ZHIYONG MING

Upper Limb Musculoskeletal Disorders

With Special Reference to Sympathetic Nerve Functions and Tactile Sensation

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium ML2, Medistudia building, University of Kuopio, on Friday 13th April 2007, at 12 noon

Institute of Biomedicine
Department of Physiology
University of Kuopio

KUOPION YLIOPISTON JULKAISUJA D. LÄÄKETIEDE 405
KUOPIO UNIVERSITY PUBLICATIONS D. MEDICAL SCIENCES 405
ABSTRACT

The aims of the present series of studies were to clarify peripheral neural disturbances placing a special emphasis on sympathetic functions and tactile sensation in the upper limb musculoskeletal disorders (ULMSDs).

This research consisted four individual studies: 1) Examination of the possible abnormalities in the temperature of the CTS hands; 2) Follow up studies of carpal tunnel release (CTR) by using digital infrared thermography (DIRT) 3) The responses to a cold provocation test in CTS hands; 4) To explore the sympathetic and sensory nerve pathology in non-specific neck and shoulder pain (NS-NSP) by using DIRT, skin evaporation and tactile threshold measurements.

The main findings of these studies were: 1) in the hands of CTS suffers, the skin temperature in the median nerve distribution area was significantly different (higher in mild cases and lower in severe cases) from innervated by the ulnar nerve. In the CTS hands of the CTR group, the temperature of median nerve distribution area was disturbed before the operation, but it had recovered when the measurements were performed six months after the CTR; 2) At the start of the cold provocation test, the whole hand of the healthy subjects became colder but subsequently, the hands became even warmer than before the test. However, in the distribution area of the median nerve of the hands in CTS subjects, this reaction was delayed or even totally absent; 3) In the hands of the NS-NSP subjects, the finger tip temperature and the skin surface evaporation were lower and the tactile thresholds were higher compared to the healthy hands.

These findings indicate that: 1) the dysfunction in the regulation of the local circulation in the territory of the affected nerves in the ULMSDs e.g. in CTS and NS-NSP, may play an important role in the pathophysiology of the condition; 2) dysfunction of SNS and tactile sensation may develop before there are any structural changes in the ULMSDs to be detected by X-Ray, CT, MRI or ultrasonography; 3) Reflex vaso-regulatory responses via central nervous system (CNS) may also be activated since abnormalities in the recorded measures were also obtained outside the territory of the affected nerve; 4) DIRT, skin evaporation and tactile threshold measurements are seem to be useful in the examination of the altered neural function in the ULMSDs and in the follow-up of the development as well as its recovery.

National Library of Medicine Classification: WE 140, WE 708, WE 805, WL 102.5, WL 500, WL 610, WN 205, WR 102

Medical Subject Headings: Carpal Tunnel Syndrome; Musculoskeletal Diseases; Neck Pain; Neural Conduction; Peripheral Nervous System Diseases; Shoulder Pain; Skin Temperature; Sympathetic Nervous System; Thermography; Upper Extremity
To my wife Ping An and my son Lang Ming
ACKNOWLEDGEMENTS

This study was performed in the Department of Physiology, University of Kuopio, the Department of Clinical Neurophysiology, Kajaani Central Hospital and the Department of Hand Surgery, Kuopio University Hospital during the year 2003 - 2006

First of all, I would like to thank all of the people who have participated in this study for their support.

I wish to express my deepest gratitude to my supervisor, Prof. Osmo Hänninen, D. M. Sc. PhD, for his excellent supervision, encouragement, constructive criticism of my study and his very thoughtful support both in my studies and my personal life during these years.

I am most grateful to my supervisor, Prof. Matti Närhi, D.D.S., Ph.D., for his excellent supervision, encouragement, constructive criticism of my work and his very thoughtful support both in my professional and personal life during these years.

I owe my special thanks to my supervisor, Chief Physician Jouko Siivola, M.D., Ph.D. for his advice in clinical neurophysiology and his support and help in collecting the subjects of the study.

I am very grateful to Prof. Panu Vilkki, M.D., PhD. and Docent Veikko Häkkinen, M.D., Ph.D., the official reviewers of my thesis, for their constructive comments and suggestions for improving the manuscript.

I owe my deep gratitude to Dr. Seppo Pietikäinen, M.D. and Prof. Olavi Airaksinen, M.D., Ph.D. for their crucial collaboration, advice, and guidance during these years and help in collecting the subjects of the study. I also owe my gratitude to Mrs. Arja Pietikäinen, Dr. Seppo Pietikainen's wife, for her encouragement and help both in my study and my personal life during these years.

I am deeply grateful to my co-authors Docent Unto Nuosiainen, M.D., Ph.D., Mrs. Nina Zaproudina, M.D. and Ms. Hanna Parkkinen, M.B., for their collaboration and advice.

I owe special thanks to Mr. Hannu Harmonen, laboratory engineer, Mrs. Taina Vihavainen, chief laboratory technician, Mrs. Orvokki Pääkkonen and Mr. Sami Pääkkonen for their technical support. I also owe many thanks to Dr. Jouni Nuutinen, from Delfin Technologies Oy, for his technical support and providing the device for skin evaporation measurements.

I want to thank Dr. Ewen MacDonald, Pharm. D., for revising the language of this thesis.

