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Assessment of Small Sensory Fibers in Carpal Tunnel Syndrome Using Quantitative Sensory Testing

by

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ABSTRACT

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in humans. The gold standard for diagnosing CTS is considered to be nerve conduction studies (NCS). However, there are patients who complain of a lot of symptoms with minimal findings in NCS. One of the reasons for this discrepancy is that the NCS just assess the large myelinated fibers. The objective of the present study is to evaluate the small sensory fibers in different stages of CTS. 58 CTS subjects and 44 healthy control subjects were recruited. The thermal and heat pain thresholds were assessed in the CTS and control groups, by the quantitative sensory testing (QST) using the CASE IV machine. Cold and warm threshold was increased in all three stages of CTS. Heat pain threshold was increase in severe CTS patients. We concluded that small sensory fibers are affected in early stages of CTS.

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ABREVIATIONS AND UNITS

The following abbreviations, definitions and units have been used throughout this thesis.

º C	degree Celsius
CTS	carpal tunnel syndrome
CTS-Q	CTS patients categorized based on their symptoms scored by Levine's Self-Assessment Questionnaire
CT	cold threshold
Ctrl	control
CV	conduction velocity
DML	distal motor latency
HPT	heat pain threshold
ICC	intraclass correlation coefficient
JND	just noticeable difference
Mod	moderate
NCS	nerve conduction studies
NRS	numeric rating scale

QST ..... quantitative sensory testing

SNAP.....sensory nerve action potential

SD ..... standard deviation

TRP.....transient receptor potential

TRPV.....vanilloid TRP

TRPM .....melastatin TRP

TRPA ..... ankyrin TRP

WT .....warm threshold

CHAPTER 1. INTRODUCTION AND OBJECTIVE

1.1 SOMATOSENSORY SYSTEM

Information from the outside world is provided to the body by the somatosensory system. External stimuli are received by receptors and if strong enough, they induce action potential formation, and are transferred to the central nervous system (CNS) via sensory afferents. The action potential is then sent to synaptic endings in the spinal cord or brainstem where the afferent signals are transmitted through the second and third order sensory order sensory neurons to the primary and secondary somatosensory cortex. The senses include hearing, vision, olfaction and cutaneous senses. Cutaneous senses encompass touch, proprioception, vibration, temperature and pain (McGlone et al. 2010; Waxman et al. 1999).

1.2 CUTANEOUS SENSORY AFFERENTS

Peripheral nerves are complex organs that can be found throughout the body reaching almost all tissues and organs to provide motor and sensory innervations. The smallest functional unit of a peripheral nerve is the nerve fiber. Peripheral nerves are being classified according to many different characteristics such as conduction velocity, function, fiber diameter and other attributes (Djouhri & Lawson, 2004). Based on the presence of myelin, two subgroups of the fibers are distinguishable: myelinated and unmyelinated nerve fibers. Myelinated fibers

are further divided into large and small fibers based on their size (Geuna et al. 2009).

Primary afferent fibers range in diameter from 0.25 μm to 20 μm and the smaller fibers are not enclosed in a myelin sheath. The speed by which action potentials are conducted along the nerve fiber depends on the presence of myelin sheath and diameter of the fiber. For large-diameter myelinated fibers the conduction velocity (CV) in meters per second equals a factor six times the diameter in μm (CV=6D). For smaller diameter fibers the factor is lower, 3.5 to 4.5. For unmyelinated fibers the factor is even smaller: at around 1.7. In peripheral nerves, the distribution of diameters (and corresponding CVs) of axon is not uniform (Dyck et al. 1984).

The largest and fastest sensory axons are called Aα and they transfer proprioceptive information from muscle stretch receptors (McGlone et al. 2010). The second largest group, Aβ-fiber, transfers pressure, stretch or hair movement sensation. Slightly myelinated Aδ-fibers and unmyelinated C-fibers carry temperature and pain sensation (Boulais et al. 2008; Pare′ et al. 2002; Johnson et al. 2000).

Afferent (large myelinated)	Function
A α	Proprioception
A β	Pressure and skin stretch

Table 1. Large myelinated afferents.

1.3 THERMOSENSITIVE AND PAIN SENSITIVE AFFERENTS

Thermosensitive and pain sensitive afferents (nociceptors), like other somatic sensory receptors, arise from cell bodies in dorsal root ganglia (or in the trigeminal ganglia) having one peripheral axon and one central axon which projects to the spinal cord or brainstem. Because their peripheral axons terminate in unspecialized free nerve endings, they are categorized according to the properties of the axons associated with them (Purves et al. 2008).

Cold sensitive afferents are mainly Aδ fibers. Experiments have shown C fibers in monkey's skin that are found to be sensitive to innocuous cold stimuli. However, psychophysical experiments in humans which used blocking of nerve fibers have shown that cold sensation is mainly mediated by small myelinated Aδ fibers (Mackenzie et al. 1975).

At normal skin temperatures, cold fibers fire continuously and the firing rate increases as the skin is cooled and decreases (or even stops firing) when the skin is warmed. Cold fibers also decrease their firing frequency over time or adapt when held at constant temperature. This characteristic helps to adapt to mild decreases in skin temperature (Dhaka et al. 2006). Each cold fiber has single or multiple small receptive fields and they are not activated by mechanical stimuli (Schepers & Ringkap, 2010).

Assessing the conduction velocity of warm fibers has shown that they belong to C fiber category of afferent axons (Darian-Smith et al. 1979). Similar to cold fibers, they have small cutaneous receptive fields and do not respond to mechanical stimuli. Warm fibers have constant activity at static

temperatures of 30°C or more and their activity decreases by cooling. Warm stimulus results in an increase in their activity. However, they quickly adapt to steady state temperature. Their maximum activity is at 40-43°C (Schepers & Ringkamp, 2010; Darian-Smith et al. 1979).

The axons associated with temperature and pain perception, being slightly myelinated or unmyelinated, conduct relatively slowly. Aδ fibers conduct at a rate of 5-30 m/s and C fibers at a rate of 2 m/s. In general, the faster-conducting Aδ nociceptors respond either to dangerously intense mechanical or both intense mechanical and thermal stimuli. The majorities of unmyelinated C-fiber nociceptors tend to respond to thermal, mechanical, and chemical stimuli, and are therefore polymodal. In summary, three major classes of nociceptive afferents supply the skin: Aδ mechanosensitive nociceptors; Aδ mechanothermal nociceptors; and polymodal nociceptors (C fibers) (Purves et al. 2008).

Pain perception involves two stages: a sharp first pain and a longer-lasting second pain. Stimulation of the large, rapidly conducting Aα and Aβ axons in peripheral nerves does not result in sensation of pain. However, by stimulation of Aδ fibers, a tingling sensation arises. If the stimulation is intense enough, a feeling of sharp pain is reported. If the intensity of stimulus in increased enough to stimulate the C fibers, then a duller, longer lasting sensation of pain is experienced (Purves et al. 2008). By raising the skin temperature above 45° C, most human subjects report pain which becomes intense as the temperature goes higher than 50°C. When the temperature changes rapidly, the perception of

temperature by the subject is determined by actual temperature step not the final skin temperature (Darian-Smith et al. 1979).

Sensation	Sensory Afferent
Cold	A δ
Warm	C fiber
First pain	A δ
Second pain	C fiber
Heat pain	C fiber

Table 2. Thermal and heat pain perception afferents.

1.4 CUTANEOUS SENSORY RECEPTORS

1.4.1 LOW THRESHOLD MECHANORECEPTORS

The mechanism by which sensory stimulus is being conducted is similar in all sensory afferents: a stimulus alters the permeability of cation channels in afferent nerve endings, which results in generating a depolarizing current in the receptor. If strong enough, an action potential is formed with a rate which is proportional to the magnitude of the depolarization. Large myelinated afferent fibers are encapsulated by specialized receptor cells called mechanoreceptors that help tune the afferent fiber to particular features of somatic stimulation (Purves et al. 2008).

The four cutaneous mechanoreceptors whose afferent fibers innervate the skin include: Merkel cell that is being innervated by slowly adapting type 1 afferents, Meissner corpuscles whose afferent fiber is rapidly adapting afferent, Pacinian corpuscles innervated by Pacinian afferents and Ruffini corpuscles that are thought to be connected to slowly adapting type 2 afferents. The mechanoreceptors reside at the end of the afferent fibers (Johnson, 2001).

Structure of Merkel cell, responsible for tactile perception of form and texture, consists of a special cell type in the basal layer of the epidermis that wraps the unmyelinated endings of the type 1 afferent fibers. The Meissner, lying just beneath the epidermis, consists of cell layers that enfold the endings of rapidly adapting afferent fibers. They respond to low frequency vibrating stimuli (Johnson, 2001).

