill out each scale¹⁸ for the sole purpose of indicating whether they were experiencing hand weakness and/or difficulties with common everyday tasks that required hand strength, at the time of testing.

4.1.4 Calculations and Statistics

Calculations. To calculate the overall percent difference in amplitude for each train, the npAmp from the 20th waveform was compared relative to the 1st waveform ($\text{npAmp}_{20\text{th}} / \text{npAmp}_{1\text{st}} \times 100$). During the routine nerve conduction studies, conduction block was considered present across the wrist if there was a greater than 20% decrease in negative peak area (npArea) between the responses obtained from palm and wrist stimulations $[(\text{npArea}_{\text{palm}} - \text{npArea}_{\text{wrist}}) / \text{npArea}_{\text{palm}} \times 100]$; temporal dispersion was considered if there was a 15% increase in npDur between these similar responses $[(\text{npDur}_{\text{palm}} - \text{npDur}_{\text{wrist}}) / \text{npDur}_{\text{palm}} \times 100]$ ¹⁹.

Statistics. Range of values, their means and standard deviations are presented throughout. Significant effects for pre- and post exercise results within groups (controls, mild CTS and severe CTS subjects) and between groups (controls versus mild CTS subjects)

using thenar negative peak amplitude results (1st, 10th and 20th responses) were determined with a two-way analysis of variance (ANOVA). When comparing pre- and post exercise results between the mild CTS and moderate to severe CTS groups, significant effects were again determined with a two-way ANOVA (percent values were used for these comparisons as a result of significant differences between these two group's npAmp values, $P < 0.05$). Significant differences in the thenar CMAP's negative peak duration (npDur) between controls and mild CTS subjects following routine median nerve stimulation at the wrist were determined with the Student's *t*-test statistic; additional *t*-tests were calculated between these two groups for the 1st thenar response (npDur) from both the pre- and post-exercise stimulus trains. Tests for normality were positive for both npAmp and percent values for all three subject groups, therefore parametric statistics were used for all comparisons.

4.2 RESULTS

4.2.1 Control Subjects and Nerve Conduction Studies

Routine median sensory nerve conduction studies in fifteen control subjects (15 limbs) revealed normal antidromic 3rd-digit sensory nerve conduction velocities (mean, 55.7 ± 3.8 m/s; range, 49.3 – 62.7 m/s) and normal sensory nerve action potential amplitudes (mean, 55.3 ± 21.9 μ V; range, 16.9 – 96.6 μ V) following wrist stimulation. Similarly, routine motor nerve conduction studies revealed normal distal thenar CMAP npAmps (mean, 13.1 ± 2.4 mV; range, 9.4 – 18.1 mV) and normal distal motor terminal latencies (mean, 3.1 ± 0.4 ms; range, 2.5 – 3.6 ms).

4.2.2 Control Subjects and RNS (30-Hz, 20 stimuli)

Figure 4.1 represents the pre- and post-exercise mean percent values for 15 control subjects (15 limbs) following 30-Hz stimulation of the median nerve at the wrist. Relative to the first thenar CMAP response (100%), there was a mean pre-exercise increase in the 20th response of +7.9% (range, -6.9 to +24.2%). Post-exercise, the mean increase was reduced to +1.5% with a greater range, particularly involving greater decreases in the 20th response (-12.7 to +19.0%).

Overall, 13/15 (87%) control subjects showed an increase in the pre-exercise 20th response. However, post-exercise, 14/15 (93%) subjects showed a decline in the 20th response relative to their pre-exercise value. Potentiation (increase in the 1st thenar response) was observed in 11/15 (73%) subjects following exercise (mean, +3.6%). Despite the changes observed post-exercise, a two-way ANOVA comparing thenar npAmp values (1st, 10th and 20th responses) revealed no main effect between the pre- and post exercise trials ($P = 0.830$).

4.2.3 CTS Subjects (mild) and Nerve Conduction Studies

Group mean Levine scores for the symptom severity and functional status scales in mild CTS subjects, were 2.6 (range, 1.5 to 4.1) and 2.1 (range, 1.1 to 3.4), respectively. All subjects either complained of weakness in the hand or wrist (Symptom Severity Scale) and/or had difficulties with at least one activity listed within the Functional Status Scale.

In twelve mild CTS subjects (3 subjects studied bilaterally totaling 15 limbs) antidromic 3rd-digit sensory nerve conduction velocities were ≤ 48.0 m/s in 11 limbs (mean, 43.8 ± 3.3 m/s; range, 36.5 – 47.6 m/s) and a greater than 0.4 ms difference between the median and ulnar 4th-digit latency response in the remaining 4 limbs. Sensory

nerve action potentials were present in all limbs studied (mean, $30.3 \pm 16.0 \mu\text{V}$; range, 7.9 – 61.8 μV). Motor nerve conduction studies revealed normal distal thenar CMAPs (mean, $12.5 \pm 2.0 \text{ mV}$; range, 9.1 – 16.2 mV) and normal motor terminal latencies (mean, $3.6 \pm 0.2 \text{ ms}$; range, 3.3 – 4.0 ms).

4.2.4 CTS (mild) and RNS (30-Hz, 20 stimuli)

Figure 4.1 represents the pre- and post-exercise mean percent values for mild CTS subjects following each train of stimulation. Relative to the first thenar CMAP waveform (100%), there was a mean pre-exercise increase in the 20th response of only +0.7% (range, -11.5 to +25.6%). Post-exercise, the 20th response now showed a mean decrease of -5.1% (range, -16.2 to +10.7%).

Overall, only 7/15 (47%) limbs studied in mild CTS subjects showed an increase in the pre-exercise 20th response, which was reduced further to 3/15 (20%), post-exercise. Again, and similar to controls, 13/15 (87%) limbs showed an immediate increase in the 1st thenar response following exercise (mean, +4.8%). Despite the changes observed post-exercise, a two-way ANOVA comparing thenar npAmp values (1st, 10th and 20th responses) revealed no main effect between the pre- and post exercise trials ($P = 0.752$).

4.2.5 CTS Subjects (moderate to severe) and Nerve Conduction Studies

Group mean Levine scores for the symptom severity and functional status scales in moderate to severe CTS subjects, were 2.8 (range, 1.5 to 4.2) and 2.2 (range, 1.0 to 4.0), respectively. Similar to the mild CTS subjects, all moderate to severe subjects either complained of weakness in the hand or wrist (Symptom Severity Scale) and/or had difficulties with at least one activity listed within the Functional Status Scale, with the

exception of one case who complained clinically with difficulties holding onto objects, but, indicated “no difficulty” with the tasks listed under the Functional Status Scale.

In fifteen moderate to severe CTS subjects (4 subjects studied bilaterally totaling 19 limbs) antidromic 3rd-digit sensory nerve conduction velocities were ≤ 48.0 m/s in 18 limbs (mean, 28.4 ± 7.5 m/s; range, 10.9 – 41.2 m/s) and absent in one case. Sensory nerve action potentials were correspondingly reduced (mean, 6.7 ± 3.8 μ V; range, 1.3 – 15.0 μ V). Motor nerve conduction studies revealed normal distal thenar CMAPs (mean, 9.4 ± 1.8 mV; range, 6.8 – 13.1 mV), but, prolonged motor terminal latencies (mean, 6.6 ± 1.3 ms; range, 5.0 – 9.6 ms).

4.2.6 CTS (moderate to severe) RNS (30-Hz, 20 stimuli)

Figure 4.1 represents the pre- and post-exercise mean percent values for moderate to severe CTS subjects following each train of stimulation. Relative to the first thenar CMAP waveform (100%), there was a mean pre-exercise decrease in the 20th response of -7.3% (range, -20.8 to +6.0%). Post-exercise, the 20th response showed a further mean decrease of -10.8% (range, -19.5 to +2.2%).

Overall, only 4/19 (24%) limbs studied in moderate to severe CTS subjects showed an increase in the pre-exercise 20th response, which was reduced further to only 1/19 (5%), post-exercise. As with controls and the mild CTS subjects, the majority of limbs 12/19 (63%) showed evidence of potentiation in the 1st thenar response following exercise (mean, +1.9%). Despite the changes observed post-exercise, a two-way ANOVA comparing thenar npAmp values (1st, 10th and 20th responses) revealed no main effect between the pre- and post exercise trials ($P = 1.000$).

4.2.7 Controls and Mild CTS Subjects

A two-way ANOVA comparing pre-exercise thenar npAmp values (1st, 10th and 20th responses) between controls and mild CTS subjects, revealed a significant main effect ($P = 0.028$); a significant main effect was also observed post-exercise between these two groups ($P = 0.042$) (Fig. 4.2). Specifically, even prior to exercise, there was a difference between controls and mild CTS subjects over the course of 20 stimuli, suggesting FDB in the CTS group.

4.2.8 CTS Subjects (Mild and Moderate to Severe)

Using percent values (1st, 10th and 20th responses relative to the 1st response), a two-way ANOVA between mild and severe CTS subjects revealed a significant main effect when comparing each group, pre- and post-exercise ($P < 0.01$).

4.2.9 CTS Subjects (mild) and Negative Peak Duration

Additional comparisons were made to assess whether thenar CMAP npDur was associated with and could account for the increased probability of FDB occurring in mild CTS subjects. In other words, was it possible for phase cancellation, due to increases in npDur, to contribute to the FDB observed in this study, pre- and post-exercise. Multiple comparisons in npDur between controls and mild CTS subjects generated from routine nerve conduction studies, the 1st CMAP recorded during the pre-exercise train of stimuli and the 1st CMAP recorded during the post-exercise train of stimuli, were all non-significant ($P > 0.05$). Furthermore, the mean npDur values for the mild CTS subjects were actually less than those obtained from control subjects for all three measures above (5.4 vs. 5.9 ms; 5.8 vs. 6.2; 6.1 vs. 6.5 ms, respectively) making it even less likely that npDur had an effect on the overall reduction in the thenar CMAP in mild CTS subjects.

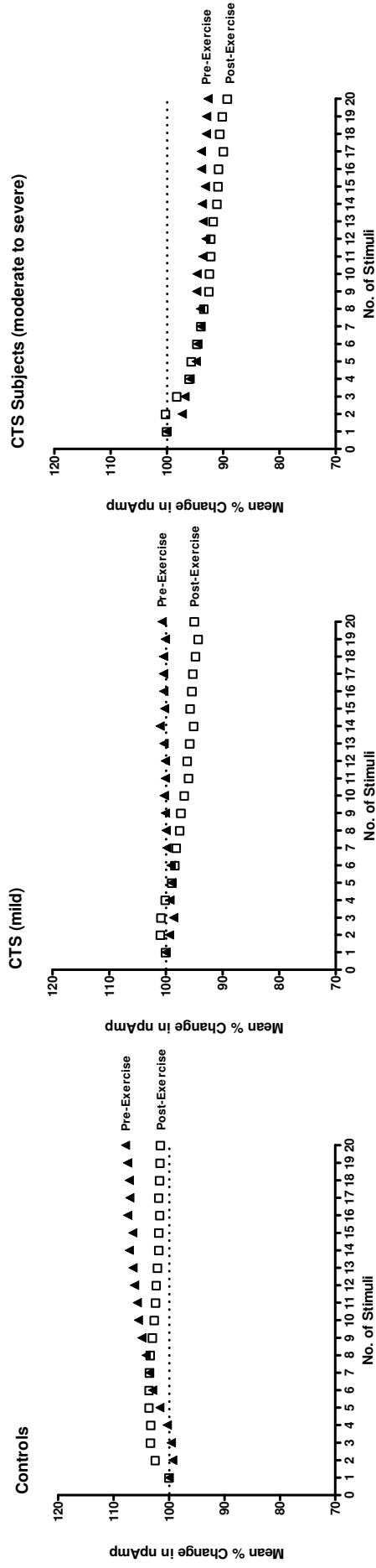


Figure 4.1. The pre- and post-exercise mean percent change in npAmp for the thenar compound muscle action potentials during high-frequency median nerve stimulation (30-Hz, 20 stimuli) at the wrist in 15 control subjects/15 limbs studied (left), 12 mild CTS subjects/15 limbs studied (centre), and 15 moderate to severe CTS subjects as defined by their median nerve distal MTL/19 limbs studies (right). All responses were compared to the first response (100%). Note the significant difference (two-way ANOVA, $P < 0.05$) in both curves for the mild CTS group compared to controls, particularly the pre-exercise curve, despite both groups having similar motor nerve conduction study results. This suggests an element of FDB, which is demonstrated at a greater degree in the moderate to severe CTS subjects. Activity-related potentiation is illustrated by the increase in the initial post-exercise mean npAmp values in all study groups (CTS = carpal tunnel syndrome, Hz = hertz, npAmp = negative peak amplitude, FDB = frequency dependent block).

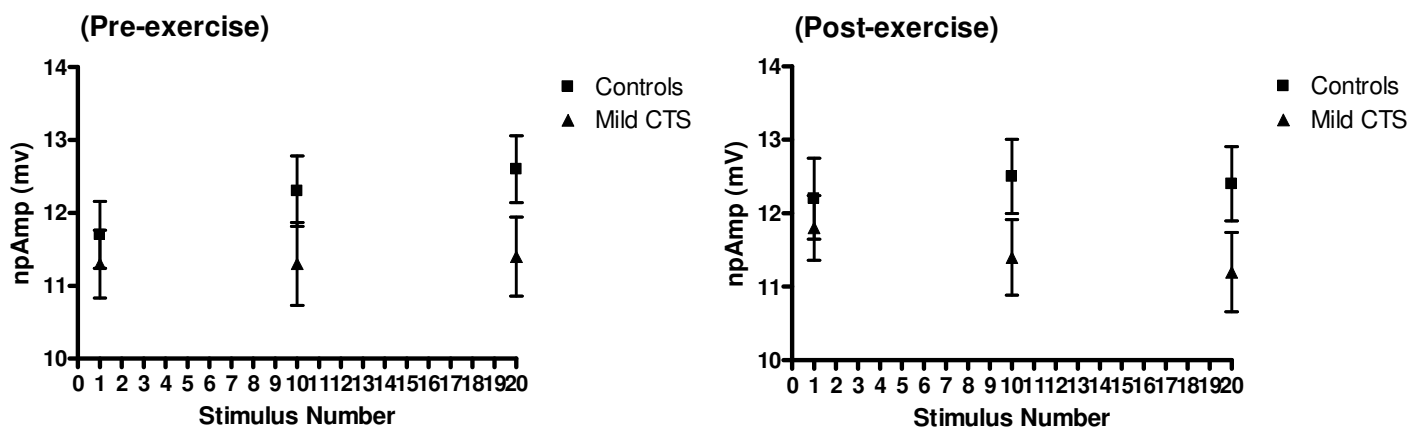


Figure 4.2. Pre- and post-exercise graphs comparing mean thenar npAmp values (1st, 10th and 20th responses) between controls and mild CTS patients following 30-Hz stimulation at the wrist. A two-way ANOVA was significant between groups for both the pre- and post-exercise conditions ($P < 0.05$) suggesting evidence of FDB in the mild CTS patients even prior to exercise (npAmp = negative peak amplitude, CTS = carpal tunnel syndrome, Hz = hertz, ANOVA = analysis of variance, FDB = frequency-dependent conduction block).