Finally, I want to thank my dearest ones: My wife Ping An for her love and support through so many years, and our son Lang Ming for showing me what is really important in life. I also want to thank my parents, Kun Ming and Xiangyun Xu, my parents-in-law, Liangchuan An and Jucui Zhang, my relatives and all my friends for their encouragement and support.

Kuopio, March 2007

Zhiyong Ming
ABBREVIATIONS:

CGRP: calcitonin gene-related peptide
CNS: central nervous system
CT: computerized tomography
CTR: carpal tunnel release
CTS: carpal tunnel syndrome;
DIRT: digital infrared thermography;
EMG: electromyography
ENMG: electromyography and nerve conduction studies.
IR: infrared
IRT: infrared thermography
LBP: low back pain
MCV: motor conduction velocity
MRI: magnetic resonance imaging
MSD: musculoskeletal disorders
NCS: nerve conduction studies
NCV: nerve conduction velocity
NGF: nerve growth factor
NMDA: N-methyl-D-aspartate
NS: nervous system
NSP: neck and shoulder pain
NS-NSP: non-specific neck and shoulder pain
SCV: sensory conduct velocity
SNS: sympathetic nervous system
TCAs: tricyclic antidepressants
ULMSDs: upper limb musculoskeletal disorders
VDU: visual display unit
TABLE OF CONTENTS

1. INTRODUCTION ............................................................................................................................ 13
2. LITERATURE REVIEW .................................................................................................................. 16
  2.1 Epidemiology of Upper Limb Musculoskeletal Disorders ......................................................... 16
  2.2 Classification of Upper Limb Musculoskeletal Disorders ......................................................... 17
    Carpal Tunnel Syndrome ............................................................................................................ 19
    Ulnar Nerve Paralysis ................................................................................................................ 21
    Radial Nerve Entrapment ............................................................................................................ 22
    Cervical Vertebrae Spondylosis ................................................................................................. 23
    Non-Specific Neck & Shoulder Pain .......................................................................................... 24
  2.3 Pain and ULMSDs .................................................................................................................... 25
  2.4 Sympathetic Nervous System and ULMSDs ........................................................................... 27
  2.5 Risk Factors of ULMSDs ......................................................................................................... 29
    Work related risk factors of ULMSDs ....................................................................................... 30
    Environment, personal characteristics and psychological factors ............................................. 33
  2.6 Pathophysiology of ULMSDs ................................................................................................. 34
    Muscle Injury .............................................................................................................................. 34
    Tendon (sheath) Injury ............................................................................................................... 35
    Nerve Injury ................................................................................................................................ 36
    Joint injury .................................................................................................................................... 38
  2.7 Clinical Manifestations of ULMSDs ....................................................................................... 38
  2.8 Diagnosis of ULMSDs ............................................................................................................ 39
  2.9 Treatments and Prevention ..................................................................................................... 41
3. AIMS OF THE STUDY ................................................................................................................. 44
4. SUBJECTS AND METHODS ....................................................................................................... 45
  4.1 Subjects ..................................................................................................................................... 45
  4.2 Methods .................................................................................................................................... 47
    Subjective Symptoms ............................................................................................................... 47
    Nerve Conduction Studies (NCS): ............................................................................................ 47
1. INTRODUCTION

The upper limb musculoskeletal disorders (ULMDSs) include a variety of musculoskeletal problems and peripheral neural deficits (especially neck shoulder pain (NSP) and carpal tunnel syndrome (CTS)) (Silman and Newman 1996; Hutson 1997). This problems are relatively common in the general population already today and will most probably be even more common in the future e.g. due to the increase in the use of computers and vibrating tools (Mody and Woolf 2003). The conditions that can create a risk suffering from these disorders include: too frequent repetitive monotonic movements, exertion of too much force, awkward working positions, working too long without breaks, adverse working environment e.g. hot, cold, and psychosocial factors e.g. high demands, too tight time schedules and lack of control. (Gomzi 1994; Kuorinka and Forcier 1995; Ranney, Wells et al. 1995; Yassi 2000)

The pathophysiology of the ULMSDs is still largely unclear (Barr, Barbe et al. 2004). Step by step the risk factors will cause dysfunction and damage muscles, tendons, peripheral nerves, and joints. X-ray, electromyography and nerve conduction studies (ENMG), computerized tomography (CT) and magnetic resonance imaging (MRI) are commonly used to study and confirm the diagnosis of ULMSDs. The X-ray, CT and MRI are useful for studies of the affected structures and ENMG can reveal the possible changes in the electrical activity of the muscles and nerves. In many patients, the results of all these measurements are, however, within the normal limits even when the individuals experience considerable clinical symptoms. For example, the nerve
conduction studies (NCS) are the best means for assessing the function of the median nerve and therefore for confirming the suspected cases of CTS. Nonetheless many patients show normal NCS values even though they exhibit typical clinical CTS signs. (Redmond and Rivner 1988; Werner and Andary 2002) Actually, NCS can only reveal the function of the myelinated nerve fibers, but it does not depict that of the unmyelinated ones (e.g. sympathetic fibers).

The main symptoms of ULMSDs are pain, especially aches, and restrictions in the limits of limb movement (Hutson 1997) but occasionally ULMSDs can cause also swelling. The basis of the development of the symptoms may be injuries to the muscles, tendons, joints as well as nerves, which all may be work related (Novak, Barr et al. 2004).