Pacinian corpuscle is a large, layered onion-like structure with as many as 70 layers. It wraps a single nerve ending and is sensitive to deformation. It provides information about the objects held in hand by responding to transient and vibratory stimuli. Ruffini corpuscle, located in the connective tissue of the dermis, has a relatively large spindle shaped structure. Its association with connective tissue matrix of the skin، makes it selectively sensitive to skin stretch (Johnson, 2001).

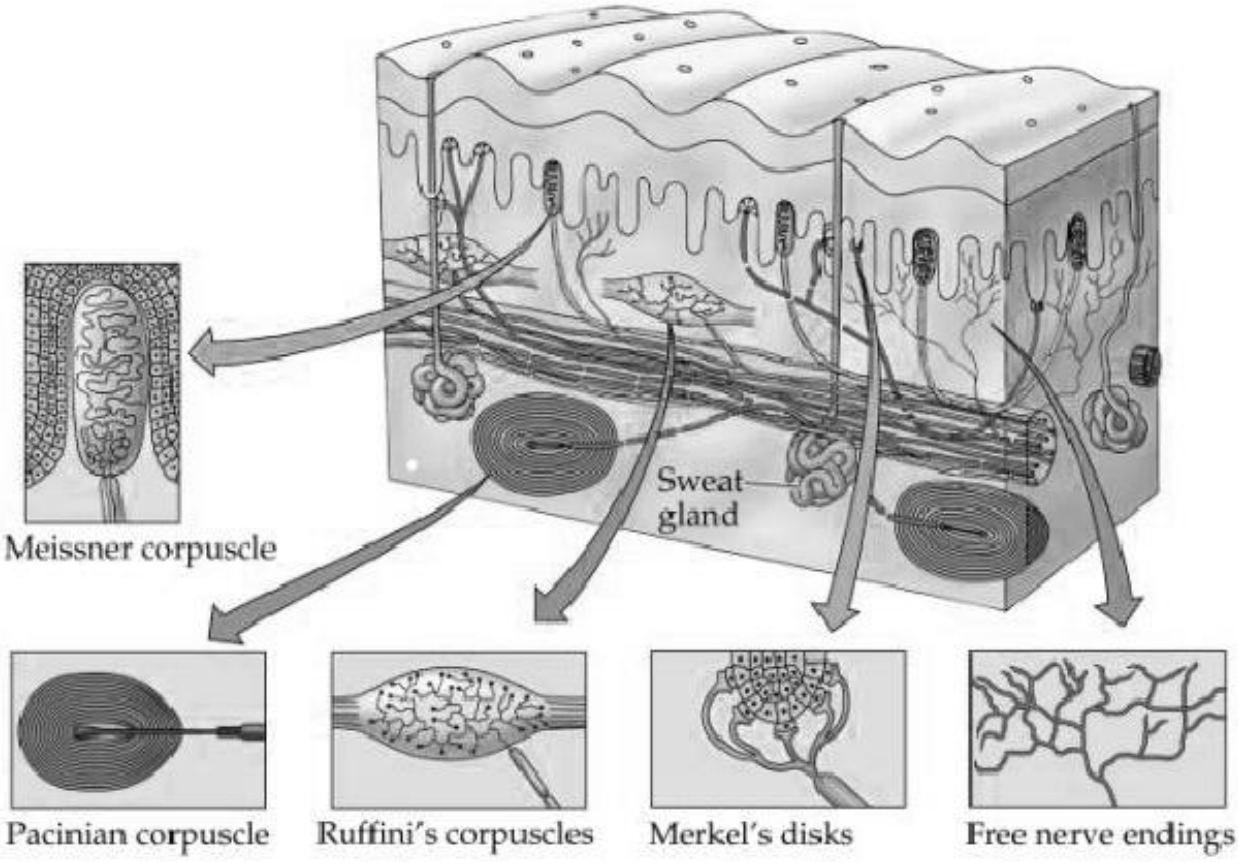

Fig1. Mechanoreceptors of hairy skin.

1.4.2 THERMORECEPTORS

Afferent fibers that lack specialized receptor cells are referred to as free nerve endings among which are afferents that transmit temperature and pain sensation. Free nerve endings that initiate the sensation of pain are called nociceptors (Purves et al. 2008).

However how different stimuli are perceived as heat, cold and pain? This has been made possible by molecules called thermoreceptors and nociceptors. These molecules belong to a group of nonselective cation channels, called transient receptor potential (TRP) ion channels which get their name from a Drosophila phototranduction mutant. Thermo TRPs are activated by temperature (Dhaka et al. 2006). Structurally, TPR channels resemble voltage-gated potassium or cyclic nucleotide-gated channels, having six transmambrane domains with a pore between domain 5 and 6. Under resting conditions the pore is closed. When stimulated, they allow an influx of sodium and calcium that result in the generation of action potentials in the nociceptive and thermoceptive fibers (Purves et al. 2008).

So far, 28 of these receptors have been recognized in human skin and they can be categorized into 6 families. Of these, members of 3 families: the vanilloid TRP channels (TRPV), the melastatin or long TRP channels (TRPM), and the ankyrinTRP channels (TRPA) are of particular interest as thermoreceptors (Schepers & Ringkamp, 2010; Mackenzie et al. 1975; Bandell et al. 2007).

There are few proposed mechanisms by which these ion channels are activated by heat and cold. They include indirect activation via membrane–

bound factors or directly through conformational change of the channel. However, none of these mechanisms have been able to completely explain the thermosesitivity of these receptors (Dhaka et al. 2006). There is a possibility that different thermoreceptors respond to changes in temperature in different ways.

1.4.2.1 COLD RECEPTORS

The thermoreceptor responsible for conveying non-noxious cold is transient receptor potential melastatin 8 (TRPM8) which is also expressed on some of the dorsal root ganglion neurons as well. The temperature range that they are responsive to is below 26°C and above 12°C. The genetically modified animals, in which TRPM8 is knocked out, show reduced reaction to cold temperature. However, their responses to noxious cold was not affected indicating that TRPM8 in responsible for transmission of nonpainful cold stimuli (Schepers & Ringkamp, 2010; Jordt et al. 2003; McKemy, 2005). TRPM8 is found on both Aδ and C fibers (Dhaka et al. 2006).

Activation of ion channels transient receptor potential channel 1 (TRPA1) induces feeling of cold pain. The average temperature threshold for activation of TRPA1 is 17°C which is approximately the threshold of noxious cold for human beings. Similar to TRPM8, TRPA1 is expressed on both Aδ and C fibers. However, it is not coexpressed with TRPM8 which suggests separate functions for these receptors in cold perception (Dhaka et al. 2006).

1.4.2.2 WARM AND HEAT RECEPTORS

Receptors for warmth perception include transient receptor potential vanilloid 3 (TRPV3) and transient receptor potential vanilloid 4 (TRPV4). They respond to temperatures above 33°C and between 24 and 34°C, respectively (Schepers & Ringkamp, 2010). Transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential vanilloid 2 (TRPV2) are the receptors for transmission of heat pain. TRPV1 responds to heat levels above 43°C which is in the noxious range. TRPV2 is activated by temperature range above 52°C (Schepers & Ringkamp, 2010; Levine & Alessandri-Haber, 2007).

1.5 CENTRAL PATHWAYS FOR PAIN AND TEMPRATURE

Perception of somatosensory stimuli is started by stimulation of cutaneous receptors which are innervated by sensory afferents. The cell bodies of these nerve afferents are located in dorsal root ganglia. Dorsal root ganglia have two projections, a peripheral axon which projects to receptors and one central axon which extends to central nervous system. Central axons enter the central nervous system via dorsal root and from there they enter the dorsal horn of the spinal cord. Once in the dorsal horn they give off branches to the second order neurons which then cross the midline and ascend to the brainstem and thalamus in the anterolateral quadrant of the contralateral half of the spinal cord. Second order fibers in the anterolateral system project to thalamus and from there the 3rd order neurons project to the primary and secondary sensory cortex (Purves et al. 2008; Lynn, 1975; Willis, 2007).

1.6 CENTRAL PLASTICITY

The adult human brain undergoes plastic changes after alterations in the sensory information flow from peripheral receptors and nerve fibers. Reorganization has been observed at different levels of the adult somatosensory system in human beings (Chen et al. 2002; Navarro, 2009).

Although reorganization of cortical map is in its maximum efficiency during childhood development, plasticity can occur in adult brain cortex, as well (Barnes & Finnerty, 2010). A significant area of the somatotopic map of the somatosensory cortex in the post-central gyrus belongs to the digits of the hand, with D1 being located in the ventrolateral and D5 in the dorsomedial area of the map. It has been shown that deafferentation of primary sensory cortex from some of the digits results in expansion of adjacent fields from intact digits into the deafferentated areas. In opposition, electrophysiology and fMRI studies have shown that increased afferentation by tactile stimuli can lead to enlargement of the S1 cortical receptive field (Napadow et al. 2006).