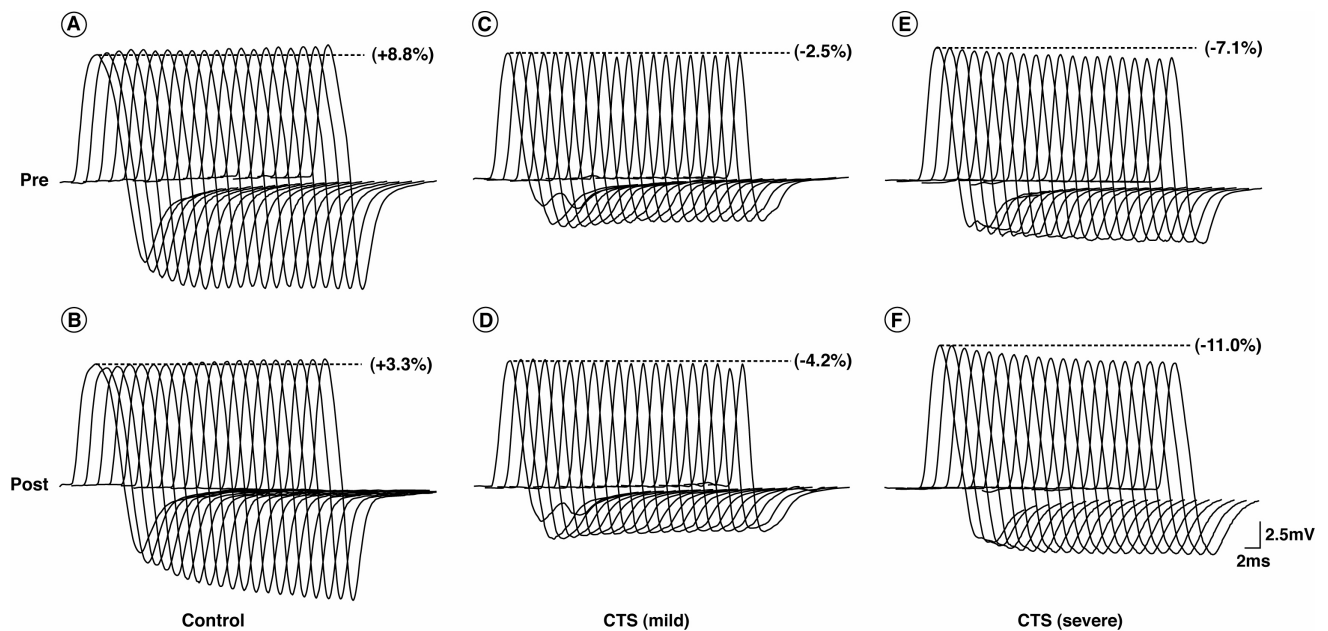


Figure 4.3. Pre- and post-exercise examples of thenar motor recordings following stimulation (30-Hz, 20 stimuli) of the median nerve at the wrist from a control subject (**A, B**), a mild CTS subject (**C, D**) and a moderate to severe CTS subject (**E, F**). In the control example, note the typical pre-exercise increase in the 20th response relative to the 1st response. However, in the two CTS examples (**C, E**), the 20th response was smaller in each case, with the severe CTS case showing the greatest percent reduction (FDB) consistent with previous studies^{1, 2}. In all post-exercise trains, the 20th response was reduced relative to its pre-exercise percentage (in brackets) suggesting evidence of axonal hyperpolarization as a result of electrogenic Na⁺ /K⁺ pump activity. Lastly, in all post-exercise studies above, the 1st response increased slightly relative to its pre-exercise value due to activity related potentiation. Dashed lines indicate the peak of 1st response (100%) (mV = millivolts, ms = milliseconds, Hz = hertz, CTS = carpal tunnel syndrome, FDB = frequency-dependent conduction block, Na⁺ = sodium, K⁺ = potassium).

4.3 DISCUSSION

This study examined the effect of high frequency median nerve stimulation, pre- and post-exercise, in patients with mild and severe CTS. The most important finding was that FDB was observed, even prior to exercise, in mild CTS patients complaining of hand weakness, despite having normal conventional median motor nerve conduction study results. This suggests that although median distal motor terminal latencies and thenar CMAPs were within normal limits, there were a proportion of myelinated motor axons in which the safety factor was compromised presumably on the basis of some level of demyelination, the primary pathophysiology associated with FDB⁴⁻⁸. The results from this study also showed that there was an exacerbation to the degree of FDB following exercise in the mild and severe CTS groups and that exercise even contributed to reductions in the post-exercise potentiation observed in most control subjects.

Conventional NCS techniques rarely require stimulation of motor nerves at rates above 1-Hz and in most cases single shock stimulation of well under 0.5-Hz is used in an attempt to achieve supramaximal stimulation with minimal discomfort to the patient. However, the downside is that these low rates of stimulation fail to reflect or simulate the physiological firing rates of myelinated motor axons associated with everyday activity or during moderate to maximal contractions^{3, 20}. We chose to examine patients with typical CTS symptoms, including hand weakness, but with normal median motor nerve conduction studies to determine whether FDB could be demonstrated in the median motor fibers using a mean physiological rate of stimulation (30-Hz, 20 stimuli) or following 60 s of MVC of the abductor pollicis brevis muscle. In this mild CTS group, with abnormal sensory nerve conduction studies only, there was a significant drop (FDB) in the pre-exercise thenar

CMAP over 20 stimuli when compared to controls (Fig. 4.2). In fact, more than half the limbs studied in mild CTS subjects (53%, 8 of 15 limbs) showed a decrease in the pre-exercise 20th thenar response relative to the 1st response, whereas in controls, a decrease in the 20th response was observed in only 13% of the limbs studied (2 of 15 limbs).

HFNS alone causes axonal hyperpolarization (frequency-dependent hypoexcitability) in healthy axons; however, the wide safety margin for conduction normally prevents the occurrence of FDB. When this margin of safety is critically impaired, for example, from the effects of demyelination, conduction block can occur as a result of the driving current failing to meet increased nodal thresholds due to increases in nodal capacitance^{4, 21}. Experimentally, FDB has been demonstrated in animals⁴⁻⁸ and in humans with specific demyelinating conditions^{9, 10}; therefore, the observation of FDB in mild CTS subjects suggests evidence of demyelination in at least some percentage of the myelinated median motor axons. Other causes for decreases in the thenar CMAP such as failure of transmission at the neuromuscular junction or phase cancellation due to increases in npDur are less likely based on previous results where lower rates of stimulation (routinely used to show decrement in diseases of the neuromuscular junction), in more severe CTS subjects, were normal¹ and based on the results of the current study in which there were no significant differences in npDur between controls and the mild CTS group, respectively.

Increases in motor nerve threshold also occur during contraction (activity-dependent hypoexcitability or hyperpolarization) in both healthy and patient populations. MVCs of 60 s have been shown to increase nerve threshold by 24% in healthy myelinated thenar motor axons, which wanes over 15 mins following contraction²². Furthermore, voluntary contraction has produced conduction block across experimental damage to

single internodes in peripheral nerves of healthy human subjects²³ and following exercise in human demyelinating disease^{9, 10}. Although post-exercise results in all 3 subject groups demonstrated a reduced trend in the overall curve relative to their respective pre-exercise results (Fig. 4.1), these differences were not significant. Understandably, it would be unexpected for healthy controls to show a significant trend between the pre- and post exercise results due to the nerve's safety factor²⁴, but it's plausible a slight downward trend over 20 stimuli could occur when combining two protocols (exercise and HFNS) designed to cause a greater increase in axonal hypoexcitability.

Surprisingly, the moderate to severe CTS subject group, with a presumed greater degree of demyelination based on their increased distal motor latencies, showed less of a post-exercise downward trend compared to controls and mild CTS subjects (Fig. 4.1). Reasons for this are unclear and although it has been shown that there is a period of increased excitability in human cutaneous afferents following prolonged repetitive activity²⁵, possibly due to extracellular accumulation of K^+ ²⁶ within the restricted diffusion space under the myelin²⁷, this excitability period occurs well after the train of stimuli used in this study. It is possible however, that there is a distinct separation between pathological and healthy motor axons within a nerve in focal entrapment or compressive neuropathies. This has been observed in patients with ulnar neuropathy localized to the elbow¹² and may possibly explain why further increases in FDB were not observed in the moderate to severe CTS group following exercise. That being said, higher stimulation rates and/or longer stimulus trains following exercise may have generated further decreases in npAmp in both CTS groups, but the potential discomfort in the conscious subject precludes the use of such protocols. Regardless, the pre-exercise evidence of marked FDB, in this

more severe group of CTS subjects, was consistent with previous studies^{1,2} and was significantly greater than what was observed in the mild CTS group. This of course would be expected considering the greater prolonged distal motor latencies observed in the severe CTS group, presumably on the basis of more severe demyelination.

As in previous studies^{1,2,12}, it was necessary to establish the response to 30-Hz stimulation in controls, pre- and post-exercise as this was the necessary template from which to compare results obtained from our patient population. The pre-exercise results were remarkably consistent between all four studies and although the post-exercise results in controls were slightly reduced relative to pre-exercise values, there was still an increase between the 1st and 20th thenar CMAPs. Furthermore, as expected, there was an initial increase in the control group's post-exercise thenar CMAPs as a result of activity related potentiation^{13-15,17}. This increase was also present in the two CTS subject groups, but less obvious in moderate to severe CTS cases (Figs. 4.1 and 4.3).

The presumed mechanism responsible for the occurrence of FDB in this study, based on the pre-exercise, short duration trains of 20 stimuli at 30-Hz, lasting less than 1 s, is the activation of slow K⁺ conductance²⁸⁻³². This produces axonal hyperpolarization and is associated with a positive afterpotential, P₁ wave³³. Longer impulse trains activate the electrogenic Na⁺ /K⁺ pump causing a more profound and longer lasting depression in axonal excitability^{4, 26, 29, 34-40} and is associated with a positive afterpotential, P₂ wave³³. This study however, failed to show any significant increases in FDB following 60 s of MVC, despite both patient groups demonstrating further reductions in the post-exercise 20th thenar response. It is possible that the study was underpowered to show any significant changes within each CTS group between pre- and post-exercise trials or that the degree of

contraction was affected by deafferentation or submaximal efforts, however, the observation of immediate post-exercise potentiation makes the latter less likely.

In conclusion, the results of this study have demonstrated that FDB occurs in mild CTS patients, when compared to controls with similar routine motor nerve conduction study results. This suggests that the median motor fibers may be partially responsible, along with median sensory deafferentation, for the hand weakness or the difficulties with normal everyday tasks often described by patients with mild CTS based on electrophysiological findings⁴¹. This also suggests that although the median distal motor latencies were well within normal limits, there were a proportion of motor fibers where the safety factor for impulse transmission was reduced, presumably as a result of demyelination, thus resulting in conduction block when the system was stressed with a physiological rate of 30-Hz stimulation. These results provide further evidence that routine NCSs, which typically examine large myelinated peripheral motor nerves using non-physiological rates of stimulation (1-Hz or less), fail at times to properly assess slower conducting fibers with latencies and conduction velocities that are “hidden” within the recorded CMAP.

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CHAPTER 5

FREQUENCY-DEPENDENT CONDUCTION BLOCK IN ULNAR NEUROPATHY LOCALIZED TO THE ELBOW

5.0 INTRODUCTION

Frequency or activity dependent conduction block (FDB or ADB) occurs when trains of high-frequency nerve impulses are blocked across segments of demyelination. This phenomenon has been demonstrated in animals¹⁻⁵, human demyelinating diseases^{6, 7} and more recently in focal neuropathy⁸. During these conditions of demyelination, the internal longitudinal current fails to meet increased nodal thresholds as a consequence of increased membrane capacitance resulting in saltatory conduction failure and conduction block. This implies that the margin of safety for nerve transmission has been reduced to near unity⁹, which in normal healthy nerve is sufficient to prevent the occurrence of FDB or ADB with physiological rates of activation or stimulation.

The results from a recent study that examined FDB in chronic carpal tunnel syndrome, indicated that the extent of FDB was related to the severity of demyelination (prolongation of motor terminal latency)⁸. The question remains however, whether all forms of entrapment or compressive neuropathies such as ulnar neuropathy at the elbow, radial neuropathy at the spiral groove or peroneal neuropathy at the fibular head, carry similar FDB or electrophysiological characteristics, particularly when comparing chronic versus more acute presentations where it has been shown that fascicles and even nerve fibers within fascicles sustain varying degrees of damage¹¹⁻¹³.

A version of this chapter has been published.

Watson BV, Doherty TJ. Frequency-dependent conduction block in ulnar neuropathy localized to the elbow. *Clin Neurophysiol* 2010; 121:2111-2116.

The present study was undertaken to determine whether FDB can be demonstrated in patients with ulnar neuropathy localized to the elbow. In contrast to our previous study, which examined patients with chronic symptoms (12 weeks to 33 years) of carpal tunnel syndrome (CTS) and with no evidence of conduction block⁸, the current study examined ulnar neuropathy patients with shorter duration onset (2-16 weeks) coupled with significant conduction block. We hypothesized that FDB would occur across the elbow in these more severe examples of demyelination with conduction block, and that the degree of FDB would be greater than that observed for carpal tunnel syndrome without conduction block⁸. Results from this study may show that changes in nerve threshold are dissimilar for two distinct forms of focal nerve injury.

5.1 METHODS

5.1.1 Subjects

Fifteen healthy control subjects with normal ulnar nerve conduction (9 men and 6 women; age, 37.4 ± 8.4 years; age range, 25 to 54 years) and 10 patients (8 men, 2 women; age, 46.3 ± 14.5 ; age, range, 27 to 70 years) with clinical and electrophysiological evidence of moderate to severe ulnar neuropathy at the level of the elbow (as defined below) were asked to participate in this study. Mean duration of symptoms for the patient group was 7 weeks (range, 2 to 16 weeks) with no past history of similar symptoms. Five patients developed their symptoms suddenly, while the remaining five patients reported a more gradual onset. There was no previous trauma or precipitating event in any of the cases. Subjects with clinical or electrophysiological evidence of a generalized peripheral neuropathy were excluded. All subjects gave informed consent to the experimental

protocol, which was approved by the Research Ethics Board of the University of Western Ontario.