A number of functional changes in NS may take place in the pain generation and processing in ULMSDs. Peripheral neural dysfunction may occur in ULMSDs due to local inflammation and/or compression. The peripheral nerves i.e. the median nerve contains motor and sensory fibers and also sympathetic efferents which actually regulate the local vasomotor networks and the sweat glands (Guyton and Hall 2001).

If the sympathetic fibers are injured, changes in the vasomotor activity and dysfunction of sweat glands in their innervation area would be expected to occur and this would lead to changes of skin temperature and moisture. Damage to muscles, nerves and joints in ULMSDs, may also cause an antidromic activation of C-fibers. It has been shown that the activation of the unmyelinated and thin myelinated nociceptive nerve fibers results
in a release of sensory neuropeptides, substance P and calcitonin gene-related peptide (CGRP) from the nerve terminal endings. Substance P and CGRP are potent vasodilators and are able to cause an increase in the local circulation and, accordingly, warming up of the tissue. (Comstock, Ochoa et al. 1986) Thus, the exploration of the skin surface temperature and evaporation of the related area may assist in understanding the functional abnormalities of the affected sympathetic nerves, and possibly, also those of the fine afferents. Those measurements may also shed more light on the mechanisms of these changes and the pathophysiology of ULMSDs.

The purpose of the present series of studies was to clarify the usefulness of infrared thermography (IRT) and skin evaporation measurements in ULMSDs as indicators of the sympathetic pathophysiology. The tactile threshold measurement was used as a reference examination to clarify the function of sensory nerve fibers. Compared to ENMG, CT and MRI, these alternative methods i.e. DIRT, skin evaporation and tactile threshold measurements are inexpensive and straightforward to apply. They are also non-invasive and are really accepted by patients. Therefore they may be useful in clinical practice, especially in the follow-up of operated patients.
2. LITERATURE REVIEW

2.1 Epidemiology of Upper Limb Musculoskeletal Disorders

Upper limb musculoskeletal disorders (ULMSDs) are painful disorders of muscles, tendons, joints and nerves. Most of these disorders are chronic and work related. CTS, tendonitis, and NSP are the most common ULMDs. (Kilbom, Armstrong et al. 1996; Yassi 2000; Davis, Wellman et al. 2001; Paoli and Merllié 2001; Ming and Zaproudina 2003; Ming, Narhi et al. 2004) These disorders affect the back, upper limbs, and neck and evoke clear symptoms e.g. pain. An eight-year study of workers’ compensation claims associated with upper extremity disorders in the State of Washington (U.S.) found that the most frequent abnormalities were those involving the hand and wrist, with the next most frequent disorder being the shoulder followed by the elbow (Silverstein, Welp et al. 1998).

Since office-bassed employment has become very common today, ULMSDs now represent an important challenge to clinicians (Kilbom, Armstrong et al. 1996). Musculoskeletal pain complaints are the second commonest reason for consulting a doctor and account for about 10 to 20% of primary care visits (Rasker 1995). They are the leading cause of long-term absence from work (> 2 weeks) in many countries (Brage, Nygard et al. 1998). Their direct and indirect costs are considerable, and their management consumes a significant proportion of the gross national product of many countries (Mody and Woolf 2003).

In some occupations, the incidence of ULMSDs is much higher than in others. For
example, It has been reported that 27% of office workers who use a computer experience discomfort in the neck and shoulder (Sauter, Schleifer et al. 1991).

2.2. Classification of Upper Limb Musculoskeletal Disorders

It is very difficult to define the musculoskeletal disorders within traditional disease classifications (Van Eerd, Beaton et al. 2003). This debate with respect to terminology and case definitions has discouraged clinical practitioners from effectively approaching the diagnosis and management of these conditions. However, considerable progress has recently been made. Previously, these disorders were more commonly referred to as repetitive strain injuries or cumulative traumas, and in fact these conditions have been classified by a number of definitions, such as repetitive motion injuries, repetitive strain injuries, cumulative trauma disorders, occupational cervicobrachial disorders, over-use syndrome, regional musculoskeletal disorders and soft tissue disorders. (Rempel, Harrison et al. 1992; Canadian Centre for Occupational Health and Safety 1999; Yassi 2000) Most of these names do not accurately describe these conditions. For example, the term "repetitive strain injuries" indicates that repetition causes these disorders, but awkward postures, working environment also known to contribute to the development of such conditions (Sauter, Schleifer et al. 1991; Kilbom, Armstrong et al. 1996; Canadian Centre for Occupational Health and Safety 1999; Yassi 2000). The terms are used synonymously, and in the absence of agreement, at present the term Upper Limb Musculoskeletal Disorders (ULMSDs) is recommended. However, there are no internationally accepted criteria for those conditions; there have recently been demands for the creation of some kind of international system of classification (Van Eerd, Beaton
et al. 2003).

Generally, ULMSDs can be divided into:

1) Specific ULMSDs: All the disorders of this type are well studied, but still in some of them, the pathophysiology is unclear. Table 1 lists the classification of these disorders.