Another study showed decreased spatial extension of median nerve representation in S1 in CTS patients and invasion of the deprived cortical zone by fields receiving input from intact peripheral nerves, namely, by representations of the little finger, innervated by ulnar nerve, and the dorsum of the thumb, innervated by the radial nerve (Druschky et al. 2000).

In a study performed by Tecchio et al., they showed that CTS patients with larger digit 1 to digit 5 cortical representation distance reported less impairment in daily activities than patients with restricted hand sensory cortical

extension. Those patients who suffered exclusively from numbness and tingling symptoms, with minor or no pain, demonstrated larger than normal sensory hand cortical extension (Tecchio et al. 2002).

Although central plasticity is thought of as a mechanism for restoration of function of the injured nerve and organ, plastic changes following peripheral nerve injury do not always result into better outcome. On the contrary, some believe that reorganization of somatosensory systems is related to development of neuropathic pain and phantom pain in amputees (Navarro et al. 2007). Furthermore, upon nerve injury and later during the regeneration, the axonal growth does not always result in the reinnervation of the distal stump by the matched regenerating proximal nerve fiber which in turn can result in abnormal input or output from the central nervous system and importantly the cortical map. This misdirection can result in reorganization of the somatosensory cortex with a new mapping of the skin areas originally innervated by the damaged nerve (Navarro et al. 2007).

1.7 NERVE COMPRESSION

The mechanisms proposed for the compression neuropathies formation are (a) repeated compression which leads to ischemia, edema formation in the subedoneurial space and the synovium and eventually fibrosis, (b) reduced nerve gliding and mechanical deformation due to scar tissue leading to and (c) localized mechanical pressure from structures such as the flexor retinaculum causing local nerve damage (Rempel & Diao, 2004; Dahlin et al. 1986). It has

been widely accepted that large myelinated nerve fibers are more vulnerable to the effects of nerve compression. Histological studies have shown thinning of myelin along degeneration and regeneration of fibers (Rempel et al. 1999; Mackinnon, 2002).

On the other hand, some animal studies as well as human studies have shown other additional findings (Tsuboy et al. 2007; Fern & Harrison, 1994). It has been implicated that in early stages of compression, the principle mechanism for nerve damage induction is decreased intraneural microvascular flow and ischemia (Tecchio et al. 2002). Ischemia causes impairment in fast and slow axonal transport. Animal studies have shown that thinly-myelinated and unmyelinated nerve fibers are more susceptible to the effects of nerve ischemia which occurs in the early stages of nerve compression (Fern & Harrison, 1994). This finding is in line with the patterns of symptom presentation in CTS in which patients tend to complain of numbness, tingling and pain in the early stages of CTS at a time when other sensory hand function such as vibration and tactile perception, which is transferred by large myelinated nerve fibers, and motor power are still preserved.

1.8 CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome (CTS) is a neuropathy caused by entrapment of the median nerve at the wrist, defined by the carpal bones and the transverse carpal ligament. CTS is the most frequent entrapment neuropathy, with

prevalence rates of 9.2% in women and 6% in men and 3.8% in general population (Alfonso et al. 2010; Uchiyama et al. 2010).

The median nerve arises by two roots, one from the lateral cord C5, C6 and C7 and the other from the medial cord C8 and T1 of the brachial plexus. It innervates the sensory and motor function of the thumb and second, third and the lateral aspect of the fourth digits. Median nerve's function is vital not only for the fine fractionated movements of the hand but also sensory feedback during hand movements.

Symptoms of CTS include dull aching discomfort in the hand or upper arm, hand paresthesia and weakness in the hand, accompanied by dry skin, swelling or color changes of the hand (Patijn et al. 2011). Patients complain of frequent awakening during the night with a sensation of swollen, numb hand. Some of them may report of severe pain in the wrist which can sometimes radiate to upper arm and shoulder as well (Jarvik et al. 2004). As the disease progresses motor deficit appears and the patient complain of hand weakness which can represent by dropping objects. In the final stages, atrophy of the thenar eminence occurs (Alfonso et al. 2010).

In early stages of CTS, patients complain of a lot of clinical symptoms such as burning pain, tingling and numbness. At present, the gold standard for the diagnosis of CTS is based on a combination of primary symptoms plus abnormal median nerve conduction studies. However, some believe that nerve conduction studies may confirm but not rule out the CTS and a number of

studies have failed to document a correlation between electrodiagnostic findings and the severity of CTS symptoms (Alfonso et al. 2010; Kilmer & Davis, 2002).

In a study done by Longstaff et al., no relationship was found between the nature or duration of pre-operative symptoms and the severity of the electrophysiological impairment. Furthermore, no relationship could be identified between preoperative nerve conduction studies and the outcome of the carpal tunnel release surgery (Longstaff et al. 2001). In another study done by Buch-Jaeger et al., nerve conduction studies were done on 112 patients with clinical symptoms of carpal tunnel syndrome, 60 of them bilaterally. In only 61% of these patients, the nerve conduction studies revealed positive results and in the remaining 39%, the results were negative (Buch-Jaeger &Foucher, 1994).

In the Italian multicenter study of CTS, which was done on 1123 hands with idiopathic CTS, results showed that the symptoms and pain scores decrease in CTS patients with paralysis of thenar muscles and in cases with extreme neurophysiologic impairment (Padua et al. 1999). Furthermore, CTS patients are usually advised to have the carpal tunnel surgery based on the results of nerve conduction study. However, some investigators have found that clinical symptoms do not correlate well with distal motor latency (DML), which is one of the important indexes used in nerve conduction studies to assess the severity of median nerve damage in CTS (Stevens, 1978).

In a randomized controlled trial, the relationship between the outcome measures for the severity of CTS patients symptoms and complaints and nerve conductions studies in patients treated for CTS, were investigated. Results

showed modest correlation (<0.4) between the neurophysiologic and clinical outcome measures (Schrijver et al. 2005).

One of the proposed reasons for this discrepancy between symptom severity and nerve conduction study findings is that electrodiagnostic studies only assess large myelinated nerve fibers which in median nerve represent only 50% of the total fibers of the nerve at the level of the carpal tunnel (Buch-Jaeger & Foucher, 1994). On the other hand, symptoms of pain and numbness, which make the patients seek medical attention, are conveyed by small myelinated and unmyelinated sensory fibers which cannot be examined by electrodiagnostic studies.

Though pain and tingling that bother the patients most is conveyed by small sensory fibers, they have not been adequately examined in CTS. The few investigations done in this area have shown the possibility of small sensory fiber involvement in CTS. A recent study done by Tamburin et al. indicated that Aδ-fibers are affected in milder stages of CTS (Tamburin et al. 2010). However, their study failed to show involvement of C-fibers in CTS. In another study, Westerman et al. showed that both warm and cold thermal thresholds were elevated in CTS patients that might suggest involvement of both Aδ and C-fibers (Westerman& Delany, 1991). However, they tested the skin of the thenar area that is innervated by palmar branch of median nerve, which does not pass through the carpal tunnel.

Nygaard et al. found impairment in the function of small sensory fibers in severe CTS which recovered rapidly after surgical decompression of the

median nerve. They concluded that since the function of small myelinated and unmyelinated fibers came back earlier than the large myelinated ones, the latter ones are more affected in CTS (Nygaard et al. 1996). On the other hand, in another study done by Lang et al., the function of small myelinated and unmyelinated fibers recovered more slowly than the large myelinated fibers, after the surgical decompression of the median nerve (Landg et al. 1995). The discrepancy between the findings of different studies could be due to different factors such as the area of the hand tested and the methods used to test the small sensory fibers.

1.9 QUANTITATIVE SENSORY TESTING

Although thermal and heat pain thresholds are not the only modalities conveyed by small sensory fibers, they provide a subjective means for evaluation of these fibers. They have been widely used in different studies and disease states which involve small sensory fibers such as diabetic neuropathy and neuropathic pain (Westerman& Delany, 1991; Nygaard et al. 1996; Backonja et al. 2009; Dyck et al. 1983; Jamal et al. 1985). Sensory nerve conduction studies can only evaluate large myelinated fibers. For this reason, tools have been designed to evaluate and quantify small sensory nerve functions, noninvasively (Siao & Cros, 2003).

1.9.1 BACKGROUND

One of the methods which have been used to assess the small sensory fibers is through examination of thermal and heat pain thresholds. One of the greatest barriers in investigating the temperature sensitivity of the skin has been technical limitation for controlling the condition of stimulation. Earlier methods involved dipping one or several of the extremities in water tanks which were maintained at constant temperatures. Investigators faced technical difficulties when trying these methods which some of them were changes in skin temperature because of the evaporation effects of air (Neff, 1970).

Other methods included mapping of the cold and warm spots of the skin with cylinders which were cooled or warmed by floating them in hot or cold water. Another method involved quantitative temperature stimulation of the skin by radiant energy (Neff, 1970). However, none of these methods provided a reliable and user-friendly method for determining the skin temperature sensitivity and thresholds.