5.1.2 Electrophysiological Data Collection

Controls. Consistent with our previous study⁸, it was necessary to establish the response to 30-Hz repetitive nerve stimulation in controls, as this was the background data to which ulnar nerve stimulation in our patient group was compared. Control studies using high-frequency nerve stimulation (HFNS) were performed by applying 20 stimuli at a rate of 30-Hz (total time of stimulation, 0.667 s) to the ulnar nerve at the wrist (W) and above the elbow (AE) while recording over the motor point of the hypothenar eminence (G1) with the reference electrode (G2) placed over the fifth metacarpophalangeal joint. Although stimulation below the lesion could have been achieved by either stimulating directly below the elbow (4 to 5 cm distal to the medial epicondyle) or at the wrist, stimulation at the wrist was chosen to avoid the potential movement artifact caused by contraction of the flexor carpi ulnaris and flexor digitorum profundus muscles during the 30-Hz protocol.

Ulnar Neuropathy Patients. Routine ulnar motor nerve conduction studies were performed separately to ensure that all inclusion criteria were met (conduction velocity across the elbow ≤ 40 m/s; forearm conduction velocity ≥ 50 m/s; distal hypothenar compound muscle action potential (CMAP) obtained from wrist stimulation ≥ 6.6 mV; evidence of conduction block across the elbow segment $>40\%$). These criteria were chosen based on our laboratory control values and to represent moderate to severe conduction block and slowing across the elbow with no or very little evidence of motor axonal involvement.

HFNS (20 stimuli) of the ulnar nerve at the wrist and above the elbow, at a frequency of 30-Hz, was then performed in all 10 cases while recording over the hypothenar eminence. Thirty-hertz stimulation was applied to the wrist to determine whether FDB occurred distal to the compression site. Both studies were completed within minutes of one another.

Follow-up Studies. Three of the ten patient subjects studied were seen in follow-up between 4 and 8 weeks from their initial study and the above protocol repeated to assess the status of the recovering blocked fibers.

In all studies, surface disposable recording electrodes (Ag/AgCl Mactrode Electrodes; GE Medical Systems, Milwaukee, Wisconsin) were used and secured with tape to prevent displacement, particularly during higher frequency levels of stimulation. In an attempt to minimize hand movement during the procedure, the hand was secured firmly, but comfortably within a wrist splint and the fifth digit was held in place by a laboratory staff member. The elbow was flexed comfortably between 60° and 90°. The skin was prepared using 70% isopropyl alcohol and when necessary in subjects with rough, oily or greasy skin, One-Step Skin Prep (3M, London, Ontario, Canada) was used to mildly abrade the skin to reduce impedance. All waveforms were collected, analyzed and stored using a standard EMG system (Advantage Medical, London, Ontario, Canada). Negative peak amplitude (mV), negative peak area (mVms), and negative peak duration (ms) were measured for all individual waveforms collected. Supramaximal stimulation (15 - 20% greater than maximal stimulation) was used in all cases. Limb temperature was maintained at $\geq 32^{\circ}$ C with the aid of a portable heat lamp, when necessary.

5.1.3 Calculations and Statistics

Calculations. Negative peak amplitude (npAmp) was used to assess the degree of FDB⁸. To calculate the overall percent difference in amplitude for each train, the npAmp from the 20th waveform was compared relative to the 1st waveform ($\text{npAmp}_{20\text{th}} / \text{npAmp}_{1\text{st}} \times 100$). During the routine nerve conduction studies, conduction block was considered present across the elbow if there was a greater than 40% decrease in npArea between the responses obtained from below elbow (BE) and above elbow (AE) stimulations $[(\text{npArea}_{\text{BE}} - \text{npArea}_{\text{AE}}) / \text{npArea}_{\text{BE}} \times 100]$; temporal dispersion was considered to be present if there was a 15% increase in negative peak duration (npDur) between these similar responses $[(\text{npDur}_{\text{BE}} - \text{npDur}_{\text{AE}}) / \text{npDur}_{\text{BE}} \times 100]$ ¹⁰.

Statistics. Range of values, their means and standard deviations are presented throughout. Significant effects for wrist and above elbow stimulation results in controls using hypothenar negative peak amplitude results (1st, 10th and 20th responses) were determined with a two-way analysis of variance (ANOVA).

5.2 RESULTS

5.2.1 Control Subjects and RNS (30-Hz, 20 stimuli)

Distal hypothenar CMAPs were within laboratory normal limits of ≥ 6.6 mV (mean, 10.9 ± 1.5 mV; range, 7.8 to 13.3 mV). In response to 30-Hz RNS at the wrist, 11 of 15 subjects showed an overall increase in the hypothenar npAmp (mean increase, +12.3%; range, +1.1 to +23.3%), whereas the remaining 4 subjects showed only a minimal decrease in npAmp ($\leq -7.8\%$). Similarly, during HFNS stimulation above the elbow, 10 of 15 subjects showed an overall increase in the npAmp (mean increase, +6.5%; range, +0.8 to +16.0%),

while the remaining 5 subjects showed only a minimal decrease ($\leq -8.8\%$). Mean control values for the wrist and above elbow sites of stimulation, over 20 stimuli at 30-Hz are shown in Figure 5.1.

5.2.2 Ulnar Neuropathy Subjects and Nerve Conduction Studies

Table 5.1 outlines the raw data from the ulnar motor nerve conduction studies in all 10 patients. Routine motor nerve conduction studies revealed normal hypothenar distal compound muscle action potentials (mean, 10.0 ± 1.4 mV; range, 7.2 to 11.3 mV) with normal forearm motor conduction velocities (mean, 55.7 m/s; range, 50.6 to 63.8 m/s). Across the elbow, the mean percent conduction block using npArea was 72.0% (range, 48.5 to 91.3%) with a mean conduction velocity of 29.2 m/s (range, 20.5 to 38.1 m/s). The mean hypothenar CMAP negative peak duration was 7.2 ms from stimulation below the elbow (SD, 1.1 ms; range, 5.9 to 10.0 ms) and 6.5 ms from stimulation above the elbow (SD, 1.2 ms; range, 5.0 to 9.2 ms). Specifically, 9 of 10 cases showed shorter npDur latencies above the elbow than below and in the remaining case there was only a .2 ms (5.9 to 6.1 ms) increase above the elbow. Thus, there was no evidence of temporal dispersion influencing our results.

5.2.3 Ulnar Neuropathy Subjects and RNS (30-Hz, 20 stimuli)

Figure 5.2 illustrates the results from all 10 subjects during HFNS above the elbow. None of the subjects showed any convincing evidence of FDB and in all cases studied, the change in the 20th hypothenar response relative to the 1st did not fall outside the range of normal values (-8.8 to +16.0%). Three of ten cases did show a decrease in the 20th CMAP response relative to the 1st CMAP, however, these changes were minimal relative to the very small initial CMAP. Specifically, there was only a 0.1, 0.1 and 0.4 mV change in

amplitude from the 1st to the 20th CMAP. In response to 30-Hz RNS at the wrist and similar to controls, 8 of 10 ulnar neuropathy subjects showed an overall increase in the npAmp (mean increase, +9.6%; range, +2.7 to +22.9%), while the remaining 2 subjects showed only a minimal decrease in npAmp consistent with control values (< -7.8%). Figure 5.3 represents a typical study seen from a patient with ulnar neuropathy.

5.2.4 Ulnar Neuropathy Subjects and Follow-Up

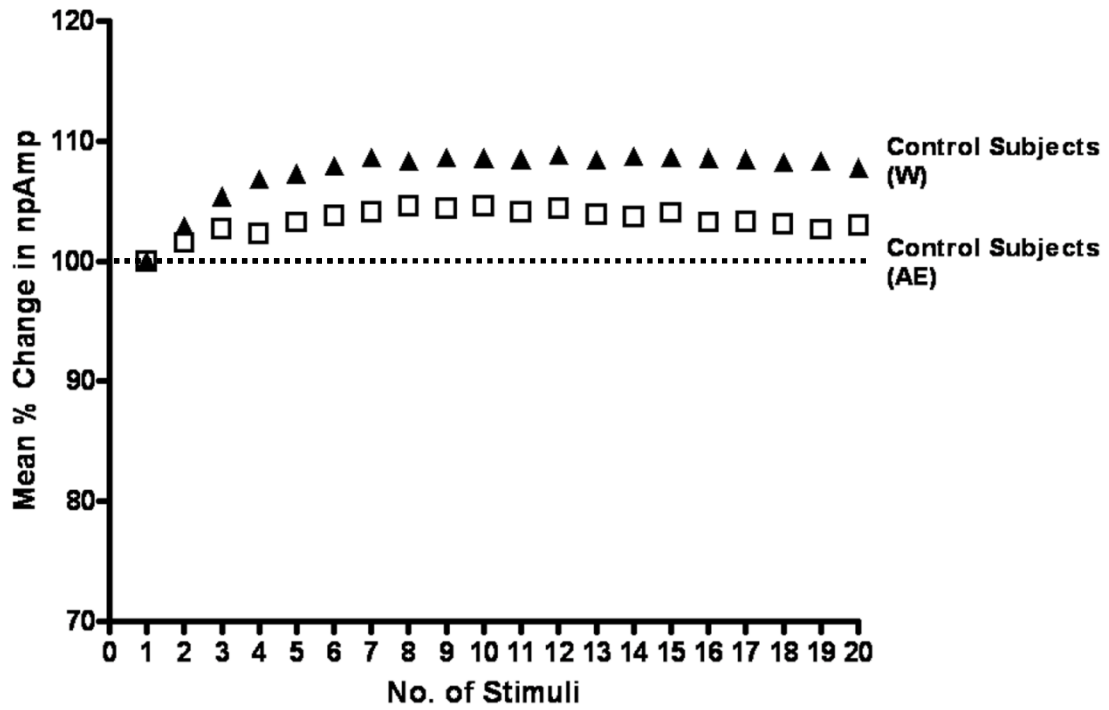
Marked electrophysiological recovery in conduction block was observed in 2 of 3 subjects seen in follow-up, however, conduction block and slow conduction across the elbow was still evident in all cases, ranging from 23% to 61% and from 31.4 m/s to 43.7 m/s, respectively. FDB was observed across the elbow in 2 of 3 subjects tested (23% and 15% decrease in 20th CMAP response) within 8 weeks from their initial study; in the remaining subject, there was no evidence of FDB seen within this follow-up time frame, however, only 11% improvement in conduction block was observed and there was no improvement in the overall conduction velocity across the elbow. Figure 5.4 illustrates FDB in the recovering fibers in one of the follow-up subjects. The FDB observed followed a similar pattern to that which was demonstrated in CTS subjects (Fig. 5.5).

Table 5.1. Ulnar motor nerve conduction study results in ulnar neuropathy patients

Subject	CMAP (Hypothenar)						Conduction Velocity				
	npAmp			npArea			npDuration			BE-W (m/s)	AE-BE (m/s)
	W (mV)	BE (mV)	AE (mV)	W (mVms)	BE (mVms)	AE (mVms)	W (ms)	BE (ms)	AE (ms)		
1	11.2	11.0	4.3	48.5	49.0	17.9	7.3	7.4	7.1	59.5	26.0
2	9.9	9.5	2.5	34.4	34.1	8.2	6.1	6.7	6.1	54.3	26.7
3	11.2	10.6	4.5	42.9	42.7	17.0	6.5	6.5	6.1	55.2	38.1
4*	11.3	9.3	3.6	38.4	35.2	12.3	6.7	6.9	6.7	58.5	35.6
5*	11.0	9.2	1.7	35.3	31.7	5.4	6.7	7.1	5.4	50.6	25.8
6*	9.2	8.3	2.0	25.8	25.5	5.5	5.9	6.7	5.0	51.3	20.5
7	9.8	9.9	1.9	33.5	33.5	5.7	6.7	6.7	5.6	63.8	24.0
8	7.2	6.6	0.5	24.0	23.3	2.0	7.7	8.1	7.5	52.5	29.3
9	8.7	8.4	2.8	46.9	46.3	13.0	10.1	10.0	9.2	54.3	31.0
10	10.9	9.9	4.5	30.5	29.9	15.4	6.0	5.9	6.1	57.4	35.2
Mean	10.0	9.3	2.8	36.0	35.1	10.2	7.0	7.2	6.5	55.7	29.2
SD	1.4	1.3	1.4	8.3	8.5	5.6	1.2	1.1	1.2	4.1	5.7

* **Martin-Gruber Anastomosis**

CMAP = compound muscle action potential, npAmp = negative peak amplitude, npArea = negative peak area, npDuration = negative peak duration, W = wrist, BE = below elbow, AE = above elbow, BE-W = below elbow to wrist segment, AE-BE = above elbow to below elbow segment, mV = millivolt, mVms = millivolt millisecond, ms = millisecond, m/s = meters per second



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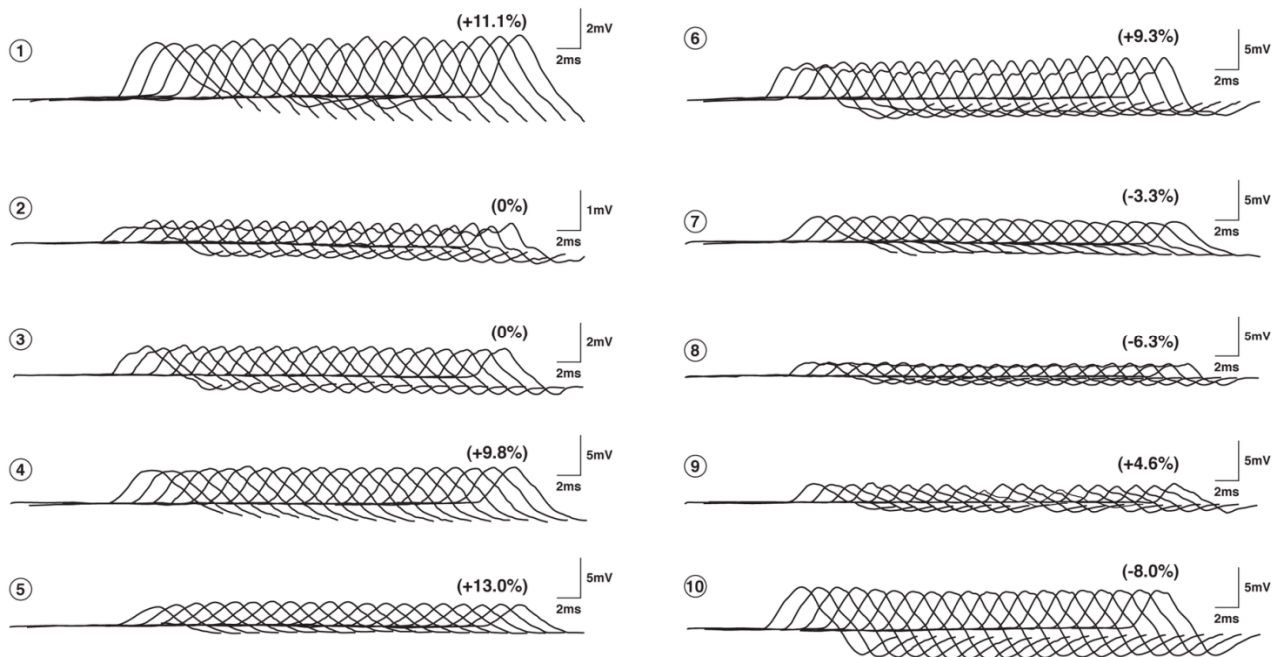


Figure 5.2. HFNS (30-Hz, 20 stimuli) of the ulnar nerve (hypothenar recording), above the elbow, in all 10 ulnar neuropathy subjects. Note there was no obvious evidence of FDB in these remaining “unblocked” fibers, with the exception of subjects #1 and #9 in that a few of the waveforms “dropped” in amplitude during stimulation. A repeat study in subject #9 again showed a drop in waveforms at sites nearly identical to the initial study. This suggests that it was less likely due to technical factors and that the margin of safety in some of the remaining fibers was reduced. Regardless, not one study demonstrated what was observed in patients with CTS (see Fig. 4.5.) (mV = millivolts, ms = milliseconds, HFNS = high-frequency nerve stimulation, Hz = hertz, FDB = frequency-dependent conduction block).