**Table 1:** *Specific Upper Limb Musculoskeletal Disorders, modified from (Silman and Newman 1996):*

<table>
<thead>
<tr>
<th>Disorders of neck and shoulder</th>
<th>Bursitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tendon related disorders</td>
</tr>
<tr>
<td></td>
<td>Tendinitis of the shoulder</td>
</tr>
<tr>
<td></td>
<td>Bicipital tendinitis</td>
</tr>
<tr>
<td></td>
<td>Infraspinatus tendinitis</td>
</tr>
<tr>
<td></td>
<td>Supraspinatus tendinitis</td>
</tr>
<tr>
<td></td>
<td>Subscapularis tendinitis</td>
</tr>
<tr>
<td></td>
<td>Rotator cuff lesions</td>
</tr>
<tr>
<td></td>
<td>Impingement syndrome</td>
</tr>
<tr>
<td></td>
<td>Frozen shoulder</td>
</tr>
<tr>
<td></td>
<td>Cervical vertebrae spondylitis</td>
</tr>
<tr>
<td></td>
<td>Thoracic outlet syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorders of the elbow, wrist and hand</th>
<th>Epicondylitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lateral epicondylitis</td>
</tr>
<tr>
<td></td>
<td>Medial epicondylitis</td>
</tr>
<tr>
<td></td>
<td>Beat elbow and olecranon bursitis</td>
</tr>
<tr>
<td></td>
<td>Conditions affecting the shoulder</td>
</tr>
<tr>
<td></td>
<td>Cubital tunnel syndrome (CUTS)</td>
</tr>
<tr>
<td></td>
<td>Ulnar tunnel syndrome</td>
</tr>
<tr>
<td></td>
<td>Radial tunnel syndrome</td>
</tr>
<tr>
<td></td>
<td>Carpal tunnel syndrome (CTS)</td>
</tr>
<tr>
<td></td>
<td>Pronator and anterior intersosseous syndrome</td>
</tr>
<tr>
<td></td>
<td>Tenosynovitis</td>
</tr>
<tr>
<td></td>
<td>De Quervains tenosynovitis</td>
</tr>
<tr>
<td></td>
<td>Intersection syndrome</td>
</tr>
<tr>
<td></td>
<td>Beat hand</td>
</tr>
<tr>
<td></td>
<td>Hand and wrist pain</td>
</tr>
</tbody>
</table>

| Vibration Exposure | Hand-arm vibration syndrome |
2) Non-specific ULMSDs: non-specific and poorly understood especially with regards to their etiology and pathology. The Non-Specific Neck & Shoulder Pain is an example. The patients experience serious uncomfortable symptoms, unfortunately these are not substantiated by unequivocal clinical findings (Bogduk 1988; Siivola 2003).

Among these disorders, the brachial plexus injuries, non-specific neck and shoulder pain (NS-NSP) and cervical vertebrae spondylosis are quite common. The present studies also focused on those disorders.

**Carpal Tunnel Syndrome**

Carpal tunnel is an anatomic space on the palm side covered by the inelastic transversal carpal ligament over the eight small carpal bones of the wrist. There are ten structures that transverse the carpal tunnel, and they include the 4 tendons of digitorum superficialis, 4 tendons of the flexor digitorum profundus, flexor pollicis longus and the median nerve (Fig. 1) (Fuller 2004).
Carpal tunnel syndrome (CTS) is the most common form of the entrapment neuropathies, each member of the general population seems to have a 10% lifetime risk of being affected (Mondelli, Giannini et al. 2002). This syndrome becoming more common, especially in repetitive task workers such as computer terminal users (Kimura 1983; Stevens, Witt et al. 2001). It occurs when the median nerve, which runs from the forearm into the hand, becomes compressed or squeezed at the wrist (Katz, Larson et al. 1990; Fuller 2004). The median nerve controls sensations, vasomotor activity and activity of the sweat glands to the palm side of the thumb and fingers but not the little finger and ulnar side of the ring finger (Fig. 1). It also contains the motor nerve fibers that control the small muscles in the hand that move the fingers and thumb (Waxman 2003).
2003). As the carpal tunnel is a rigid passageway formed by nonelastic ligament and bones, the inflammation of the surroundings around the median nerve will result in nerve compression. As a result, pain, weakness, or numbness in the hand and wrist, radiating up to the arm may develop. As already mentioned, CTS is the most common and widely recognized of the entrapment neuropathies in which the body's peripheral nerves are compressed or traumatized. (Nathan and Keniston 1993; Atcheson 1999; Mondelli, Giannini et al. 2002; Fuller 2004)

Ulnar Nerve Paralysis

The entrapment neuropathy of the ulnar nerve is the second most common neuropathy of the upper extremity (Corwin 2006). Because of its superficial position at the elbow, the ulnar nerve is often injured by excessive pressure in this area (leaning on the elbow during work or while driving a car). The Guyon’s canal at the wrist is the second commonest location of the entrapment (Posner 2000; Huang, Samadani et al. 2004). Pressure or injury to the ulnar nerve may cause dysfunction of the innervated muscles and impairment of the sensation as well as disruption of vasomotor activity and sweat gland function (Silver, Montagna et al. 1964; Uno 1977). Numbness and tingling in the ring finger and little finger are common symptoms of ulnar nerve entrapment (Fig. 2). These occur more often when the elbow is bent, such as when driving a car or talking on the phone. The weakness of grip and difficulty with finger coordination may occur in some cases, and if the nerve is strongly compressed or has been compressed for a long time, then muscle wasting and function loss of the intrinsic muscles in the hand can take
Radial nerve compression or injury may occur at any point along the nerve’s anatomical course and may have variable etiologies (Trojaborg and Sindrup 1969; Lowe, Sen et al. 2002). The most frequent site of compression is in the proximal forearm in the area of the supinator muscle, and it involves the posterior interosseous branch and this can cause the posterior interosseous nerve syndrome (Sturzenegger and Rutz 1991). Compression is thought to occur after separation of the branches to the radial wrist extensors and the radial sensory nerve. After emerging from the supinator, the nerve may be compressed before it bifurcates into its medial and lateral branches, causing a complete paralysis of the digital extensors and dorsoradial deviation of the wrist secondary to paralysis of the extensor carpi ulnaris. If compression occurs after the nerve has bifurcated, then selective paralysis of muscles occurs, depending on which
branch is involved. Compression of the medial branch evokes paralysis of the extensor carpi ulnaris, extensor digiti quinti, and extensor digitorum communis. Compression of the lateral branch causes paralysis of the abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus, and extensor indicis proprius. Most commonly, entrapment occurs at the proximal edge of the supinator. The sensation changes may take place in the area innervated by radial nerve (see Fig. 3). (Sturzenegger and Rutz 1991; Stern 2005)