One of the methods that made great progress in measuring skin thermosensitivity involved placing a thermode in constant contact with the skin. The temperature of the thermode was controlled by circulating water from various tanks. The temperature of the thermode was changed by switching from one tank to another. Later, this method was refined by using the Peltier principle to produce different thermal stimuli. According to this principle, when a direct current is passed through the junction of two conductors of different material, the junction will warm up or cool down, depending of the direction of the current flow. The

development of this method made it possible make precise measurements of the skin thermosesitivity (Neff, 1970). Later automated versions of these methods were developed which were run by computer software.

The first set of automated QST equipments was introduced by Fruhstorfer et al. They used the method of Marstock, which was later named the method of limits, to measure the thermal and heat pain thresholds in 100 patients with different central and peripheral neuropathies and compared the results with normal subjects. They concluded that the method and the QST machine is easy to apply, reliable and fast in determining the thermal thresholds (Fruhstorfer et al. 1976). Since then, different methods and equipment have been produced for measuring the thermal and heat pain thresholds.

Quantitative sensory testing (QST) refers to a broad range of psychophysical methods of stimulation which have been used for more than a century as the primary approach for the study of human somatic sensory physiology, including temperature and pain and perception (Backonjia et al. 2009). It consists of techniques used to measure the intensity of stimuli needed to produce specific sensory perception. The perception of thresholds to light touch or pressure, vibration, thermal (cold and warm) and pain may be measured with QST (Siao & Cros, 2003). The main goal of QST is to provide standardized stimuli to elicit a quantifiable level of response (Gruener & Dyck, 1994).

With the aid of QST, large myelinated nerve fibers are assessed with light touch and vibration testing and small myelinated and unmyelinated sensory nerve fibers are assessed with thermal and pain testing (Siao & Cros,

2003). Conventional sensory nerve conduction studies (NCS) evaluate the large myelinated nerve fibers and QST is one the only few methods which assess the small sensory fibers (Goadsby & Burke, 1994; Gruener & Dyck, 1994; Fruhstorfer et al. 1976).

1.9.2 METHODS

The availability of computerized QST equipments has allowed the use of detailed testing algorithms and has decreased sources of error. Several instruments and testing algorithms have been developed which would be discussed in the following sections.

1.9.2.1 METHOD OF LIMITS

The original Marstock method of determining thermal thresholds uses the method of limits. The thermal stimulator (thermode) is applied to the skin, and the temperature of the thermode is increased until the subject feels a warm sensation and gives a signal by pressing a button. This signal results in a reversal of the temperature change of the thermode (from warm to cold). The subject then gives another signal as soon as a cool sensation is perceived which would be the disappearance threshold. The second signal reverses the direction of temperature change again, leading to another cycle. After several cycles, the initial rises in threshold stabilize, allowing one to measure the thresholds (Siao & Cros, 2003). In this method warm and cold threshold are evaluated together. In the modified Marstock method, warm and cold threshold are assessed separately.

As soon as the subject perceives a warm or cool sensation, the button is pressed and the temperature of the thermode returns to baseline (Siao & Cros, 2003).

There are disadvantages in this method. Thermal threshold calculation by this method is dependent on the reaction time of the subject which could be a problem in older age individuals. The full cooperation and vigilance of the subject affect the variability of the results (Siao & Cros, 2003).

1.9.2.2 METHOD OF LEVELS

In this method stimuli of predetermined intensity are used and after each stimulus is presented, the subject is asked if she perceived the stimuli or not. The subject's response determines the next level of stimulus intensity (higher or lower). (Siao & Cros, 2003).In this method, reaction time is not a problem. However, the subject must be able to recognize the internal noise level in order to be able to recognize the external stimuli which could be sometimes confusing.

1.9.2.3 FORCED-CHOICE METHOD

In this method two time period are presented to the subject. However, only one of the two time periods contains the stimulus of the predetermined intensity. The subject then has to choose which time period contains the stimulus (first or second). Another force-choice method that has been described is called the spatial force-choice paradigm. The subject is presented with two stimulating probes with stimulus present at only one of them. The subject is asked to touch each probe and identify which one has the stimulus (Siao

& Cros, 2003). Although this method does not have the limitations of the previous methods and the subject does not need to remember the level of internal noise, some of the subjects find it challenging. The other disadvantage of this method is that it is time consuming (Siao & Cros, 2003).

1.9.2.4 4, 2 AND 1 STEPPING ALGORITHM WITH NULL STIMULI

This method was introduced by Dyck et al. as a faster method to estimate the thermal and pain threshold. In comparison to force-choice method, this test can be completed in a lesser amount of time and it does not have the limitations of the method if limits. It uses predetermined intensities with null stimuli in between. After each stimulus is presented to the subjects, they would indicate whether they have perceived the stimulus or not, by pressing a button (Siao & Cros, 2003). The full description of this method is explained the method chapter.

1.9.2.4.1 REPRODUCIBILTY OF THE 4, 2 AND 1 STEPPING ALGORITHM WITH NULL STIMULI

Although thermal QST is a psychophysical test and needs full concentration and cooperation of the patients, different studies have shown good reproducibility of the results. In a multicenter study done by Peltier et al, the results of the thermal QST had good reproducibility with intraclass correlation coefficient (ICC) of 0.81 (Peltier et al. 2009). In another multicenter study, the reproducibility of the thermal QST was high with ICC > 0.6 (Bird et al. 2006).

These findings indicate that with careful patient selection the limitations of QST could be overcome.

1.10 OBJECTIVES and HYPOTHESIS

The objective of the present study is to assess the involvement of small myelinated fibers in different stages of CTS. Our goal is to test the hypothesis that small sensory fibers in the median nerve are affected in mild stages of CTS with no involvement of small sensory fibers in the ulnar nerve.

CHAPTER 2. METHODS

2.1 DEMOGRAPHICS

The patient population consisted of 3 groups of CTS patients. They were recruited from 2 hospitals in Edmonton. The inclusion criteria for the CTS subjects are: 1) numbness and/or tingling or paresthesia in the median nerve distribution, 2) nocturnal awakening or sleep disturbance, 3) electrophysiological tests reveal median nerve compression, 4) normal ulnar nerve function, 5) good cognitive function and 6) willingness to participate in the study. The exclusion criteria are: 1) other coexisting serious medical or neurological conditions 2) additional injury to either the symptomatic arm or hand and 3) poor cognitive function.

The area of hand tested in patient group consisted of the distal phalanx of the 3^{rd} and 5^{th} digits of the affected hand in the patient group. The CTS subjects were categorized into 3 groups of mild, moderate and severe CTS. The categorization was based on NCS results. The NCS tests used to diagnose CTS which are according to the guidelines of the American Academy of Neurology, American Academy of Physical Medicine and Rehabilitation and American Academy of Electrodiagnostic Medicine (Jablecki et al. 2002). These included:

1. Distal motor latency (DML) (from the wrist to thenar eminence) of the median nerve.

2. Sensory nerve action potential (SNAP) of the median nerve

Categorizations of the CTS patients were done according to the following criteria (Padua et al. 1997):

1. Mild: Abnormal digit-wrist SNCV and normal DML.

2. Moderate: Abnormal digit-wrist SNCV and abnormal DML.

3. Severe: Absence of SNAP and abnormal DML.

The control group consisted of healthy, age-matched subjects with no evidence of CTS who were willing to participate in the study. The area of hand tested in this group consisted of the distal phalanx of the 3rd and 5th digits of their right hand.

2.2 THERMAL THRESHOLDS

Thermal thresholds including cold threshold (CT) and warm threshold (WT),were determined according to the 4, 2 and 1 stepping algorithm using CASE IV (WR Medical Electronics Co., USA) (Dyck et al. 1993). Cold and warm stimuli were delivered through a 30 × 30 mm² thermode attached snugly to the skin of palmar surface of the distal phalanx of the 3rd and 5th digit. All the patients were fully instructed about the procedure before the test.

For the CT, stimulus temperature ranges from 29.937 C° (level 1) to 9 C° (level 25) were used. For the WT, the temperature ranges were between 34.032 C° (level 1) and 44 C° (level 21). “The testing began at an intermediate

level (level 13). The stimulus was increased (if not felt) or decreased (if felt) by four steps to the point of first turnaround. Then stepping continued in steps of two. After the second turnaround, stepping was by steps of one. A total of 20 stimuli were used, with 5 of them being randomly distributed null stimuli. For cool pulses, temperature of the thermode decreased from the skin temperature to a predetermined lower level, and then returned to the baseline temperature. For a warm pulse, the thermode temperature increased, and then decreased. The threshold was calculated as the mean of the turnaround levels arrived at by single stepping" (Dyck et al. 1993).