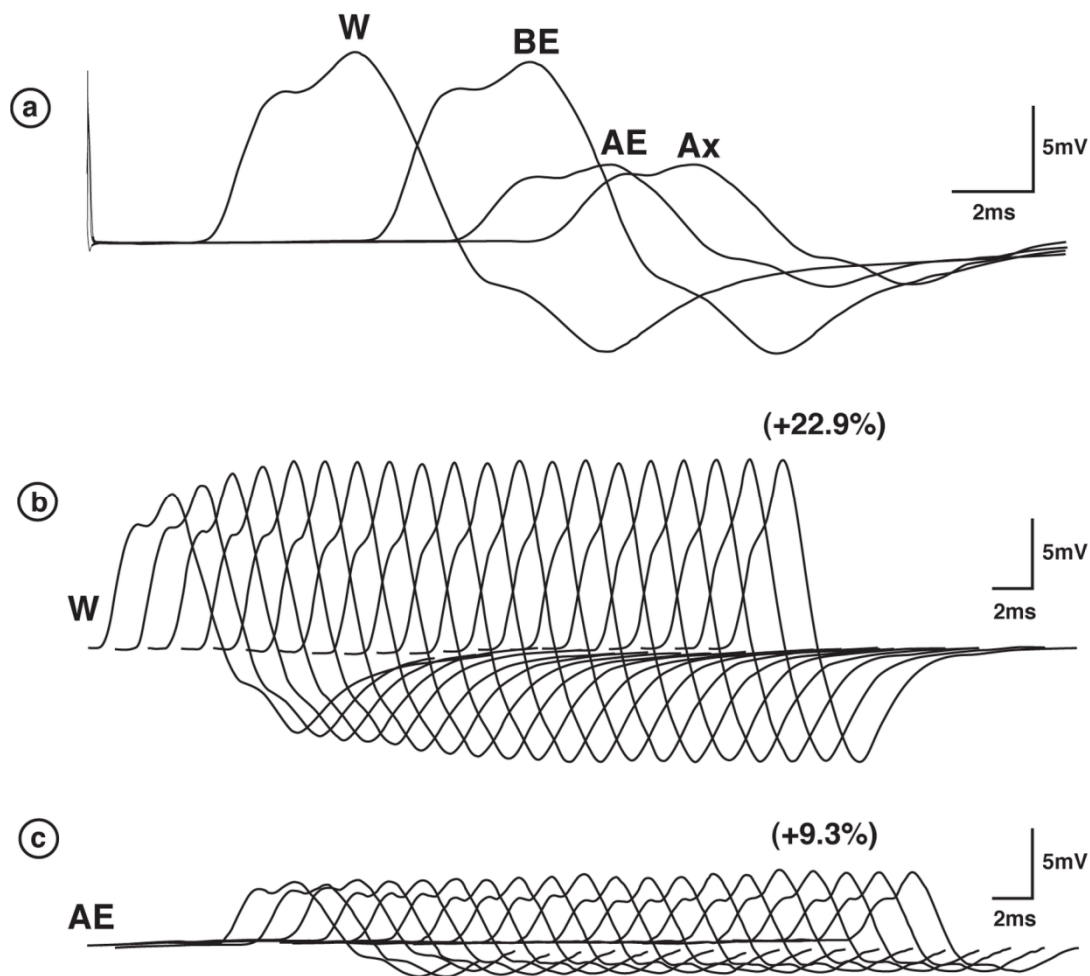


Figure 5.3. An example of a typical study (subject #6 from Fig. 4.2.) observed in all patient subjects examined. Trace “a” represents a routine segmental ulnar motor nerve conduction study demonstrating conduction block across the region of the elbow, between BE and AE sites of stimulation. Traces “b” and “c” represent the results from HFNS (30-Hz, 20 stimuli) at the wrist and above the elbow. Note that stimulation distal to the conduction block (W) elicited a similar pattern to what was observed in control subjects (expected), but, stimulation proximal to the elbow failed to show any evidence of FDB despite significant evidence of demyelination (unexpected) (W = wrist, BE = below elbow, AE = above elbow, Ax = axilla, mV = millivolts, ms = milliseconds, HFNS = high-frequency nerve stimulation, Hz = hertz, FDB = frequency-dependent conduction block).

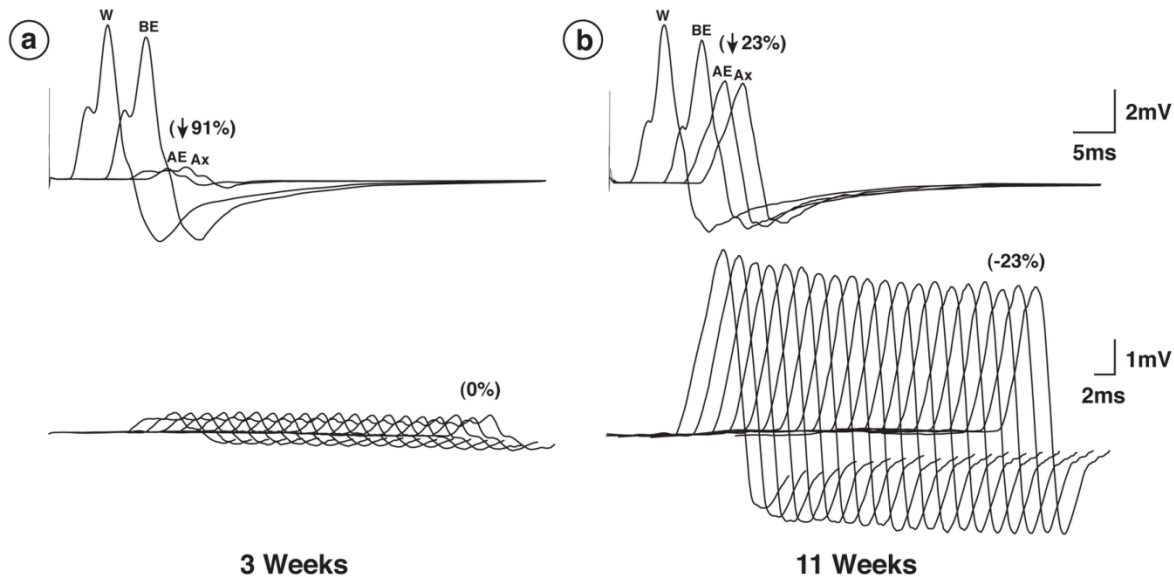
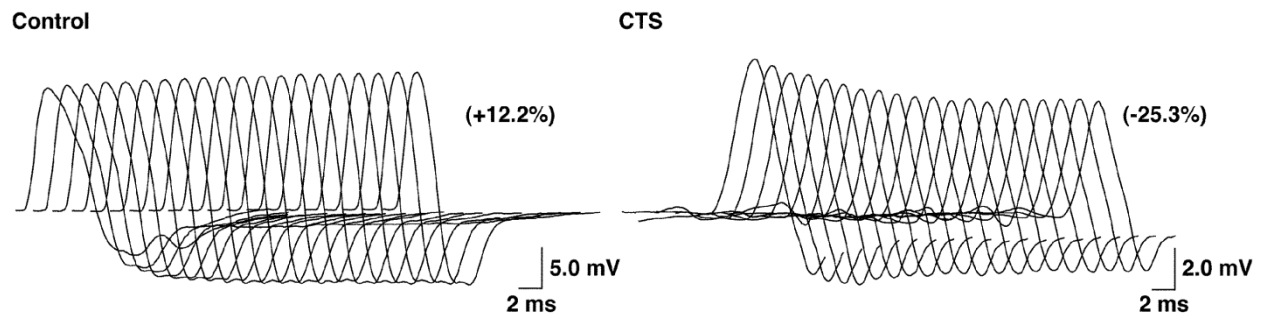


Figure 5.4. Follow-up studies in one patient demonstrating evidence of FDB. Trace “a” represents the initial nerve conduction studies with evidence of 91% conduction block (top trace) and HFNS (bottom trace). Trace “b” (bottom) represents the follow-up results, 11 weeks post-onset (8 weeks from initial study), and evidence of FDB (23%). Note that the conduction block across the elbow had improved by 68% (top trace) and presumably it was a portion of these recovering, but “immature” remyelinating fibers that were responsible for the evidence of FDB (W = wrist, BE = below elbow, AE = above elbow, Ax = axilla, mV = millivolts, ms = milliseconds, HFNS = high-frequency nerve stimulation, FDB = frequency- dependent conduction block).



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5.3 DISCUSSION

This study examined the effects of high-frequency ulnar nerve stimulation in acute/sub-acute ulnar neuropathy with conduction block localized to the elbow. It was hypothesized, as a result of the significant conduction block and slowing demonstrated through conventional nerve conduction testing, that FDB would occur to a greater degree in these subjects, than that demonstrated previously in CTS with slowing and no block⁸. Surprisingly, our results failed to demonstrate any evidence of FDB in the remaining conducting fibers across the elbow at the time of the initial studies. However, early follow-up studies in two of three patients did show evidence of FDB, presumably in the recovering but immature remyelinating motor fibers.

Reasons for the early absence of FDB in this focal demyelinating neuropathy are unclear. However, what can be deduced from these results is that the margin of safety for nerve transmission was intact in the remaining conducting fibers across the elbow during stimulation of these fibers at a physiological frequency of 30-Hz. Thus, it appears in this particular neuropathy that there are motor fibers that are initially blocked and motor fibers that are apparently spared of significant damage to their myelin, thus showing little vulnerability for FDB.

Overall, the combination of blocked fibers and slow conduction velocities across the elbow suggest that there was variable damage to the myelin throughout the ulnar nerve in all subjects, between or possibly within individual fascicles. Indeed, it has been shown that in acute or chronic nerve injuries, adjacent fascicles and even nerve fibers within fascicles do sustain varying degrees of axonal and myelin damage¹¹⁻¹³. In the current study, the remaining conducting fibers were shown to have conduction velocities well below the

normal distribution for large myelinated nerve fibers¹⁴⁻¹⁶ suggesting that there was some degree of myelin injury, although apparently not enough to demonstrate FDB. Previous work has shown that only mild change in internodal parameters is necessary to cause interference with conduction, in the absence of block^{17,18}.

The results of this study have shown that identical protocols of high-frequency RNS have demonstrated significant differences between two of the most common focal neuropathies, ulnar neuropathy localized to the elbow and CTS⁸. However, it is important to take into consideration that there were major differences between both studies. In the CTS study⁸ the history was more chronic (mean symptom duration of 6.3 years) and without evidence of conduction block across the carpal tunnel, whereas in the current study, the ulnar neuropathy was more acute in its presentation (mean symptom duration of 7.0 weeks) with marked conduction block across the elbow. Although it's certainly possible that there was superimposed, sub-clinical injury to the ulnar nerve prior to these "acute" presentations, it was unlikely that it was substantial as they were all previously asymptomatic. In terms of the extent or length of the lesion in both neuropathies, it's possible that there were more internodes affected in CTS due to its chronic nature thus rendering the median nerve more vulnerable to FDB. It's also plausible there was axonal damage within the CTS subject group, which could affect the integrity of the neuromuscular junction, despite our best attempts to exclude these patients. Future studies comparing the more chronic cases of ulnar neuropathy localized to the elbow without evidence of conduction block may yield similar results that were demonstrated previously in CTS⁸.

Although our initial hypothesis was rejected in that FDB did not occur in the remaining ulnar motor fibers across the elbow when first tested, the occurrence

of FDB was very much anticipated during nerve recovery because of the presumed “immature” state or reduced margin of safety that might occur during the early remyelinating process in previously blocked fibers. Indeed, when examining 3 subjects within 8 weeks of recovery, two showed evidence of FDB similar to what was observed previously in CTS subjects⁸. In the remaining case, very little recovery had occurred relative to the initial study, which may explain why FDB was not observed during follow-up testing.

Despite being unable to demonstrate FDB initially within our patient group, we showed with remarkable consistency, that in control subjects, the ulnar nerve reacts very similar to the median nerve when stimulating at 30-Hz, regardless of the site of stimulation⁸. The characteristic increase in amplitude during high-frequency stimulation has also been observed in other control studies that have used similar frequency levels of stimulation^{19, 20}.

In conclusion, high-frequency RNS failed to demonstrate FDB in the remaining motor fibers across the elbow, in relatively acute ulnar neuropathy with conduction block, localized to the elbow. This was contrary to what was observed in the more chronic condition of CTS where FDB was demonstrated and directly related to the degree of conduction slowing in the median motor fibers across the carpal tunnel⁸. Follow-up studies did however demonstrate evidence of FDB during the early remyelinating stage, presumably within the previously blocked motor fibers. Our results suggest that the margin of safety for nerve transmission is intact in the remaining ulnar motor fibers across the elbow, despite the evidence of significant conduction slowing, and that there may be a separate mechanism involved in focal ulnar neuropathy that differs from CTS.