Fig. 3. Radial nerve sensory innervation area of the skin of the dorsal (left) and palm (right) aspects of the hand

Cervical Vertebrae Spondylosis

Cervical Vertebrae Spondylosis, also known as ‘cervical arthritis’ or ‘cervical radiculopathy’, refers to the degenerative changes in the spine that particularly affect the cervical (neck) vertebrae and/or intervertebral discs (Ross 2005). These changes gradually narrow the space in the vertebral foramen, the hollow part of the vertebrae that hosts the spinal cord. This narrowing results in compression of the nerves that lead
from the spinal cord in the neck. As these nerves become compressed, they become inflamed and may cause pain in the neck that may radiate also to the arms (Kotrych, Bohatyrewicz et al. 2005). The condition most commonly begins around the age of 40-50 (Mayer, Anagnostis et al. 2002; Brigham and Women's Hospital 2003). Nearly everyone over the age of 50 shows some degree of degeneration in the structures of the cervical spine, but not everyone will develop spondylosis. Those office workers who sit in front of computers all day may experience these kind of changes much earlier in their life (Kotrych, Bohatyrewicz et al. 2005).

Non-Specific Neck & Shoulder Pain

Nonspecific neck & shoulder pain (NS-NSP) refers to pain in the neck and shoulder that is not caused by a diagnosed disorder, such as a ruptured disc, and the underlying cause of this type of pain is not fully understood, thus it is called 'non-specific' (Borghouts 1998). Many people develop a stiff and painful neck for no obvious reason. It may happen after sitting in awkward position or after a minor twisting injury. Repetition and forceful exertions and awkward positions are associated with the development of neck and shoulder pain (NSP) in computer users. (Pascarelli and Kella 1993; Yassi 2000; Ming and Zaproudina 2003) Working for a long time in front of a computer, requires a static posture of the upper body. In order to keep a static posture, the muscles of the neck and shoulder become overloaded and injured. Having NS-NSP does not mean that the neck or shoulder have suffered structure changes. NS-NSP often occurs in individuals whose necks appear to be completely normal in an x-ray examination.
However, if this syndrome is simply ignored then the NS-NSP may later convert to cervical vertebrae spondylosis, disc extrusion and other structural changes in the future (Hill, Lewis et al. 2004; Ming, Narhi et al. 2004).

2.3. Pain and ULMSDs

Pain can be either acute or chronic. These two types of pain differ in their etiology, pathophysiology, diagnosis and treatment (Gifford and Butler 1997; Wall and Melzack 2005). Normally, acute pain is self-limiting and serves as a protective biological function by acting as a warning of ongoing tissue damage. It is a symptom of a disease process experienced in or around the injured or diseased tissue. The associated psychological symptoms are minimal and are usually limited to mild anxiety (Auvenshine 2000; Wall and Melzack 2005). Acute pain is nociceptive in nature, and it occurs secondarily to chemical, mechanical and thermal stimulation of A-delta and C-polymodal pain receptors (Auvenshine 2000; Guyton and Hall 2001). Chronic pain, on the other hand, does not serve any appropriate protective biological function. Rather than being a symptom of a disease process, chronic pain itself is a disease. It is unrelenting and not self-limiting and can persist for years and even decades after the initial injury. (Auvenshine 2000) It can be refractory and unresponsive to multiple treatment modalities. Other symptoms often linked to uncontrolled chronic pain include chronic anxiety, fear, depression, sleeplessness and impairment of social interaction (France and Houpt 1984). Chronic, non-malignant pain is often neuropathic in nature and involves damage either to the peripheral or central nervous system. (Guyton and Hall 2001; Wall and Melzack 2005)
Several structures have been shown to evoke pain in the neck and shoulder area and upper limbs. Nerves, muscles, bones, discs, facet joints, tendons and ligaments, when irritated or inflamed, are capable of evoking pain and other symptoms (Spitzer, LeBlanc FE et al. 1987; Cailliet 1991). Some researchers have postulated that chronic pain in the arms might be due to abnormal nerve functioning attributable to mechanical tension on the nerves and other neural structures (Quintner and Elvey, 1993).