2.3 HEAT PAIN THRESHOLD

The heat pain threshold was assessed according to the "non-repeating ascending with null stimuli" (NRA-NS) protocol using the CASE IV (WR Medical Electronics Co., Minniapolis, Minnesota, USA) (Dyck et al. 1996). Heat stimuli were delivered through the 30 × 30 mm^2 thermode attached snugly to the skin of palmar surface of the distal phalanx of the 3^{rd} and 5^{th} digit. The temperature range used for the heat pain was from 35.401 C° (level 13) and 49 C° (level 25).

"The stimulus began at an intermediate level (level 13) and increased by steps of 2 until level 21 or a ≥1 pain response, and then increased by single steps until a ≥5 pain response was attained or step 25 was tested (whichever came first). Only a single heat pulse was given for each stimulus step between

pain responses 1 and ≥5. After each stimulus event, the subject was asked to report whether the stimulus was felt as warm or hot but was without pain (0 response) or was associated with discomfort or pain (judged as 1 [least] to 10 [greatest]). In each sequence of three stimuli, one was randomly selected to be a null stimulus. The heat pain threshold consisted of intermediate heat pain level (HP5.0) which was the heat pain level for an answer of 5 or more" (Dyck et al. 1996).

2.4 LEVINE'S SELF-ASSESSMEN QUESTIONAIRE

Patients with CTS confirmed by the nerve conduction studies were asked to fill out this questionnaire which assesses the severity of symptoms and functional status in patients with CTS. The reproducibility and validity have been already evaluated and confirmed (Levine et al. 1993). The test consists of 19 questions inquiring about common CTS symptoms as well as functional impairments associated with CTS. Each question is scored on a Likert scale ranging from 1 to 5, with 5 being the most severe. The total score was used on this questionnaire to classify the severity of CTS: (a) mild, score of 20-38; (b) moderate, score of 39-57; and (c) severe, score of ≥58 (Amirjani et al. 2011).

2.5 STATISTICAL TESTING AND ANALYSIS

Cold and warm perception and heat pain thresholds were compared between CTS patients and control groups using one-way ANOVA. $P<0.05$ was considered significant. Thresholds are given as mean temperature (°C) ± standard deviation (SD). All statistical analyses were performed using the SPSS software (18.1) and GraphPad Prism Software (5.02).

CHAPTER 3. RESULTS

3.1 DEMOGRAPHICS

A total of 44 healthy normal subjects without any sign or symptoms of the CTS with the mean age of 50.5±13.1 were recruited for the control group. 23 of them were female and 21 were male. 2 of the control subjects were excluded from the study due to exclusion criteria. 58 CTS patients were recruited for the patient group with the mean age of 51.8 ±15.5. Thirty five of them were female and 23 were male. For the first part of the analysis, CTS patients were categorized according to their electrodiagnostic results into mild, moderate and severe groups. The mild, moderate and severe CTS groups included 25, 16 and 17 subjects, respectively (Table 3).

Subjects	CTS	Mild CTS	Mod. CTS	Severe CTS	Control
Number	58	25	16	17	44
Age (mean±SD)	51.8 ±15.5	47.1±13.5	52.6±14.2	59.4±13.6	50.5±13.1
Female	35	18	12	6	23
Male	23	7	4	11	21

Table 3. Demographics of the CTS patients categorized based on their NCS result.

3.2 COLD THRESHOLD

The cold threshold (CT) of the middle finger (D3) was compared between the CTS group and the control group. Mean of the CT of D3 was significantly lower in the severe group (17.5±7.7 °C), compared to the control group (27.1±2.1°C), meaning that they recognized lower temperatures as being cold compared to control subjects. Although, the same pattern was seen for the mild and moderate groups as well, the difference between the mean of mild (24.2 ± 4.5 °C) and moderate CTS (24.5±4.7 °C) and control subjects did not show any significance (Fig2).

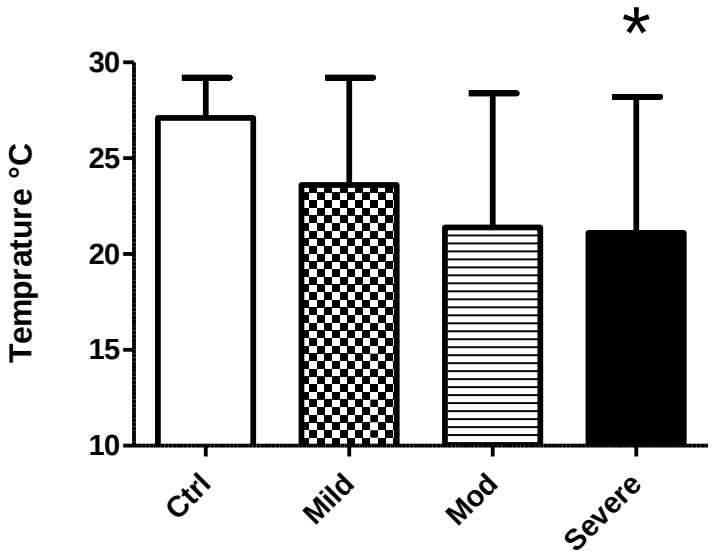

Fig2. CT of D3 of the CTS vs. Control (mean±SD)

The CT of the little finger (D5) was not significantly different in the mild group (23.9±4.8 °C) compared to the control group (25.5±4.1 °C). This holds true for the CT of the little finger between the moderate (25.7±2.9 °C), as well (Fig3). However, comparing the means for the severe groups (20.4±7.1 °C) and the control group (25.5±4.1 °C) showed significant difference in their mean threshold.

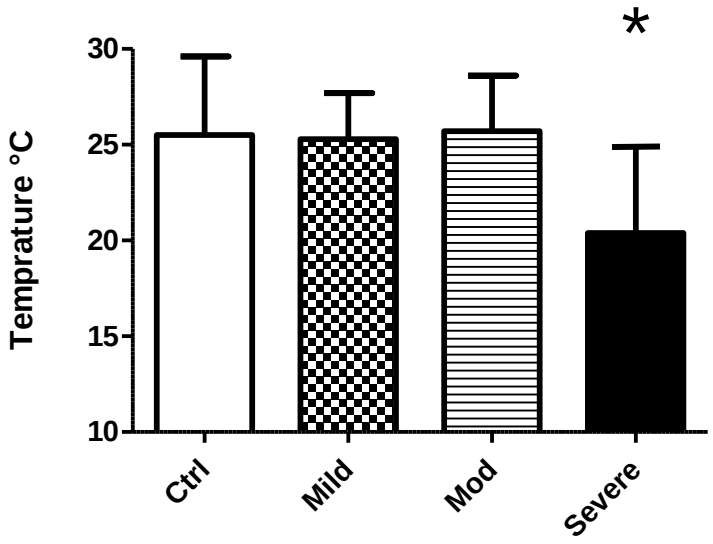

Fig3. CT of D5 of the CTS vs. Control (mean±SD)

3.3 WARM THRESHOLD

Warm threshold (WT) of D3 was significantly higher in the severe CTS group (41.2±3.5 °C) control group (37.1±2.1 °C), ($p<0.05$). However, the mean threshold of warmth was not significantly different in the mild (38.7±3.3 °C) and moderate group (38.7±3.2 C°) compared to control, (Fig4).

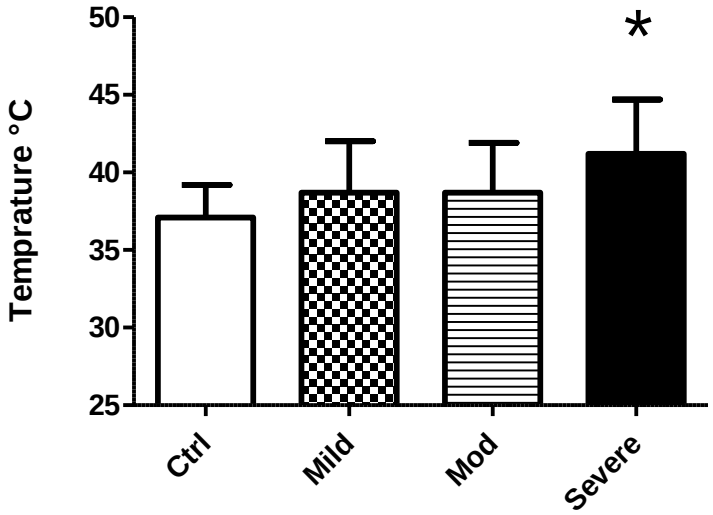

Fig4. WT of D3 of the CTS vs. Control (mean±SD)

WT of D5 was compared between the mild CTS group (38.7±3.4 °C) and the control group (37.2±2.1 °C). The mean threshold was not significantly different between the two groups ($p<0.05$). However, the WT of D5 was significantly higher in moderate (39.7±3.1 °C) and severe CTS patients (40.2±2.1 °C) compared to the control group (37.2±2.1 °C), (Fig5).