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CHAPTER 6

GENERAL DISCUSSION AND SUMMARY

6.0 GENERAL DISCUSSION

Due in part to the expanding research examining the changes in nerve excitability in peripheral nerve disease¹⁻²⁸, this thesis examined the effects of high-frequency nerve stimulation (HFNS) across sites of focal demyelination within the peripheral motor nervous system. Specifically, it was the objective of this thesis to demonstrate frequency-dependent conduction block (FDB) across common focal entrapment sites causing demyelination using physiological rates of stimulation on the order of 30-Hz²⁹ and to provide further evidence regarding the pathophysiology in carpal tunnel syndrome (CTS) and ulnar neuropathy localized to the elbow (UNE). This objective was fulfilled in the initial studies while examining the results of HFNS in controls and comparing those results to a cohort of patients with clinical and electrophysiological evidence of moderate to severe CTS. These studies were then followed by examining whether FDB could help explain the weakness often described by patients with mild CTS, despite the presence of normal conventional motor nerve conduction studies. The final study examined another focal entrapment/compressive neuropathy (UNE) to determine whether similar findings of FDB could be observed in patients with a more acute presentation of demyelination causing conduction block.

The studies that make up this thesis are the first to demonstrate FDB in the median motor nerve fibers in patients with CTS and confirm that demyelination is part of the pathophysiology of CTS and that FDB may be responsible for these patient's symptoms of

weakness and fatigue. Additionally, it was demonstrated that changes in nerve threshold also occur distal to the presumed site of demyelination, a finding also observed in animal studies^{30, 31} and more recently in human subjects³². The 4th study (Chapter 5) demonstrated that there are indeed differences in the margin of safety for nerve transmission between different focal entrapment neuropathies (CTS and UNE) when tested using identical rates of stimulation and that separate mechanisms may be involved. Finally, these studies have shown remarkable consistency within healthy control subjects when stimulating motor nerves at frequencies of 30-Hz, regardless of the nerve or location of stimulation. This consistent response in controls was the necessary template to which our patient data were compared.

The technique of HFNS, which was used in these studies, is a well established and reliable neurodiagnostic procedure used primarily for the purposes of assessing the integrity of the neuromuscular junction within clinical electrophysiological settings. However, for the purposes of this thesis, HFNS was used to assess peripheral motor nerve integrity across sites of demyelination and to reflect physiological rates of motor unit activation²⁹. Our patient cohort was required to have no evidence of axonal damage in order to reduce or eliminate any influences that a faulty neuromuscular junction or reinnervating terminal axon branches may have on study results as a consequence of this damage.

In comparison to computerized threshold tracking^{12, 13, 17, 33}, that requires maximal voluntary recruitment to assess changes in motor nerve threshold or excitability, HFNS techniques by-pass any potential sub-maximal voluntary efforts by stimulating the nerve directly. Additionally, computer threshold tracking is designed to assess the threshold

properties of the nerve directly beneath the stimulator and tests only the axons chosen for tracking³³, whereas HFNS assesses all the available motor axons over a particular length of nerve (i.e. the median nerve across the carpal tunnel or the ulnar nerve across the elbow in the current studies). Although there is some discomfort associated with HFNS, the stimulation protocol for all studies making up this thesis lasted only 0.667 s and was well tolerated by all subjects. Movement artifact, always a concern with any technique stimulating the nerve at higher frequencies, was easily prevented by securing the limb properly. Thus HFNS should be considered as an alternative technique for assessing nerve threshold across sites of demyelination, particularly along distal sites of the upper and lower limb. Lastly, the results obtained from these studies have shown that HFNS is a reliable and easy method for assessing the peripheral motor nerve's margin of safety for nerve transmission and for demonstrating FDB in diseases causing demyelination.

6.1 LIMITATIONS

Despite the success in demonstrating FDB in CTS subjects, there were a number of limitations that require discussion. With regard to the 1st study (Chapter 2), the male to female ratio and the mean age in the control group were different than the patient group. However, when viewing the similar pattern and consistency of the results in control subjects regardless of gender or age and comparing these findings to the CTS group, age and gender did not influence the results. Further, when statistically examining the relationship in controls between the change in the 20th thenar CMAP response with gender and age, there were no significant correlations that suggested that gender or age influenced the results of this study (Appendix A).

Regarding the compound muscle action potential (CMAP), despite the best attempts to recruit CTS subjects with normal distal CMAPs and with no evidence of axonal damage, it's always possible that some subjects, as a result of their nerve compression, may have undergone secondary axonal degeneration, thus potentially influencing the function of the terminal axons and neuromuscular junction and the results of FDB. That being considered, repetitive nerve stimulation (RNS) at lower frequencies, used to demonstrate decrement in diseases of the neuromuscular junction, was normal in all moderate to severe CTS subjects (Chapter 2, Fig. 2.4).

The decision to use the percent (%) difference between the 1st and 20th CMAP responses requires further comment. Although, not necessarily a limitation of this thesis, it is important to note that this % difference, calculated using the negative peak amplitude (npAmp) value, is greatly influenced by the initial (1st) npAmp size. This means that even a small change in the 20th response relative to a small 1st response will yield higher percent differences than larger 1st CMAP responses. However, two items need to be addressed. Firstly, all subjects examined in these studies had distal CMAP responses well within the normal control range, thereby reducing the potential for greater % differences (1st – 20th) in CTS subjects compared to controls simply as a result of the initial CMAP. Secondly, the actual pattern or morphology of the CMAP over 20 stimuli was a key observation when comparing CTS subjects to controls (Chapter 2, Fig. 2.3).

Lastly, maximum voluntary contraction (MVC) was necessary for the 3rd study (Chapter 4) of this thesis, however, it's possible that sub-maximal efforts were a limiting factor and may explain why there were no significant differences between pre- and post-exercise results. All subjects were required to maximally contract their thenar muscles

against resistance for 60 s and were encouraged by the author throughout the contraction, including maintaining the level of auditory feedback from the contracting muscle. That being said, it's possible that in the CTS subjects, all of whom had abnormal sensory nerve conduction studies, that sensory symptoms may have prevented them from contracting their muscle maximally.

6.2 FUTURE STUDIES

The present studies have contributed to a better understanding of the pathophysiology of focal entrapment neuropathies causing demyelination; however, future work is necessary to correlate the degree of FDB with a quantitative measure of clinical weakness or better yet, a measure of APB or ADM force. A study of this kind may help support or refute the technique of HFNS in demonstrating FDB as it would be expected that force would decrease during the stimulation train, in patients with FDB. It is important to note however, that measuring clinical strength or force in the APB muscle is not without its difficulties due to the influence of adjacent muscles with similar vectors of contraction; the ulnar nerve and contraction of the abductor digiti minimi or first dorsal interosseous muscles would provide a better research condition for this correlation as both muscle groups can be more readily isolated to provide valid measures of force. Additionally, in order to continue using HFNS as a technique to demonstrate FDB, a study correlating its results with computerized threshold tracking³³ might help validate both techniques.

Extrapolating the results from this thesis to other focal entrapments involving other peripheral motor nerves should be done with caution. Firstly, even within this thesis there were differences between median and ulnar nerve subjects; in particular, the groups that

were compared presented different clinically (chronic versus acute, respectively) and showed different levels of demyelination as demonstrated during routine nerve conduction study testing. Secondly, it has been previously shown that there are differences in the extent of axonal hyperpolarization between other potential entrapment nerves¹⁵. Therefore, future work assessing the peroneal nerve across the fibular head or the radial nerve across the spiral groove during focal entrapment may help support the differences observed in this thesis.

Another consideration for future research would be to attempt to demonstrate FDB across sites of focal demyelination at the level of the single motor axon. Using surface stimulation, single motor axons can be easily stimulated and generate reproducible motor unit action potentials recorded using similar techniques described in this thesis. The results of this thesis clearly demonstrate that FDB does not occur in all motor axons as the CMAP was still present after 20 stimuli in all CTS subjects. Applying HFNS to single axons is very feasible and is well tolerated by most subjects due to the very low stimulus intensities required to generate all-or-nothing single motor unit action potentials. This may help shed more light regarding which motor fibers are vulnerable to FDB. Also, because of the relatively benign level of stimulus intensity required, longer stimulus trains could also be used to reflect longer periods of activity, thereby assessing the contribution of Na^+/K^+ pump in the development of FDB. The major technical concerns when stimulating using HFNS are to avoid stimulating adjacent motor axons with similar stimulation thresholds and to ensure that if conduction block is demonstrated that it hasn't occurred as a result of submaximal stimulation or even due to slight movements of the stimulation

electrode. Repeat studies would be necessary to ensure that the FDB observed was occurring in relatively the same location along the train of 20 stimuli.

Lastly, the potential success of carpal tunnel release surgery in repairing the “physiology” of the median nerve would be of interest, particularly in patients whose symptoms fail to resolve, but, where the nerve conduction studies had improved. Pre- and post-surgical evaluations using HFNS may provide the surgeon with additional information regarding the success of the surgical procedure and whether the nerve is still compromised within the carpal tunnel or further distally as shown in Chapter 3 of this thesis and in other previous studies³⁴⁻³⁶.

6.3 SUMMARY

The studies that make up this thesis are the first to demonstrate FDB in patients with CTS and provide evidence that demyelination may contribute significantly to the pathophysiology and to the slow conduction observed in moderate to severe cases of CTS. Further, regarding the results of this thesis, the demonstration of FDB in the median motor nerves may be partially responsible, along with median sensory deafferentation, for the weakness in mild CTS patients despite these patients having normal conventional motor nerve conduction studies. This finding implies that routine diagnostic studies, which characteristically use low, non-physiological rates of stimulation, fail at times to demonstrate the full extent of the patient’s clinical complaints, particularly when the motor system is involved.

Additional evidence from these studies suggests that not all sites of focal compression, causing demyelination (based on nerve conduction study results yielding

very slow conduction velocities) and conduction block, yield the phenomenon of FDB when using identical rates of stimulation. The reason for this is unclear, but it does suggest that the safety factor for nerve transmission is intact in the remaining fibers that were “stressed” with HFNS.

Lastly, although HFNS was successful in demonstrating FDB across regions of focal entrapment/compression causing demyelination, and when used with short stimulus trains it is easily tolerated by patients, its routine use in a patient setting remains unclear regarding the assessment of demyelinating disease. That being said, its utilization to further understand the pathophysiology of peripheral nerve disease is encouraging in a laboratory setting and has opened the door for future research involving all segments of the peripheral motor nerve, be it demyelination or diseases of the axon.