Pain is mediated by specific nerve fibers that carry the pain impulses to the brain where their conscious interpretation may be modified by many factors (Wall and Melzack 2005). There is a complicated neuronal network in the peripheral nerves and the spinal cord involved in processing of nociceptive information. Injury to a muscle (inflammation or ischemia) or a joint (inflammation) results in sensitization of peripheral nociceptors (Raja, Meyer et al. 1988). There is then an increase in impulse transmission and increased release of neurotransmitters in the dorsal horn of the spinal cord (Wall and Melzack 2005) and the dorsal horn neurons become sensitized by the peripheral injury. They demonstrate increased background activity, increased receptive field size, and increased responses to peripherally applied stimuli. The increased release of neurotransmitters and the sensitization of dorsal horn neurons are dependent on activation of various receptors e.g. N-methyl-D-aspartate (NMDA), non-NMDA excitatory amino acid, and neurokinin 1 receptors (Sluka 1996). In addition to processing nociceptive information following joint or muscle injury, the spinal cord is involved in peripheral joint inflammation. Production of dorsal root reflexes, and consequent antidromic action potentials, are expected to result in the release of
inflammatory neuropeptides (e.g. substance P and CGRP) from the terminals of the primary nociceptive afferents at the site of the injury. The release of substance P and CGRP has been predicted to potentiate the inflammatory response in the periphery. (Sluka 1996)

2.4. Sympathetic Nervous System and ULMSDs

Sympathetic nerves originate inside the vertebral column, toward the middle of the spinal cord in the intermediolateral cell column (or lateral horn), beginning at the first thoracic segment of the spinal cord and extending into the second or third lumbar segments. Since its cell bodies are located in the thoracic and lumbar regions of the spinal cord, the SNS is said to have a thoracolumbar outflow. The axons of these nerves leave the spinal cord in the ventral branches (rami) of the spinal nerves, and then spread out as 'white rami' which connect to the two chains of ganglia located alongside the vertebral column on the left and right sides. These elongated ganglia are also known as the paravertebral ganglia or sympathetic trunks. In these hubs, there are connections (synapses) to the second order neurons which then distribute their branches to the major organs, glands, vessels and other parts of the body (see Figure 13). (Guyton and Hall 2001; Waxman 2003; Snell 2004)

In ULMSDs, the sympathetic nervous system itself may be also affected (Wasner, Brechot et al. 2002; Straub and Harle 2005; Ge, Fernandez-de-las-Penas et al. 2006). As mentioned previously, the post ganglionic sympathetic fibers proceed along with the sensory and motor fibers in the peripheral nerves. Accordingly, they may be damaged
when the nerve is compressed by surrounding tissues and as a result, vasomotor activity changes i.e. vasodilatation and/or vasoconstriction may take place. Such changes may cause impairment of the blood flow to the affected tissue area, and even lead to muscle and/or tendon injuries.

Sympathetic postganglionic neurons may also be involved in the generation of pain, hyperalgesia and neurogenic inflammation in response to pathophysiological conditions (Wall and Melzack 2005). Experiments with animal models show that the sympathetic neurons have two types of effects on the nociceptive afferents. The responses seem to be different if the sympathetic-afferent coupling develops after nerve lesion or if it take place after tissue trauma with inflammation (Baron, Janig et al. 1988; Michaelis and Janig 1998).

First, a peripheral nerve lesion generates plastic changes in the afferent sensory and sympathetic postganglionic neurons. This may lead to chemical coupling between the sympathetic and the sensory afferent systems. Such coupling may cause activation and/or sensitization of the primary afferents. The mediator is probably noradrenaline and the afferent neuron expresses perhaps even, upregulates, functional adrenoceptors (Michaelis and Janig 1998). The coupling may occur at different sites of the primary afferent, e. g., at the lesion site, at a site remote from the lesion site in the dorsal root ganglion or between nonlesioned sympathetic and afferent neurons which show collateral sprouting. The biochemical signals which trigger these changes are believed to include neurotrophic substances (such as the nerve growth factor (NGF) and their
receptors which are synthesized by the peripheral neurons, Schwann cells and other cells in response to the peripheral lesions (Wall and Melzack 2005).

Second, the sympathetic nerve terminals in the peripheral tissues may serve as mediator elements in hyperalgesia as well as during inflammation following tissue trauma without nerve lesion (Michaelis and Janig 1998; Schattschneider, Wasner et al. 2003). This function is largely independent of the activity in the sympathetic neurons and the vesicular release of transmitter substances. The signaling agents are probably synthesized and released from the sympathetic terminals or in association with them and belong to the prostaglandin family (probably PGE(2) or PGI(2)) (McMahon 1991; Michaelis and Janig 1998). Furthermore, NGF has a hyperalgesic action in inflammation which is at least in part dependent on the sympathetic nervous system. (McMahon 1991; Michaelis and Janig 1998)

2.5. Risk Factors of ULMSDs

The risk factors for ULMSDs have been documented in many studies (Cailliet 1991; Brogmsus, Sorock et al. 1996; van der Windt, Thomas et al. 2000; Miranda, Viikari-Juntura et al. 2001; Andersen, Kaergaard et al. 2002; Cassou, Derrienic et al. 2002; Ehrmann Feldman, Shrier et al. 2002; Cho, Hwang et al. 2003). Most commonly, they include (as already briefly presented): 1) work related factors, 2) personal characteristics, 3) environmental, sociocultural and psychological factors. However, the mechanism of how these factors elicit ULMSDs is not yet clear. In practice, none of these factors acts on its own, but ULMSDs most probably develop as a result of a
combination and interaction of many factors (Tittiranonda, Burastero et al. 1999; Frost, Bonde et al. 2002; Ming and Zaproudina 2003; Ming, Narhi et al. 2004).