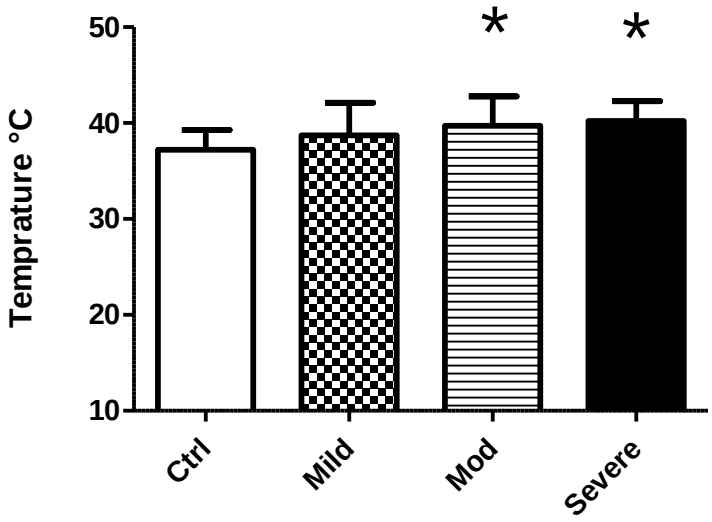

Fig5. WT of D5 of the CTS vs. Control (mean±SD)

3.4 HEAT PAIN THRESHOLD

Analysis of heat pain threshold is based on JND or just noticeable difference which is the smallest detectable difference between the starting and secondary level of heat pain stimulus. For safety issues, the equipment does not increase the temperature beyond after level 21 JND. So in order to induce heat pain in subjects without increasing the temperature, stimulus is applied over a longer period of time. However, this could cause a problem when trying to analyze the results since temperature is the same (45 °C) between level 21 and 25. However, the subjects have different experience of heat pain in each of these levels. Thus, JND was used for the sake of analysis.

HPT of D3 of the CTS affected hand was assessed between the different CTS groups who were defined according to the CTS severity and compared with the mean HPT of D3 of right hand of healthy control subjects. Comparing the mean for the HPT between the mild CTS patients i.e. mild (18.4±2.4 JND), and moderate (18.5±2.6 JND) and severe (21.5±7.3 JND) vs. control group (18.7±1.4 JND), did not reveal any significant difference, (Fig6).

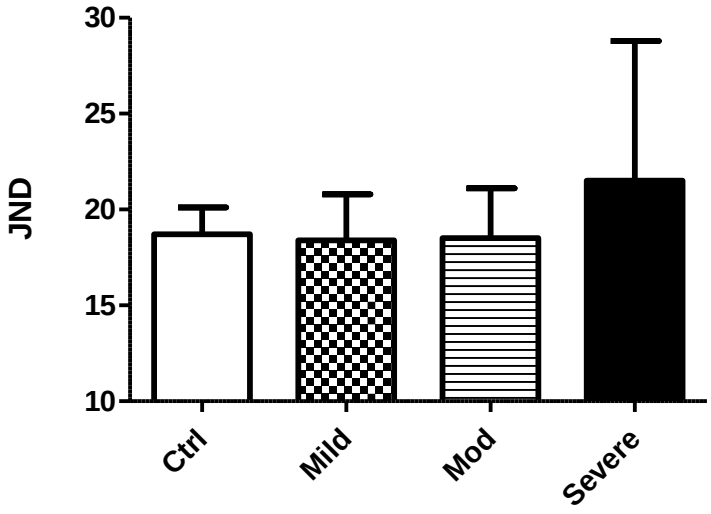

Fig6. HPT of D3 of the CTS vs. Control (mean±SD)

Comparing the HPT of D5 of the mild CTS group (17.9±3.1 JND), moderate (18.5±2.4 JND) and severe CTS patients (18.5±2.4 JND) were not significantly different from the control healthy subjects (19.1±2.1 JND), ($p<0.05$), (Fig7).

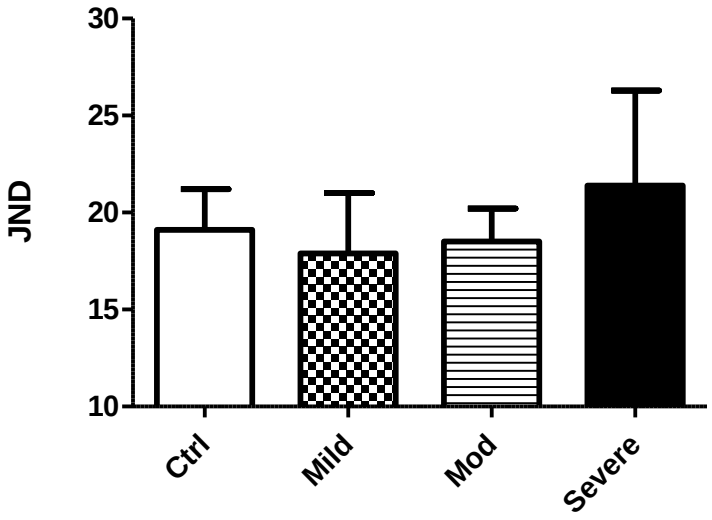

Fig7. HPT of D5 of the CTS vs. Control (mean±SD)

3.5 ANALYSIS BASED ON CLINICAL AND FUNCTIONAL STATUS

We categorized the CTS patients based on their clinical symptoms and functional status which was done based on the scores got on the Levine's questionnaire and then performed analysis of the thermal and heat pain perception thresholds.51CTS patients filled in the Questionnaire and 14 of them fell into the mild group, 25 in the moderate CTS and 12 in the severe CTS group, (Table 4).

Recategorizing the CTS subjects resulted in 14 mild subjects (categorized according to NCS) to fit into moderate group based on questionnaire score, 3 moderate CTS subject to change their group to severe and 3 to mild. From the severe group, 10 subjects were recategorized into moderate group and 2 to mild group.

CTS patients	*Mild*	*Moderate*	*Severe*
Number	*14*	*25*	*12*

Table 4. Demographics of CTS patients categorized based on Levine's questionnaire.

3.6 COLD THRESHOLD

Comparing the means of CT of D3 between the moderate CTS group (21.4±7.0 °C) and the control subjects showed significant results. The same results were reached for the severe CTS (21.1±7.1 °C) group, too. However, the mean threshold of mild CTS group (23.6±5.6 °C) was not significantly different from the control subjects. Nevertheless, a pattern was seen for mild CTS subjects having higher thresholds for warmth, (Fig8)

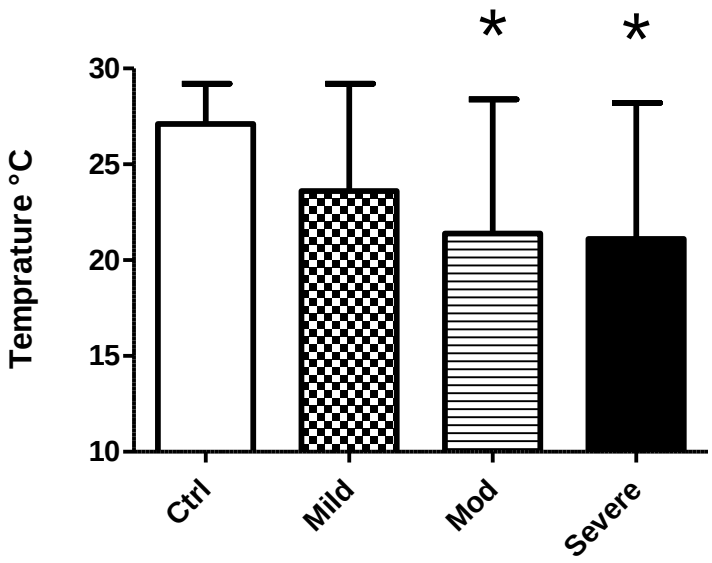

Fig8. CT of D3 of the CTS patients categorized based on their symptoms (CTS-Q) vs. Control (mean±SD)

Comparing the CT of D5 between the mild CTS group (22.4±7.4 °C) and the control subjects (25.5±4.1 °C) did not show any significant difference ($p < 0.05$). The same pattern was seen for the moderate (23.6±5.3 °C) and severe CTS group (21.9±5.7 °C), as well, (Fig9).

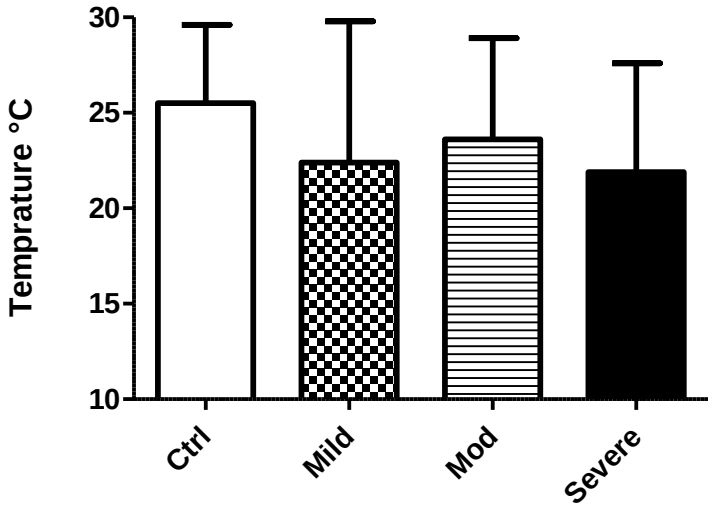

Fig9. CT of D5 of the CTS vs. Control (mean±SD)

3.7 WARM THRESHOLD

WT of D3 was not significantly higher in the mild CTS group (38.1±3.6 °C) compared to the control group (37.1±2.1 °C). This was true for the WT of the severe CTS group (38.3±2.1 °C), well. However, WT of the D3 in the moderate CTS group (39.5±3.6 °C) was significantly higher compared to the control group (37.1±2.1°C), (Fig10).