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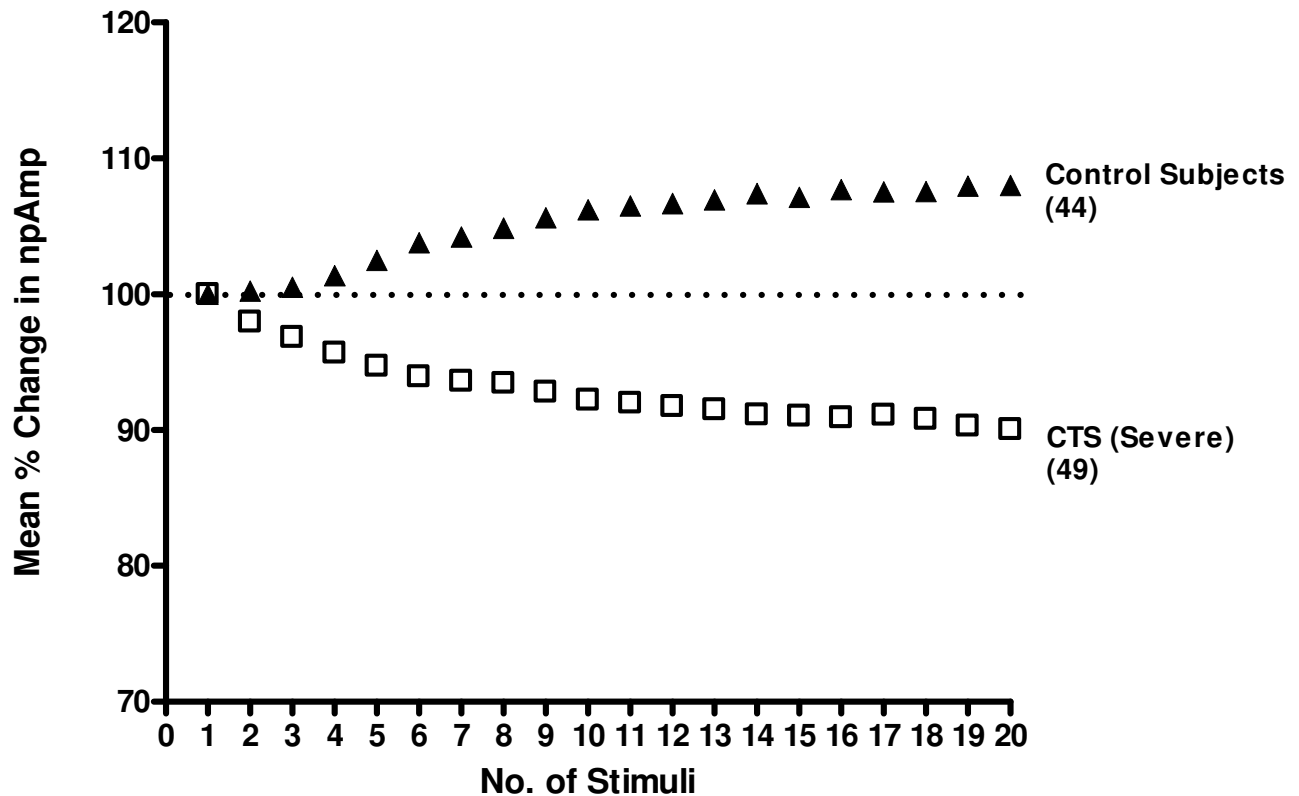
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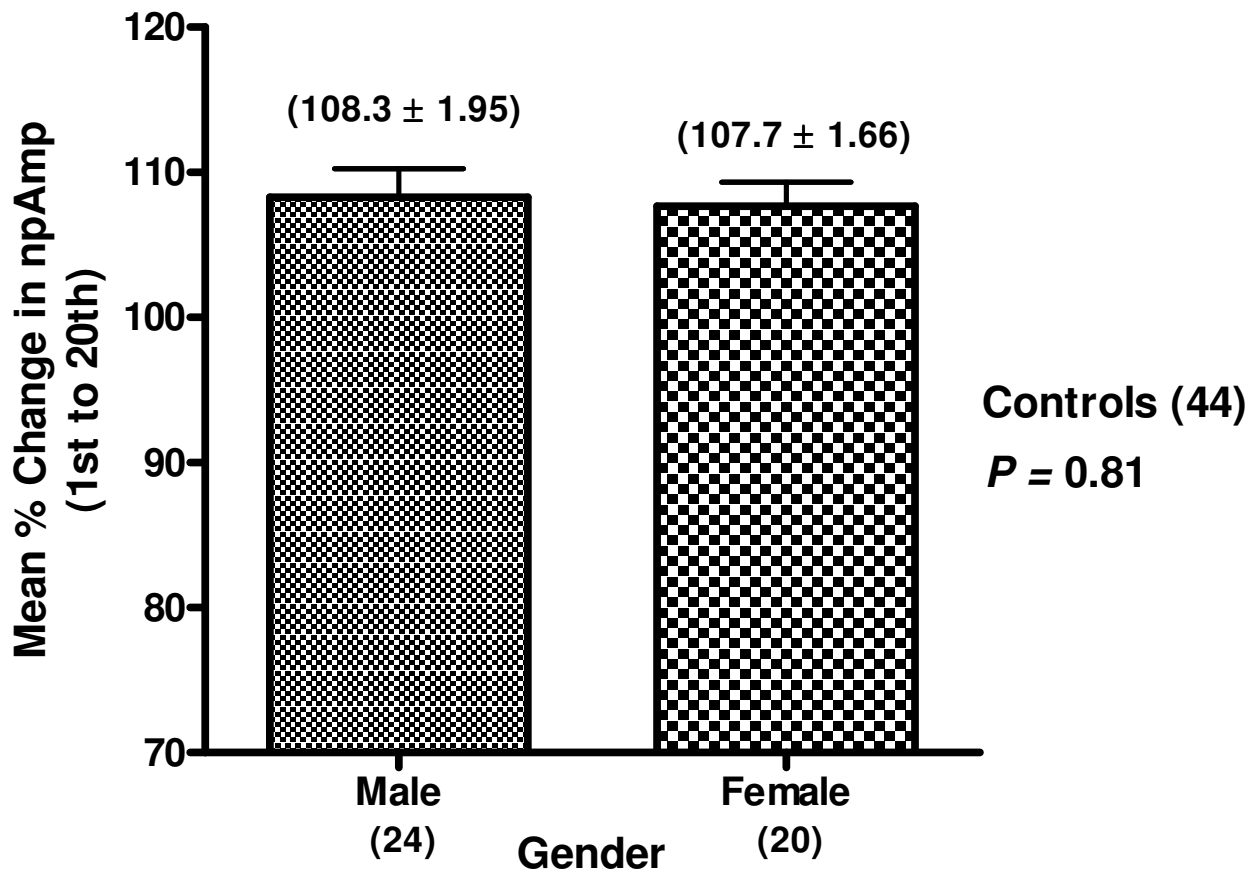
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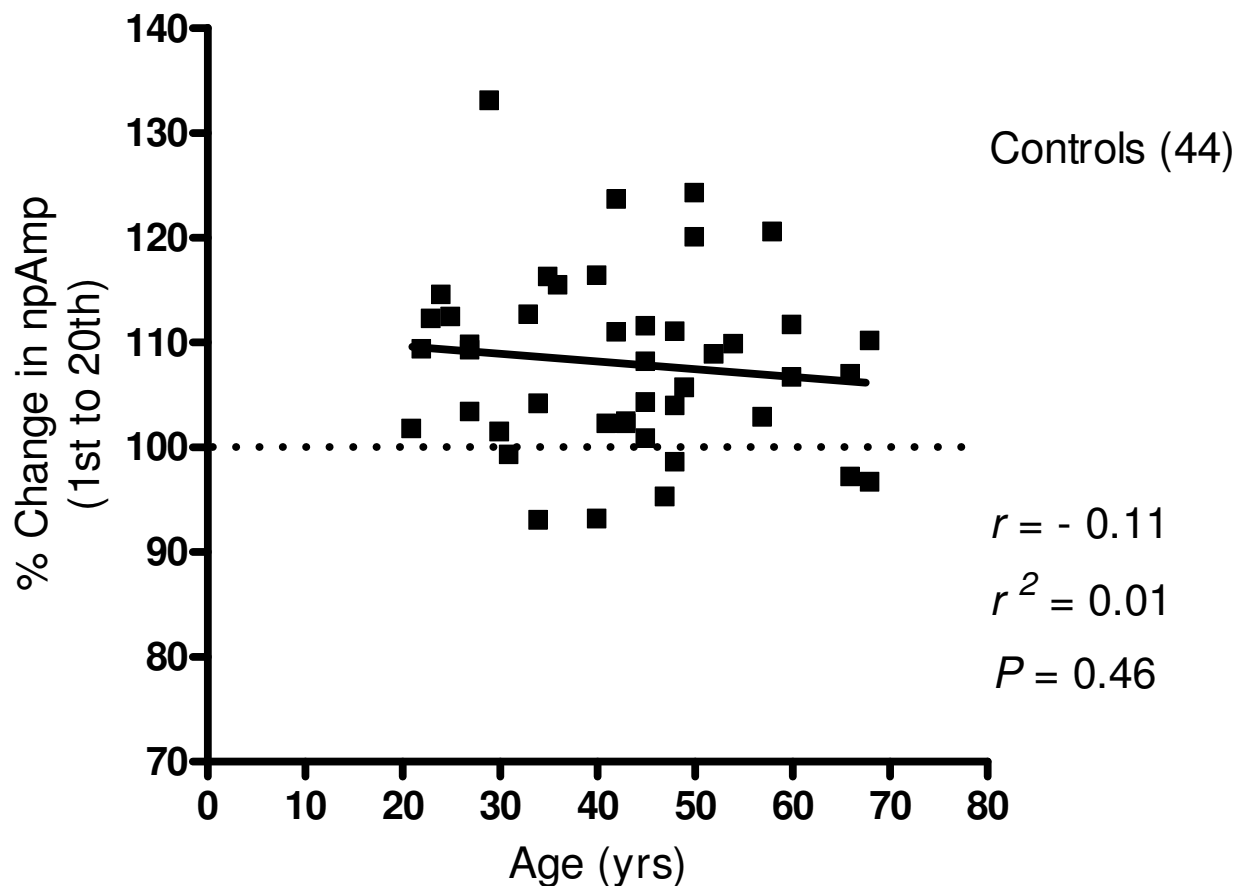
APPENDIX A



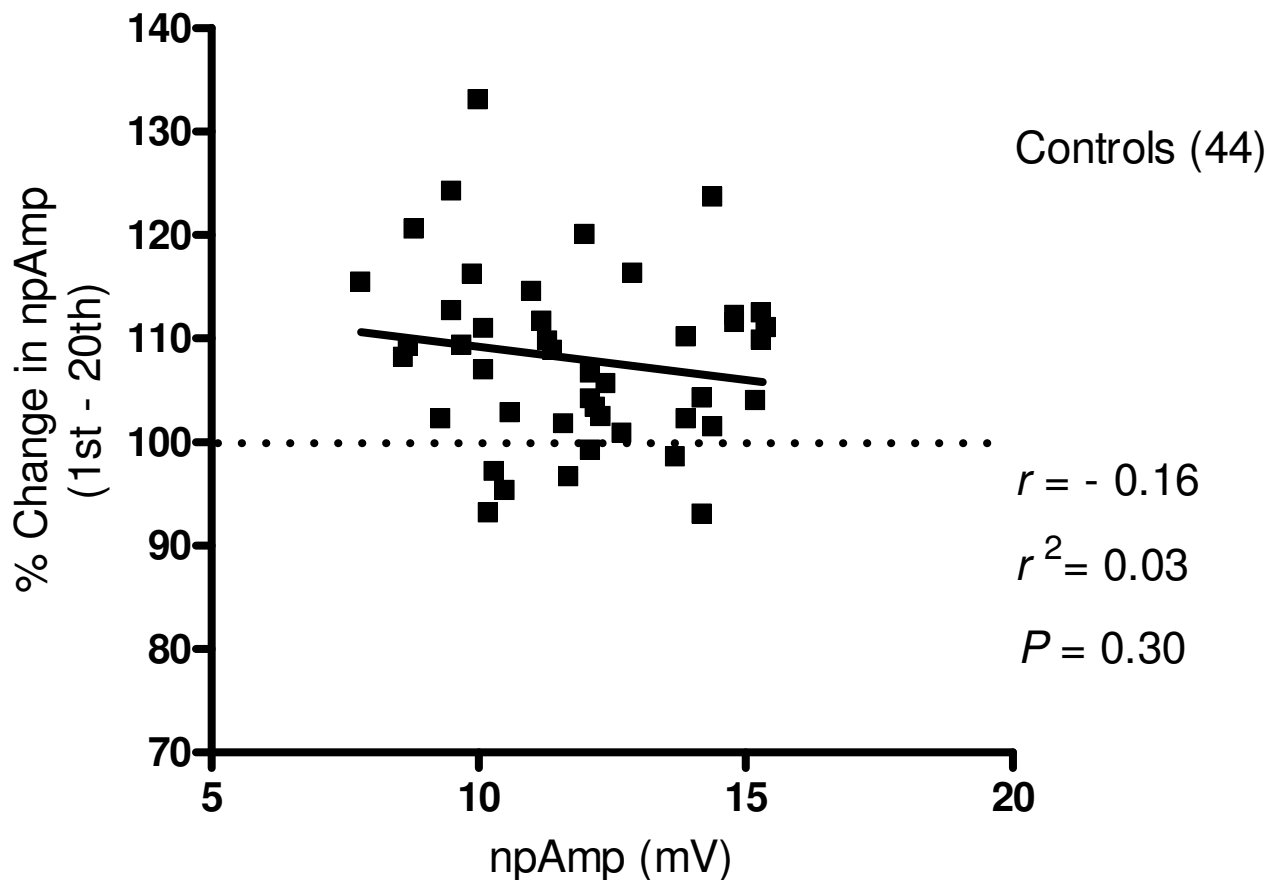
Combined data from three studies (Chapters 2, 3 and 4) of the mean thenar npAmp in controls (filled symbols; N = 44) and severe CTS patients as defined by their median nerve distal MTL (open symbols; N = 49) while stimulating the median nerve at the wrist (30-Hz, 20 stimuli), relative to the 1st response (100%). This result is similar to what was observed in Chapter 2 (controls, N = 15; CTS subjects, N = 18). Note that some controls volunteered for all three studies, but, were examined at different points in time over a 6-year period (npAmp = negative peak amplitude, CTS = carpal tunnel syndrome, Hz = hertz).



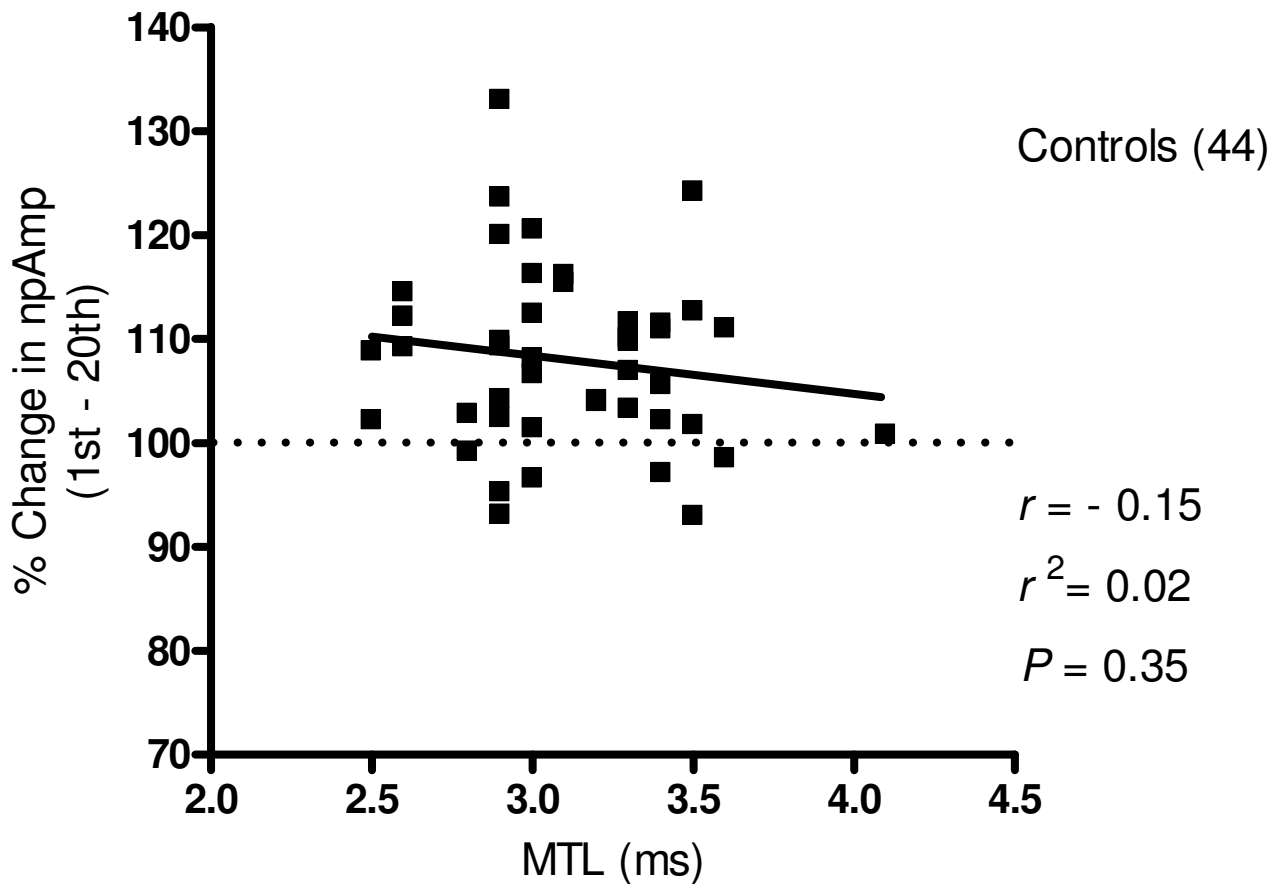
Combined data from three studies (Chapters 2, 3 and 4) comparing the relationship in controls between males (N = 24; age, 42.1 ± 12.6 years; age range, 21 to 68 years) and females (N = 20; age, 43.4 ± 14.1 years; age range, 22 to 66 years) and the mean percent change (\pm standard error of measurement) in thenar npAmp (1st to 20th) while stimulating the median nerve at the wrist (30-Hz, 20 stimuli). A Student's *t*-test was non-significant between gender groups ($P = 0.81$) suggesting that there is no relationship in controls between gender and the change in the 20th thenar response. Note that some controls volunteered for all three studies, but, were examined at different points in time over a 6-year period (npAmp = negative peak amplitude, Hz = hertz).