**Work related risk factors of ULMSDs**

The work related factors include: repetition, awkward posture, force, and the intense pace of work.

Repetitive work, especially if it involves the small muscles, is very tiring, because the muscles of the worker cannot fully recover in the short periods of time that are given between tasks (Canadian Centre for Occupational Health and Safety 1999; Yassi 2000). With time, the effort to maintain the repetitive movements, even if they involve minimal forces, steadily increases. When the work activity is continued despite the developing fatigue, injuries occur. This type of work will also irritate the tendons and induce inflammation (Johansson, Sjolander et al. 1999). Tasks requiring repetitive movements always involve other risk factors for ULMSD, such as fixed body position. A poor posture is also an important risk factor (Tittiranonda, Burastero et al. 1999; Frost, Bonde et al. 2002). There are two aspects of body position (posture) that contribute to injuries in jobs involving repetitive tasks. The first relates to the position of the part of the body that performs the actual task, usually the upper limb. For example, tasks that require repetitive movements to the extreme ranges of the joint in the wrist, elbow or shoulder e.g. computer use, are likely to lead to the appearance of painful conditions in those structures. Poor layout of the workstation and improper selection of equipment and tools can lead to such hazardous body movements.
The postural aspect that contributes to ULMSD is a fixed position of the neck and the shoulders (Kilbom, Armstrong et al. 1996). To perform any controlled movement of an upper limb, the worker must stabilize the shoulder-neck region. The muscles in the shoulder, neck and back contract and stay contracted to hold the position stable for as long as the task requires, such as when sitting in front of a computer. Basically, it is not heavy work, it is, however, necessary to maintain a static posture of the whole body. If the work lasts for a long time, in order to keep the static posture, the muscles of the neck, shoulder and upper limb become overloaded and injured, especially for those individuals who are sitting in an awkward position (See Fig. 4 A). The static contraction of muscles squeezes the blood vessels and restricts the circulation all the way down to the working muscles of the upper limb where the demand for blood flow is at its highest because of the intense muscular effort involved (Zimmermann 1991; Johansson, Sjolander et al. 1999). The results in two detrimental affects, the neck-shoulder muscles become fatigued, even though there is no movement and this contributes to the development of the pain in the neck. At the same time, the reduced blood supply to the upper limb accelerates fatigue in the moving muscles, making them more susceptible to injury. It has been documented that a prolonged muscle activity with the contraction reaching 20% of the maximum can cause myalgia (Hutson 1997).
Fig. 4. (A) Illustration of poor posture (awkward arm and neck positions, kyphosis, flat low back). (B) Illustration of a better ergonomic posture for computer users. It is recommended that the posture for computer users should be: Top of monitor at or just below the eye level; Shoulder relaxed; Elbows close to body; Arm supported and; Wrists and hands in-line with forearms (the load in shoulder area lowers with lowering of the forearms and hands) and feet flat on the floor.

In addition, the force required to do the task also plays an important role in the onset of ULMSDs. More force equals more muscular effort, and consequently, a longer recovery time between the tasks is needed as a considerable accumulation of lactic acid and other harmful metabolites takes place in the muscles during the extended contraction. (Kilbom, Armstrong et al. 1996; Baron and Janig 1998) In fact, there is evidence that strong eccentric activity can actually damage the muscle fibres. Sore muscles after eccentric contractions (typically those reported by workers who do heavy physical work) are commonly reported (Friden, Sjostrom et al. 1981; Kuorinka and Forcier 1995). With more forceful movements, the fatigue develops much more quickly. The pace of work determines the amount of time available for rest and recovery of the body between cycles of a particular task. The faster the pace, the less recovery time available and correspondingly the risk for ULMSDs will be higher (Kilbom, Armstrong et al. 1996).

In repetitive work, as a rule, there is never sufficient time for complete recovery.
Environment, personal characteristics and psychological factors

The temperature and humidity of the working environment may also play a role in the development of ULMSDs e.g. it has been documented that favours the development of NSP and CTS working in a cold environment or using vibrating tools (Hildebrandt, Bongers et al. 2002). In addition, the individual factors, which include the gender, obesity, hormonal changes, and systemic diseases (e.g. diabetes) may also contribute to the development of ULMSDs.

For example, it is clear that a significant increase in the risk for CTS is associated with obesity. It was reported that those individuals whose body mass index exceeded 29 were 2.5 times more likely to be diagnosed with CTS than slender persons defined as BMI < 20 (Werner, Albers et al. 1994; Werner, Franzblau et al. 1997). Other factors such as time working in the job and reproductive status (in women) require control before any unequivocal conclusions can be reached (Nathan, Keniston et al. 1992; Laursen and Jensen 2000; Wahlstrom, Svensson et al. 2000).