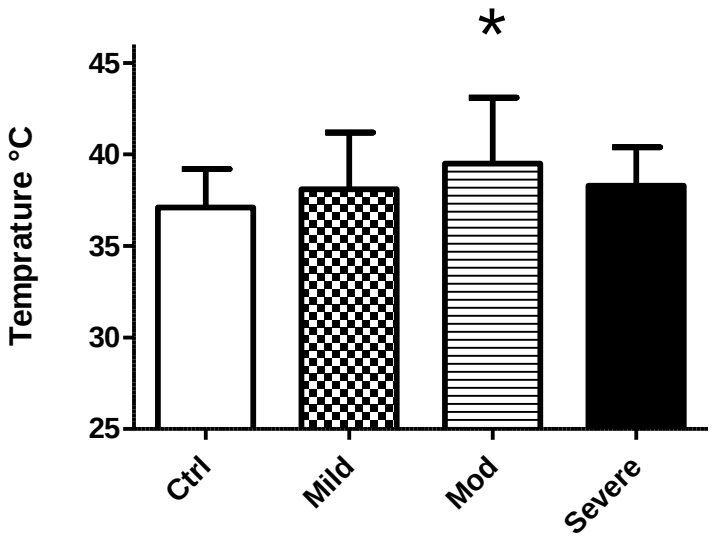

Fig10. WT of the D3 of the CTS vs. Control (mean±SD)

Comparing WT of the D5 between the CTS group and control subjects showed significant results between the mean threshold of the moderate CTS group (39.8±3.5 °C) and control subjects (37.2±2.1 °C). However, WT of the D5 was not significantly different in mild (39.8±4.1 °C) and severe CTS groups (37.8±1.8 °C), compared to the control group (37.2±2.1 °C), (Fig11).

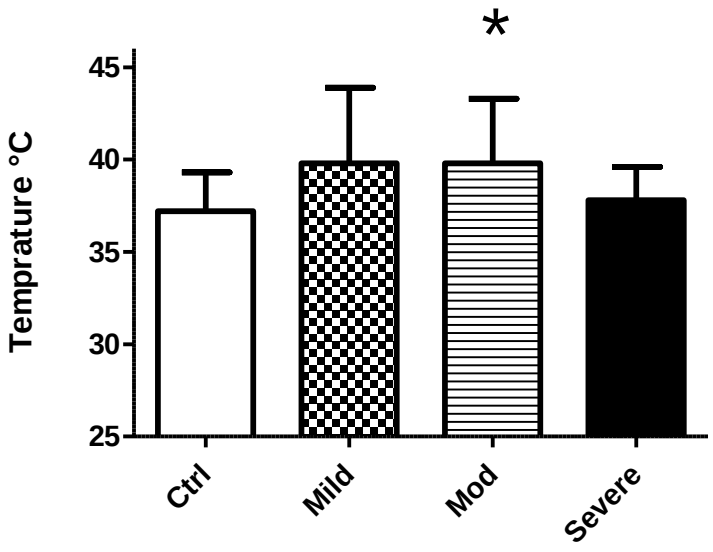

Fig11. WT of D5 of the CTS vs. Control (mean±SD)

3.8 HEAT PAIN THRSHOLD

HPT of D3 of the CTS affected hand was assessed between the different CTS groups and control subjects. The mean of HPT was not significantly different between any of the CTS groups, i.e. mild (18.1±2.5 JND), moderate (20.2±3.0 JND) and severe (20.7±4.3 JND) compared to control subjects (18.7±2.4 JND), (Fig12).

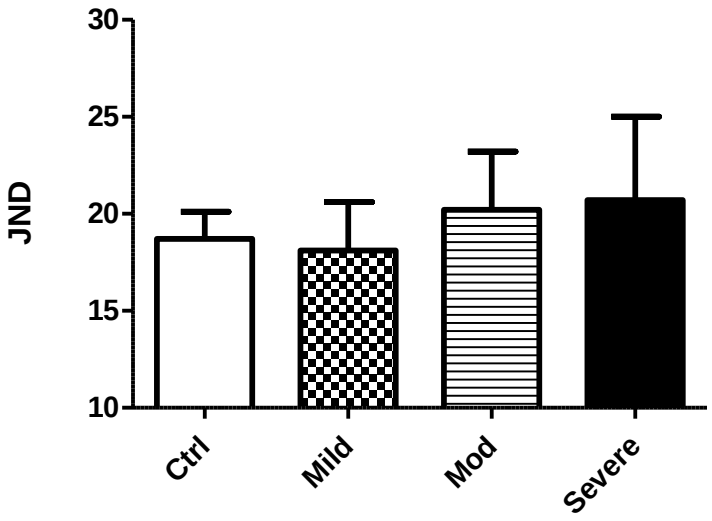

Fig12. HPT of D3 of the CTS vs. Control (mean±SD)

Comparing the HPT of the D5 of the mild CTS group (19.0±3.4 JND), moderate (19.6±4.4 JND) and severe CTS patients (21.1±6.2 JND) were not significantly different from the control healthy subjects (19.1±2.1 JND), ($p<0.05$), (Fig13).

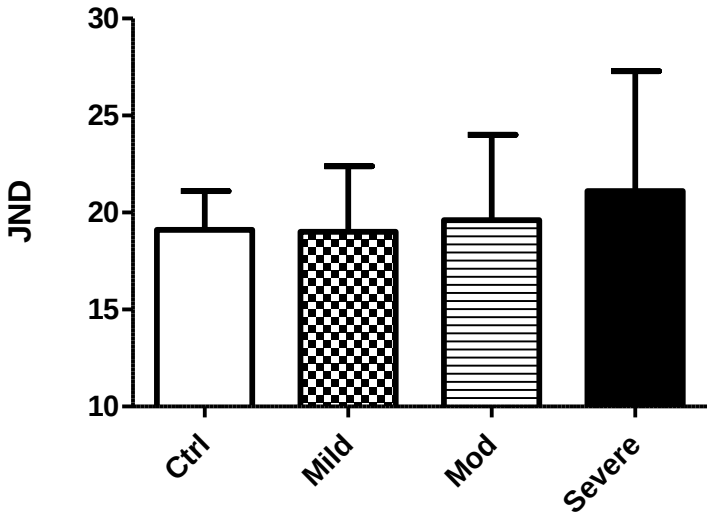

Fig13. HPT of D3 of the CTS vs. Control (mean±SD)

CHAPTER 4. DISCUSSION AND CONCLUSION

4.1 DISCUSSION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. It is generally thought that large myelinated nerve fibers are the ones most vulnerable to peripheral nerve entrapment and small sensory nerve fibers are not affected till later stages of the disease. However, there are many CTS patients with only mild large myelinated nerve involvement but yet complain of a lot of pain, numbness and decreased hand function. One of the potential reasons for this discrepancy is that nerve conduction studies only evaluate large myelinated fibers and the small sensory fibers which convey numbness, pain and tingling are left un-assessed.

We assessed the small sensory nerve fibers of the median nerve in CTS patients who had different stages of nerve damage and compared them with healthy age-matched control subjects. The assessments were done with quantitative sensory testing (QST). The evaluated sensations were cold and warm thresholds and heat pain threshold.

4.1.1 THERMAL THRESHOLDS

The cold thresholds (CT) of the middle finger of the three CTS groups were impaired compared to the control subjects. The extent of impairment is most marked in the severe CTS group and is the least in the mild group. The same results were achieved when categorizing the CTS patients according to their symptoms and functional impairment scores. The warm perception threshold (WT) was also significantly higher in moderate and severe stages of CTS patients compared to control group.

However, when categorizing the CTS patients according to the Levine's questionnaire score, only the moderate CTS group showed significant difference for the WT compared to the control. One possibility for this discrepancy may be due to the small number of subjects in the mild and severe CTS groups. A second possibility is that the C-fibers are not affected in mild and severe CTS. However, this looks unlikely since HPT, which are also conveyed by c fibers are affected in all severe CTS groups. The third possibility is that the Levine's questionnaire only evaluates symptoms that the patients have experienced in the past two weeks. Given the represented time slot is very short, there is a possibility that the questionnaire's score does not correctly represent the degree of median nerve damage.