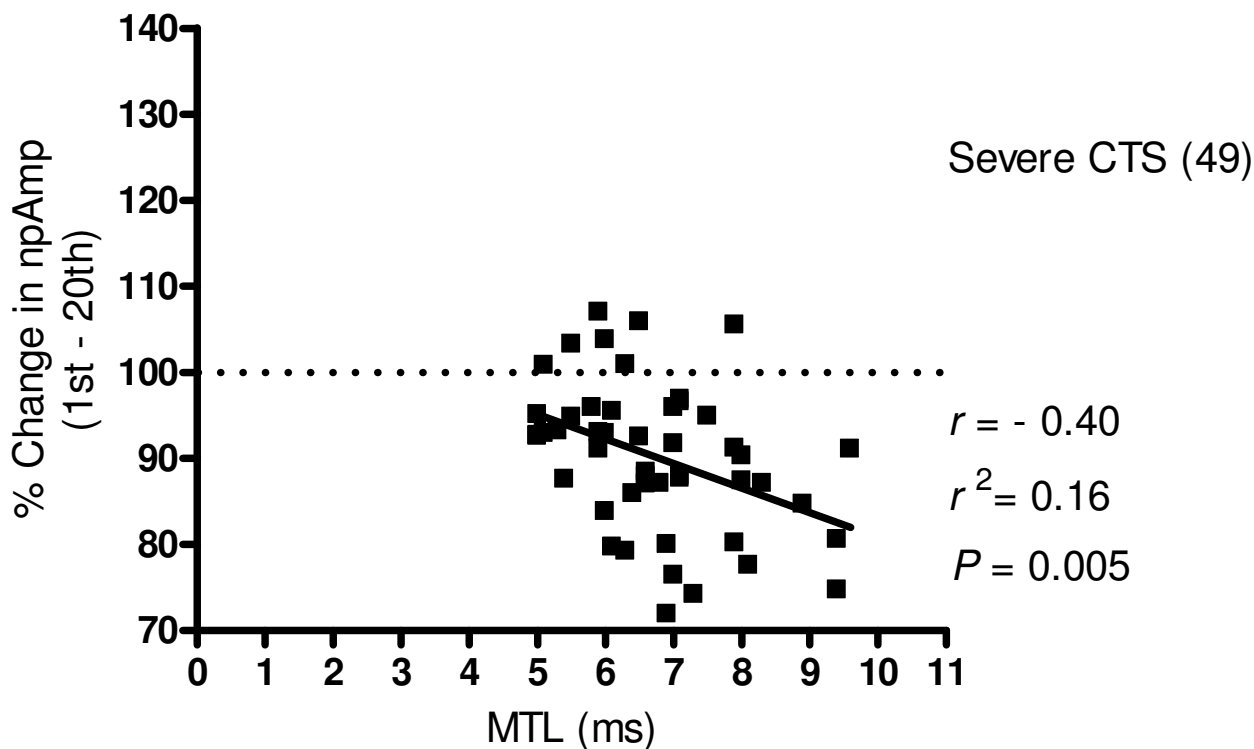
Combined data from three studies (Chapters 2, 3 and 4) showing the relationship in controls ($N = 44$) between age and the percent change in the thenar npAmp (1st to 20th) while stimulating the median nerve at the wrist (30-Hz, 20 stimuli). A non-significant correlation (Pearson product moment statistic) was found ($r = -0.11$, $r^2 = 0.01$, $P = 0.46$) suggesting that age does not influence the percent change in the 20th response. However, a greater number of controls for each decade are necessary for this result to be more conclusive. Note that some controls volunteered for all three studies, but, were examined at different points in time over a 6-year period (npAmp = negative peak amplitude, Hz = hertz).



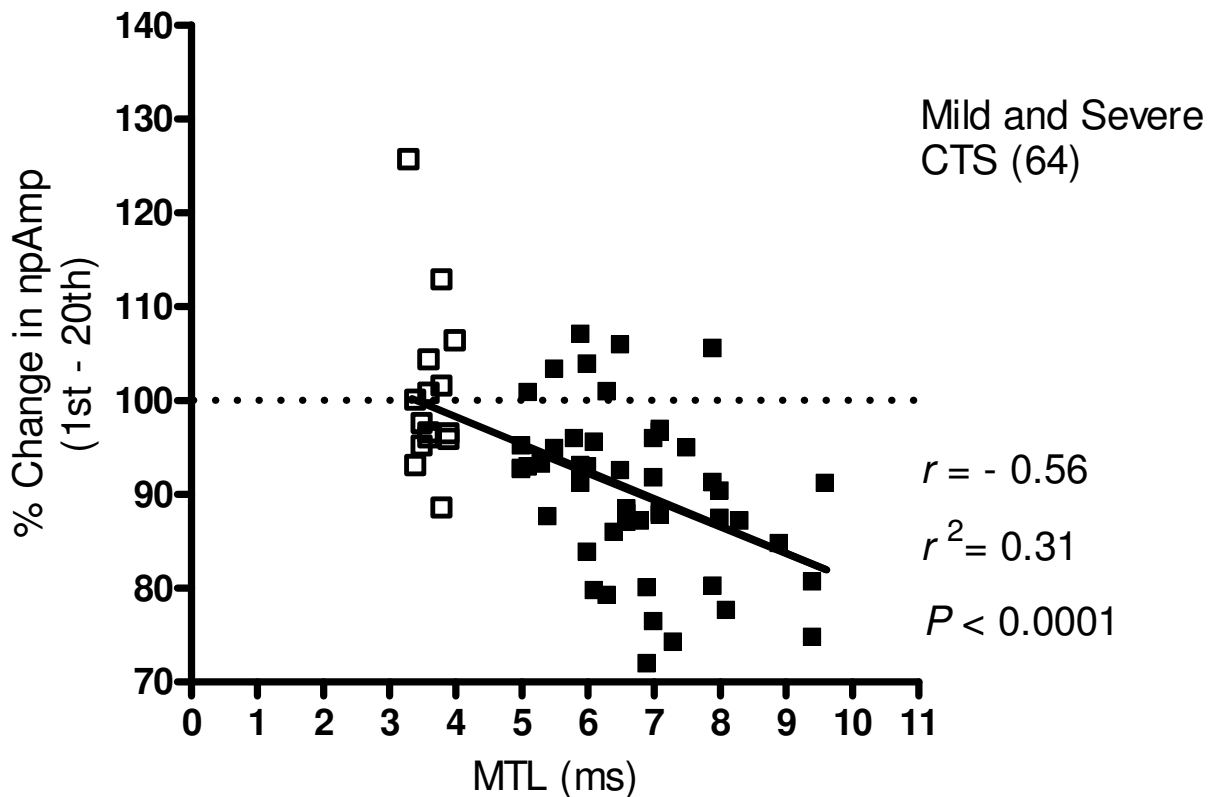
Combined data from three studies (Chapters 2, 3 and 4) showing the relationship in controls (N = 44) between the thenar npAmp obtained from conventional nerve conduction studies and the percent change in the thenar npAmp (1st to 20th) while stimulating the median nerve at the wrist (30-Hz, 20 stimuli). A non-significant correlation (Pearson product moment statistic) was found ($r = -0.16$, $r^2 = 0.03$, $P = 0.30$) suggesting that the initial size of the thenar CMAP does not influence the percent change in the 20th response, in controls. Note that some controls volunteered for all three studies, but, were examined at different points in time over a 6-year period (npAmp = negative peak amplitude, Hz = hertz, CMAP = compound muscle action potential).



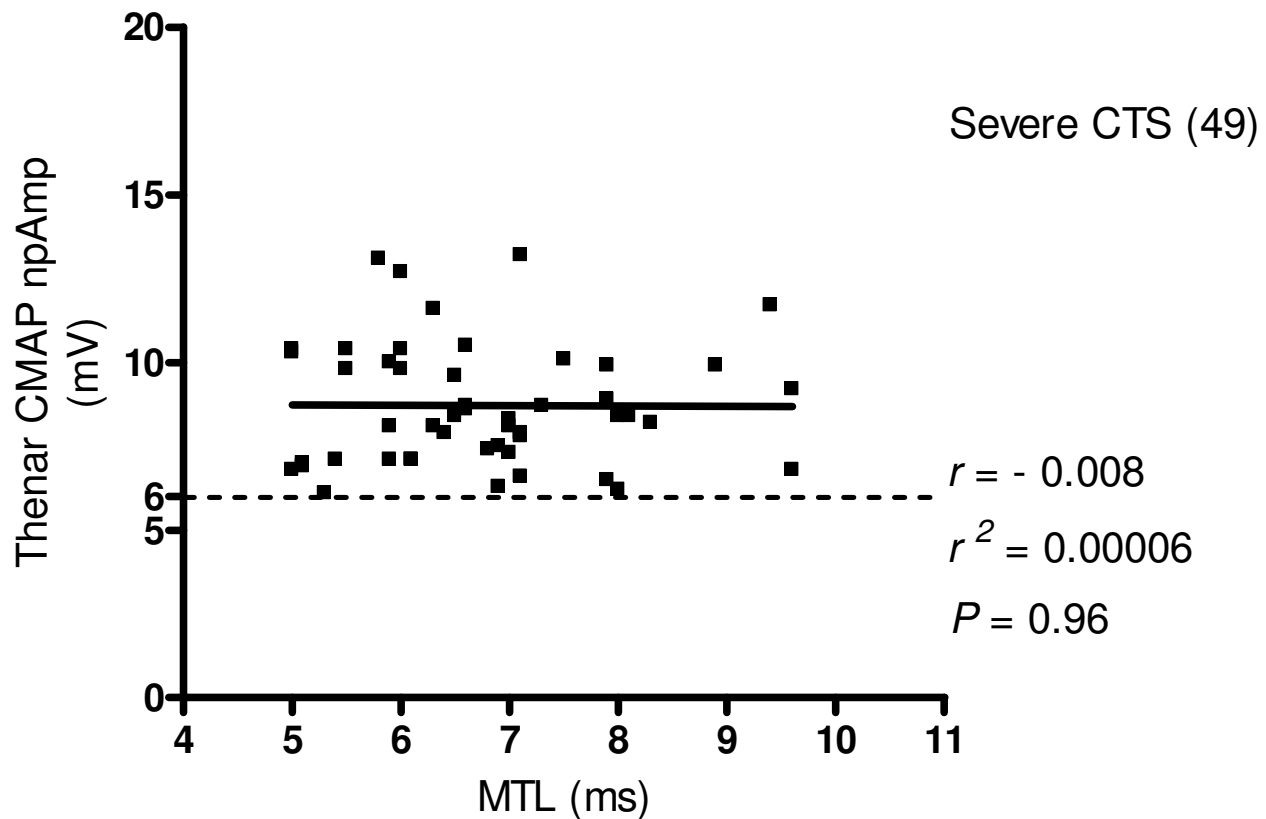
Combined data from three studies (Chapters 2, 3 and 4) showing the relationship in controls ($N = 48$) between the median MTL obtained from conventional nerve conduction studies and the percent change in the thenar npAmp (1st to 20th) while stimulating the median nerve at the wrist (30-Hz, 20 stimuli). A non-significant correlation (Pearson product moment statistic) was found ($r = -0.15$, $r^2 = 0.02$, $P = 0.35$) suggesting that the median MTL does not influence the percent change in the 20th response, in controls. Note that some controls volunteered for all three studies, but, were examined at different points in time over a 6-year period (npAmp = negative peak amplitude, Hz = hertz, MTL = motor terminal latency).



Combined data from three studies (Chapters 2, 3 and 4) showing the relationship in severe CTS patients as defined by their median nerve distal MTL (N = 49) between these MTLs obtained from conventional nerve conduction studies and the percent change in the thenar npAmp (1st to 20th) while stimulating the median nerve at the wrist (30-Hz, 20 stimuli). A moderately strong and significant correlation (Pearson product moment statistic) was found ($r = -0.40$, $r^2 = 0.16$, $P = 0.005$) and was similar to what was observed in Chapter 2 (N = 18). (npAmp = negative peak amplitude, Hz = hertz, MTL = motor terminal latency).



Combined data from three studies (Chapters 2, 3, and 4) showing the relationship in CTS patients with normal (open symbols) and severe (filled symbols) distal median nerve MTLs (N = 64) between these MTLs obtained from conventional nerve conduction studies and the percent change in the thenar npAmp (1st to 20th) while stimulating the median nerve at the wrist (30-Hz, 20 stimuli). A moderately strong and significant correlation (Pearson product moment statistic) was still found ($r = -0.56$, $r^2 = 0.31$, $P = 0.0001$) despite the normal MTLs within the mild CTS group again showing that FDB is more demonstrable in CTS patients. (npAmp = negative peak amplitude, CTS = carpal tunnel syndrome, Hz = hertz, MTL = motor terminal latency, FDB = frequency-dependent conduction block).



Combined data from three studies (Chapters 2, 3 and 4) showing the relationship in severe CTS patients as defined by their median nerve distal MTL (N = 49) between these MTLs and the initial thenar CMAP obtained from conventional nerve conduction studies while stimulating the median nerve at the wrist. A non-significant correlation (Pearson product moment statistic) was found ($r = -0.008$, $r^2 = 0.00006$, $P = 0.96$) suggesting that there is no relationship between the degree of demyelination (MTL) and the potential degree of motor axonal loss (CMAP) in CTS patients. Therefore, since the degree of FDB is related to the MTL in these patients, it is unlikely that axonal loss (if any) influenced the degree of FDB (CMAP = compound muscle action potential, npAmp = negative peak amplitude, mV = millivolts, CTS = carpal tunnel syndrome, MTL = motor terminal

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. Doherty

Review Number: 10769

Revision Number:

Protocol Title: Frequency Dependent Conduction Block in Demyelinating Neuropathies

Department and Institution: Clinical Neurological Sciences, London Health Sciences Centre

Sponsor:

Approval Date: 01-Sep-04

End Date: 31-Dec-05

Documents Reviewed and Approved: UWO Protocol, Letter of Information & Consent Form for Patients, Letter of Information & Consent Form for Controls

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 and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has received and granted full board approval to the above named research study on the 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.

This approval shall remain valid until end 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:

- changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
- all adverse and unexpected experiences or events that are both serious and unexpected
- 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. Paul Harding

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 Date: 1 Sept 04
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The University of Western Ontario
 Room 4180 Support Services 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: 10769

Review Date: February 09, 2009

Protocol Title: Frequency Dependant Conduction Block in Demyelinating Neuropathies

Department and Institution: Clinical Neurological Sciences, London Health Sciences Centre

Sponsor:
Ethics Approval Date: February 09, 2009

Revision Number: 4

Review Level: Expedited

Expiry Date: December 31, 2009

Documents Reviewed and Approved: Revised Study End Date

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 revision(s) or amendment(s) 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. Joseph Gilbert

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Office of Research Ethics

DEC 21 2009

The University of Western Ontario
 Room 4180 Support Services 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 Level: Expedited

Review Number: 10769

Revision Number: 5

Review Date: December 17, 2009

Approved Local # of Participants: 80

Protocol Title: Frequency Dependant Conduction Block in Demyelinating Neuropathies

Department and Institution: Clinical Neurological Sciences, London Health Sciences Centre

Sponsor:

Ethics Approval Date: December 17, 2009

Expiry Date: December 31, 2010

Documents Reviewed and Approved: Revised Study End Date

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 revision(s) or amendment(s) 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.