Cold and warm sensations are conveyed by Aδ and C nerve fibers, respectively. Aδ fibers are thinly myelinated and C-fibers are unmyelinated nerve fibers. The findings of the present study indicate that small sensory nerve fibers

seem to be affected in early stages of the nerve entrapment. Assessments of thermal thresholds are not part of evaluation of CTS patients at this time. However, it has been suggested by the American Academy of Neurology that it is potentially useful for assessment of sensory impairment in clinical and research scenarios (Shy et al. 2003).

Previous studies have shown that during the compression of peripheral nerves, gradual demyelination followed by remyelination occurs, mostly in the large myelinated nerve fibers (Pham & Gupta, 2009). Some studies have shown that the large myelinated nerve fibers size is decreased in CTS. In contrast, light microscopy failed to show involvement of the small myelinated and unmyelinated nerve fibers. On that basis, it was concluded that those afferents are not affected by nerve compression. However, this conclusion may not be justified as nerve fiber involvement in CTS has not been evaluated by the electron microscopy that could provide valuable information over and above that from light microscopy. For example, studies on lumbar nerve root compression have shown changes in the synapses of the small sensory nerve fibres that could not be detected by light microscopy (Kobayshi et al. 2008).

Furthermore, molecular histopathologic studies done by Frieboes et al. have shown selected sensitization of Aδ and C fibers in early stages of nerve compression. This sensitization was not seen in Aβ fibers. Their findings also showed that the pattern of pain generation in compressive neuropathies is not similar to neuropathic pain production (Frieboes et al. 2010). Those are potential

mechanisms that could potentially explain why small sensory nerve fibres are also, or even more, vulnerable to chronic nerve compression.

Our findings are in line with some previous findings. In the study done by Tamburin et al., they found Aδ and C fiber involvement in electrodiagnositcally negative CTS patients. Their findings also suggested that small sensory fibers might be affected earlier than large myelinated nerve fibers in CTS (Tamburin et al. 2010). Arendt-Nielsen examined the thin myelinated nerve fibers in CTS patients using argon laser stimulation and measuring the brain response potentials. They found no correlation between the measured parameters and the electrodiagnostic findings and concluded that chronic low force compression can affect the thinly myelinated nerve fibers (Arendt-Nielsen et al. 1991).

4.1.2 HEAT PAIN THRESHOLDS

Heat pain threshold (HPT) was significantly different in severe CTS groups compared to the control group. The severe CTS subjects perceived higher temperatures as being painful compared to controls. In other words, these subjects were hypoalgesic to heat pain. The mild and moderate CTS groups did not have any significant difference in pain perception thresholds compared to the control group.

When categorizing the CTS subjects based on their symptoms and functional score, no significant difference was found between the CTS group and controls.

The findings of this study show that C-fibers might be affected in mild and moderate stages of CTS. On the other hand, analysis of the HPT showed that C-fibers could be just affected severe stages of CTS or not affected at all. These differing findings may be explained on the following rationale.

One of the other reasons could be technical limitations. Assessment of pain perception and personal experience of pain could only be done by self-reported ratings. During the heat pain assessment experiments, before the predetermined thermal stimuli are presented to the participants, they are instructed to rate their pain perception based on a numeric rating scale (NRS), i.e. on a scale of 1 to 10 based on its severity. However, there have been reservations whether NRS can indeed provide an accurate measurement of pain perception (Fraenkel et al. 2011).

Although the type of nerves that transfer WT and HPT are both C-fibers, the receptors responsible for generating action potentials for warmth perception and heat pain are different. Receptors for warmth perception include transient receptor potential vanilloid 3 (TRPV3) and TRPV4. On the other hand, TRPV1 and TRPV2 are the receptors responsible for transmission of heat pain (Schepers & Ringkamp, 2010). This difference for the type of thermoreceptors

found on C fibers could be one of the underlying factors for the contrasting findings between warm perception and heat pain perception.

Unlike other sensations, the perception of pain is not just dependent on the strength of the stimuli. The pain experience starts by noxious stimulus exciting the nociceptors but does not end there. It can also be affected by other factors such as patient's background culture, level of anxiety, perceived control of pain and expectations for pain relief (McGrath, 1983). Furthermore, pain perception goes through extensive modulation and modification in the higher subcortical and cortical levels which can affect individual experience of pain, irrespective of their degree of peripheral nerve damage (Apkarian et al. 2005; Millan, 1999). Also, different neurotransmitters such as serotonergic and noradrenergic systems take part in the modulation of pain perception. This central transformation of pain perception can be another explanation for the discrepancy found in the C fiber damage based on WT and HPT analysis.

Our findings are line with some of the previous findings in this area. In a study done by Lang et al., they showed that both warm/cold perception threshold and heat/cold pain thresholds were elevated in CTS patients (Lang et al. 1995). However, they did not categorize the patients based on the extent of the nerve damage.

Based on the above arguments, we conclude that heat pain is not the best method for assessment of unmyelinated nerve fibers because the patients' perception of pain can be different to the noxious stimuli due to many reasons

including those presented in the previous paragraphs. A better assessment of c-fibers would be by evaluation of warmth perception threshold.

4.1.3 THERMAL AND HEAT PAIN THRESHOLDS OF LITTLE FINGER

The result of the present study, showed abnormalities in the function of the little finger of some CTS groups compared to the control subjects. Since most of the CTS patients have bilateral CTS symptoms, we chose the 5th digit as the internal control for the abnormalities found on the 3rd digit. There could be several explanations for the abnormal thermal and heat pain thresholds found in the little finger.

An argument could be that the abnormalities are probably not related to the peripheral nerves, in this case median and ulnar nerves, and be more related to changes in the central nervous system. It has been shown that in CTS patients the cortical map of median nerve sensory territory becomes smaller and it is invaded by sensory territories of other peripheral nerves such as ulnar nerve innervating the little finger (Tecchio et al. 2002). This may affect perception of sensory stimuli within other peripheral nerve territories. This could potentially explain some of the abnormal findings found in thermal and pain perception of the 5th digit.

A third possibility could be a subclinical neuropathy in the ulnar nerve which is usually found in CTS. Recovery in the function of ulnar nerve has been seen after CTS release surgery (Ginanneschi et al. 2010). However, all of

our subjects had normal function of ulnar nerve, as assessed by electrodiagnostic studies. Lastly, the abnormal findings of the little finger could potentially be due to technical limitations. Further exploration of this issue may involve using two different thermodes with different surface areas for testing of middle finger and little finger. Another way for addressing this problem could be recruiting subjects who have exclusively unilateral CTS and using the middle finger of their normal hand as an internal control.

4.1.4 PATHOPHYSIOLOGIC MECHANISM OF SMALL SENOSRY FIBER DAMAGE

The mechanisms proposed for compressive neuropathies are: (a) repeated compression which leads to ischemia, edema formation in the subendoneurial space and eventually fibrosis, (b) reduced nerve gliding and mechanical deformation due to scar tissue leading to and (c) local nerve damage as a result of localized mechanical pressure (Rempel & Diao, 2004).

It has been widely noted that large myelinated nerve fibers are more vulnerable to the effects of nerve compression. Histological studies have shown thinning of myelin along degeneration and regeneration of fibers (Rempel et al. 1999). On the other hand, some animal studies as well as human studies have shown different findings (Tsuboya et al. 2007; Fern & Harrison, 1994). It has been implicated that in early stages of compression, the principle mechanism for nerve damage induction is impaired vascular flow and ischemia (Tecchio et al.

2002). Ischemia causes impairment in fast and slow axonal transport and affects the nerve function. Animal studies have shown that thin myelinated and unmyelinated nerve fibers are more susceptible to the effects of nerve ischemia which occurs in the early stages of nerve compression (Fern & Harrison, 1994). The results of this study are applicable to all entrapment neuropathies since the pathophysiological mechanism responsible for their development follow the same rule.

4.2 CONCLUSION

The results of the present study show that the small myelinated and unmyelinated sensory nerve fibers seem to be affected in early stages of the entrapment neuropathies such as carpal tunnel syndrome. However, we cannot surely rule out the central origin of the disturbance in thermal and heat pain threshold in this project. Further experiments using fMRI or sensory evoked potentials would be helpful in this regard. It also suggests that nerve conduction studies cannot fully show the extent of nerve damage in these neuropathies. We suggest that assessment of small sensory nerve fibers should be considered as an essential part of evaluations of CTS patients in the clinical setting and also in the management plan, as well.

4.3 LIMITATIONS

The most important limitation of this study was subject recruitment. The other limitation is that results of the QST are dependent on the subject's concentration and motivation. We tried to address this limitation by choosing subjects who are fully alert and are not suffering from dementia or decreased concentration. Besides, all the subjects were given full instruction about the test and the instructions were repeated during the test as well.

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