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Chair of HSREB: Dr. Joseph Gilbert
 FDA Ref. #: IRB 0000940

V

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The University of Western Ontario
 Room 5150 Support Services Building, London, ON, Canada N6A 3K7
 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 Level: Expedited

Review Number: 10769

Revision Number: 6

Review Date: January 13, 2011

Approved Local # of Participants: 80

Protocol Title: Frequency Dependant Conduction Block in Demyelinating Neuropathies

Department and Institution: Clinical Neurological Sciences, London Health Sciences Centre

Sponsor:

Ethics Approval Date: January 13, 2011

Expiry Date: December 31, 2011

Documents Reviewed and Approved: Revised study end date.

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 revision(s) or amendment(s) 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:

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- b) all adverse and unexpected experiences or events that are both serious and unexpected;
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APPENDIX C

[Permission request for PhD thesis](#)

FROM: [Brad Watson](#)

TO:

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Sincerely,

Brad Watson

PhD Candidate

University of Western Ontario

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Title: Frequency - Dependent Conduction Block In Focal Entrapment Neuropathies
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Publisher: University of Western Ontario

Publication Date: 2012

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APPENDIX E

From: Brad Watson [
Sent: 12 April 2011 16:43
To:
Subject: Re: Permission - "Frequency-dependent conduction block in ulnar neuropathy localized to the elbow"

Dear

Thank you for the timely reply.

The portions of the chapter I wish to reuse in my integrated thesis are included on pages 95 to 99 and 102 to 104. The total chapter length includes pages 95 to 119.

Again, the title of the book is *Handbook of Clinical Neurophysiology. Peripheral Nerve Diseases*. The author/editor of the book is Jun Kimura and the series editors are Jasper R. Daube and Francois Mauguiere. I wrote the actual chapter with Dr. William F Brown. It's volume 7 in the series and its ISBN number is 0 444 51358 2.

Please let me know if there is anything else that you require.

Sincerely,
Brad Watson

Tue, May 17, 2011 9:50:15 AM

RE: Permission - "Frequency-dependent conduction block in ulnar neuropathy localized to the elbow"

From:'

[View Contact](#)

To: Brad Watson ·

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Sent: Thursday, March 24, 2011 8:49 AM
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Subject: NON-RIGHTSLINK

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The second article, also published in Muscle Nerve, is entitled, "Localization of Frequency-Dependent Conduction Block in Carpal Tunnel Syndrome", 2010, July issue, pages 120-126. I would also like to ask for permission to include this into my thesis.

I am the first author on both papers.

My email address is

Fax number is
Contact phone

Sincerely,

Brad Watson

From: Permissions
To: Brad Watson <
Sent: Wed, March 30, 2011 3:14:36 PM
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APPENDIX G

From: Brad Watson

Sent: 24 March 2011 14:09

To: Rights and Permissions (ELS)

Subject: Permission - "Frequency-dependent conduction block in ulnar neuropathy localized to the elbow"

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Sincerely,

Brad Watson

(first author)

From: >
To: Brad Watson
Sent: Fri, March 25, 2011 7:56:47 AM
Subject: RE: Permission - "Frequency-dependent conduction block in ulnar neuropathy localized to the elbow"

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CURRICULUM VITAE
Bradley V. Watson

EDUCATION:

- 2006-2012 Ph.D. The University of Western Ontario
School of Kinesiology
Thesis: Frequency-dependent conduction block in
demyelinating focal neuropathies
- 2004-2005 M.Sc. Student
School of Kinesiology
The University of Western Ontario
(Fast Track to PhD December 2005)
- 1982-1986 Honours B.Sc.
School of Kinesiology
The University of Waterloo

AWARDS:

- 2004 Harvey F. Sullivan Scholarship
London Health Sciences Centre
London, ON
- 2002-2004 Lawson Health Research Institute Internal Research Fund.
"The reliability change index in the electrodiagnosis of
entrapment neuropathies: how much change is significant?"
Co-applicant with Dr. M. Nicolle and Dr. S. Wiebe

CERTIFICATIONS:

- June, 1988 Registered EMG Technologist - RT (EMG)
The Association of Electromyography Technologists of
Canada. Canadian Society of Clinical Neurophysiologists
(EMG section) - Certificate #52
Quebec City, QC

PUBLICATIONS:**Book Chapters:**

Brown WF, **Watson BV**. Recording of electrical activity in nerve trunks and conduction in human sensory and motor nerve fibers. In: Brown WF, Bolton CF, Aminoff MJ editors. *Neuromuscular Function and Disease: Basic, Clinical, and Electrodiagnostic Aspects*. Philadelphia: WB Saunders Company; 2002. p 21-55.

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Watson BV, Doherty TJ. Frequency-dependent conduction block and its localization in carpal tunnel syndrome. Proceedings of AANEM Annual Scientific Meeting, Providence, RI, 2008.

Symonette C, **Watson BV**, Koopman WJ, Nicolle MW, Doherty TJ. Muscle strength and fatigue in patients with generalized myasthenia gravis. Proceedings of AANEM Annual Scientific Meeting, Providence, RI, 2008.

Amirjani N, **Watson BV**, Nicolle MW. The impact of the recording electrode position on the CMAP amplitude and area. Proceedings of AANEM Annual Scientific Meeting, Providence, RI, 2008.

Shoesmith C, Krahn A, **Watson BV**, Blackler K, Nicolle M. Safety of nerve conduction studies in individuals with cardiac pacemakers. Proceedings of 61st Annual Meeting of the American Academy of Neurology, Seattle, WA, 2009.

Berger MJ, **Watson BV**, Doherty TJ. M-wave amplitude during voluntary activity: implications to twitch interpolation. Proceedings of AANEM Annual Scientific Meeting, San Diego, CA, 2009.

Watson BV, Doherty TJ. Frequency-dependent conduction block in mild carpal tunnel syndrome. AANEM Annual Scientific Meeting, San Francisco, 2011.

Acknowledgements (Published):

Brown WF, Bolton CF. Clinical Electromyography - Second Edition. *Butterworth-Heinemann Publishers*, Boston, 1993.

McLachlan RS, Brown WF. Pyridoxine dependent epilepsy with iatrogenic sensory neuropathy. *Can. J. Neurol. Sci.* 1995; 22:50-51.

Voegtle T. The effects of an acute inversion ankle sprain on neuromuscular function. Master's Thesis. The University of Western Ontario, Kinesiology Department, 1999. Advisor.

Federico P, Zochodne DW, Hahn AF, Brown WF, Feasby TE. Multifocal motor neuropathy improved by IVIg (Randomized, double-blind, placebo-controlled study). *Neurology* 2000; 55:1256-1262.

INVITED PRESENTATIONS:

Postoperative ulnar neuropathies. The Association of Electromyography Technologists of Canada (Aetc), Ottawa, ON, 1989.

Collision - a means of assessing conduction in the brachial and lumbosacral plexus' and the adjacent spinal roots in median, ulnar and peroneal motor fibers. The Association of Electromyography Technologists of Canada (AETC), Toronto, ON, 1993.

Central motor conduction time using magnetic stimulation. The Association of Electromyography Technologists of Canada (AETC), St. John's, NL, 1994.

Miller Fisher Syndrome (atypical clinical and neurophysiological presentation). The Association of Electromyography Technologists of Canada (AETC), Victoria, BC, 1995.

Frequency-dependent conduction block in carpal tunnel syndrome. Special Interest Group Session: Motor Unit Physiology. American Association of Neuromuscular & Electrodiagnostic Medicine Annual Meeting, Phoenix, AZ, 2007.

Magnetic stimulation of the cranial nerves. Recent Advances in Transcranial Magnetic Stimulation (RATS), Niagara-on-the-Lake, ON, 2007.

Localization of frequency-dependent conduction block. Special Interest Group Session: Motor Unit Physiology. American Association of Neuromuscular & Electrodiagnostic Medicine, Providence, RI, 2008.

Electrophysiology in Guillain Barre Syndrome. Canadian Association of Neuroscience Nurses Update Conference, London, ON, 2010.

Back to the basics: nerve conduction studies and EMG. Seventh Annual Neuromuscular Conference and EMG Workshop, London, Ontario, 2010.

INVITED WORKSHOPS:

Surface EMG recordings (with Dr. William F. Brown). American Association of Electrodiagnostic Medicine (AAEM) Annual Scientific Meeting, Washington, DC, 1989.

Surface EMG recordings (with Dr. William F. Brown). American Association of Electrodiagnostic Medicine (AAEM) Annual Scientific Meeting, Chicago, IL, 1990.

Motor unit potential triggering - motor unit estimates - Special Interest Group (with Dr. William F. Brown). American Association of Electrodiagnostic Medicine (AAEM) Annual Scientific Meeting, Chicago, IL, 1990.

Surface EMG recordings workshop (with Dr. William F. Brown). American Association of Electrodiagnostic Medicine (AAEM) Annual Scientific Meeting, Vancouver, BC, 1991.

Motor unit potential: estimates (with Dr. William F. Brown). American Association of Electrodiagnostic Medicine (AAEM) Annual Scientific Meeting, Toronto, ON, 2002.

Electrodiagnosis of disorders of neuromuscular transmission (with Dr. Michael W. Nicolle). First Annual Neuromuscular Conference and EMG Workshop, London, ON, 2003.

Electrodiagnosis of disorders of neuromuscular transmission (with Dr. Michael W. Nicolle). Second Annual Neuromuscular Conference and EMG Workshop, London, ON, 2004.

Electrodiagnosis of disorders of neuromuscular transmission (with Dr. Michael W. Nicolle). Third Annual Neuromuscular Conference and EMG Workshop, London, ON, 2005.

Nerve conduction studies, troubleshooting and pitfalls. Fourth Annual Neuromuscular Conference and EMG Workshop, London, ON, 2006.

Challenging nerve conduction study cases. Fourth Annual Neuromuscular Conference and EMG Workshop, London, ON, 2006.

Magnetic stimulation of the cranial nerves (with Dr. William F. Brown). Recent Advances in Transcranial Magnetic Stimulation (RATS), Niagra-on-the-Lake, ON, 2007.

Pitfalls and clinical pearls of nerve conduction studies: a case based practical overview. 55th Canadian Association of Physical Medicine and Rehabilitation Annual Scientific Meeting, London, ON, 2007.

Nerve conduction studies, troubleshooting and pitfalls. Fifth Annual Neuromuscular Conference and EMG Workshop, London, ON, 2007.

Difficult nerve conduction studies. Fifth Annual Neuromuscular Conference and EMG Workshop, London, ON, 2007.

Nerve conduction studies, troubleshooting and pitfalls. Sixth Annual Neuromuscular Conference and EMG Workshop, London, ON, 2008.

Difficult nerve conduction studies. Sixth Annual Neuromuscular Conference and EMG Workshop, London, ON, 2008.

Nerve conduction studies, troubleshooting and pitfalls. Seventh Annual Neuromuscular Conference and EMG Workshop, London, ON, 2010.

MULTI-CENTRE RESEARCH TRIALS:

Double blind, randomized, placebo controlled, parallel group study of vigabatrin in patients with uncontrolled complex partial seizures. Nordic Dow, 1992 - 1994.

Amyotrophic Lateral Sclerosis, Ciliary Neurotrophic Factor Study. Regeneron Pharmaceuticals Inc., 1993 - 1994.

A double-blind, parallel, multicentre comparison of Acetyl-L-Carnitine (ALCAR) and placebo in the treatment of diabetic peripheral neuropathy for prevention of progression. F. Hoffman La Roche Ltd, 1994 - 1996.

rh-NGF in diabetic neuropathy. Hoffman-LaRoche Limited, 1997-1999.

Consultant (Electrophysiology). Topmat-NP-005 Investigators' Meeting. The R.W. Johnson Pharmaceutical Research Institute, Dallas at Las Colinas, Irving, TX, February 12-13, 2001.

Consultant (Electrophysiology). Topmat-NP-005 Investigators' Meeting. The R.W. Johnson Pharmaceutical Research Institute, Hotel Inter-Continental, Central Park South, New York, NY, May 14-15, 2001.

Consultant (Electrophysiology). CTR1476G 2305 Investigators' Meeting. Novartis Pharmaceuticals Corporation, Wyndham Emerald Plaza, San Diego, CA, April 22-25, 2002.

EAA-090 in diabetic neuropathy. Wyeth Research, May 2004 - 2005.

A randomized, double-blind, placebo-controlled, dose-ranging study to determine the safety and efficacy of Avonex, when used in subjects with chronic inflammatory demyelinating polyradiculopathy (CIDP). Biogen Ltd., February 2004 - 2005.

Epidemiology of Diabetes Interventions and Complications (EDIC). Longitudinal study in partnership with St. Joseph's Hospital (Diabetic Research Centre), 2006.

Neuropath Validation Study. Excel Tech Limited, Oakville, ON, 2006.

COMMUNITY LECTURES AND TEACHING:

London Secondary School Coop Education, London, ON, 1994 - 2005.

Clinical Neurological Sciences Nursing Staff, London Health Sciences Centre, University Campus, London, ON, 1996.

The Canadian Medical Hall of Fame/Canada Trust Annual Youth Symposium, London Health Sciences Centre, University Campus, London, ON, May 1997-1999.

PROFESSIONAL AFFILIATIONS:

Education Committee - The Association of Electromyography Technologists of Canada, 1989-1991.

Diagnostic Technical Services Committee Member, University Hospital, London, ON, 1990-1994.

Board Member/Examiner - Board of Registration of Electromyography Technologist of Canada, 1993-1997.

Clinical Neuroscience Team Committee Member, University Hospital, London, ON, 1994-2010.

Board Member – The Association of Electromyography Technologist of Canada, 2003-2005.

RELATED WORK EXPERIENCE:

Vice President of Operations	NeuroSource Medical Inc. London, Ontario – 2011-Present
Lab Co-ordinator	EMG Lab/Neuromuscular Clinic – London Health Sciences Centre London, Ontario – 2006-2010
Lab Co-ordinator	EMG Lab - University Hospital London, Ontario - 1995-2006
Charge Technologist	EMG Lab - University Hospital London, Ontario - 1990-1995
Senior Technologist	EMG Lab - University Hospital London, Ontario - 1989-1990
Technologist (Registered)	EMG Lab - University Hospital London, Ontario - 1988-1989
Technologist (Non-registered)	EMG Lab - University Hospital London, Ontario - 1987-1988

PROFESSIONAL MEMBERSHIPS:

1987 - Present The Association of Electromyography Technologists of Canada