ULMSDs are much more common among women than in men (Ashbury 1995; de Zwart, Broersen et al. 1997; Preston 1999; Ola Leijon 2005). The explanation for these gender differences in work related ULMSDs might be exposure differences or differences in exposure levels between male and female workers. The exposure differences between male and female workers may, in turn, be explained by the segregation of men and women into different sectors of the labor market, different occupations, or different work tasks. Moreover, gender segregation in the labor market may also entail both

It is important to recognise that also sociocultural factors play a role in ULMSDs (Hagberg 1996; Jensen, Borg et al. 1998; Wahlstrom, Svensson et al. 2000). It is believed (Hagberg 1996) that a diagnosis of general cervicobrachial pain may be strongly related to psychological and social factors. Psychological factors and personality type are also determinants of muscle tension (Hagberg 1996). A patient with neck pain may be exposed to an awkward posture at work but also to social stress at work or at home. Both factors contribute to the sustained contraction of the trapezius muscles, and may induce pain and stiffness. It has been claimed that psychological factors must be considered when assessing the history of a patient with a disorder related to computer use (Jensen, Borg et al. 1998; Wahlstrom, Svensson et al. 2000; Bongers, Kremer et al. 2002; Lundberg 2002).

2.6. Pathophysiology of ULMSDs

The most common pathological changes in ULMSDs are muscle, tendon and nerve injuries (Ranney, Wells et al. 1995; Sluka 1996; Novak, Barr et al. 2004).

Muscle Injury

The muscles use fatty acids and glucose for their energy consumption when working. Metabolic by-products such as lactic acid, accumulate during static contraction. Calcium ions may play a central role in the development of muscle fiber injury during
prolonged muscle activity and Ca\textsuperscript{2+} accumulation may cause mitochondrial Ca\textsuperscript{2+} resorption, which has been suggested to result in structural damage and energy depletion. (McArdle and Jackson 1997; Gissel 2000). A long lasting contraction also reduces the blood flow and the access of oxygen into the muscle tissue and causes cumulative ischemic injuries. (Johansson, Sjolander et al. 1999) The results in inflammation which is accompanied by concomitant swelling, nerve compression (e.g. median and ulnar nerve compression) and the development of pain originating from the muscles, tendons and ligaments (Johansson, Sjolander et al. 1999). The severity of the pain depends on the duration of the muscle contractions as well as the recovery time between contraction periods. During rest, the blood flow becomes restored and the irritant by-products produced by anaerobic energy metabolism (e.g. lactic acid) can be removed from the muscle tissue.

**Tendon (sheath) Injury**

Tendons consist of numerous bundles of fibers whose function is attach the muscles to the bones. They transmit the force of the muscle contraction to the bone to cause the movements. Tendon disorders related to repetitive or frequent work activities and awkward postures occur in two major categories of tendons; those with sheaths, found mainly in the hand and wrist, and those without sheaths, generally found around the shoulder, elbow, and forearm. (Guyton and Hall 2001)

The tendons of the hand are enclosed in the sheaths through which the tendon slides. The cells of the inner walls of the sheaths produce a lubricating fluid to ease the tendon
movements within the sheath (Guyton and Hall 2001). With repetitive or excessive movement of the hand, this lubrication system may fail. The fluid production may not be sufficient, or the composition of the fluid may change e.g. it may have poor lubricating qualities (Guyton and Hall 2001). As a result, inflammation and swelling of the tendon and the sheath, known as tendonitis and tenosynovitis, will develop. If such a condition continues for a long period of time, fibrous tissue may be formed. The fibrous tissue thickens the tendon sheath, and hinders the tendon movement. (Kurppa, Waris et al. 1979; Rempel, Harrison et al. 1992)

Tendons without sheaths are also vulnerable to repetitive motions and awkward postures. In fact, when a tendon is repeatedly tensed, some of its fibres can be torn apart. The tendon becomes thickened and bumpy and can become inflamed (Verdon, Ranney et al. 1996). In some cases, such as in the shoulder, tendons pass through a narrow space between the bones. A bursa filled with lubricating fluid is often formed between the tendons and the bones as an anti-friction structure. Should the tendons become thickened and less smooth, the bursa is subject to considerable friction and ultimately becomes inflamed. (Hoppmann 1993)

**Nerve Injury**

Nerve signals control the activity of the muscles, and also other functions such as visceral function, blood circulation, sweating, etc. They also carry information about the temperature, touch, proprioception and pain to the brain (Guyton and Hall 2001; Waxman 2003). The nerves in limbs are surrounded by muscles, tendons, and ligaments.
In connection with repetitive motions and awkward postures, the tissues surrounding the nerves may become irritated and swollen and then this can compress the nearby nerves and evoke neurological changes. For example, in CTS, the median nerve may be compressed by surrounding tendons. A progressive impairment of the nerve conduction appears, resulting gradually in increasing degrees of numbness and a tingling sensation, and subsequently in muscle weakness. In advanced cases, the outcome is impaired movement coordination, diminished muscle strength, thenar muscle atrophy and hand–wrist pain (See Fig. 1). (Katz, Larson et al. 1990; American Association of Neurological Surgeons 2001; Werner and Andary 2002; Fuller 2004) Dryness of skin, and poor circulation to the extremities, may also appear, this probably being because of the sympathetic fibres have also been injured by the compression (Werner and Andary 2002).

Chronic irritation of, or pressure-induced damage to the nerve may also affect the intraneural microvasculature, resulting in ischemia due to compression of the vasa nervorum, disruption of the blood-nerve barrier, and venous congestion, which may lead to epineurial edema and increased endoneural fluid pressure (Schon 1994). In the early stages, the symptoms may be intermittent or even cease after exercise in parallel with a recovery of the intraneural circulation and drainage of the intraneural edema (Mackinnon 2002). As the condition proceeds, the prolonged edema of the epineurium may become converted into fibrotic changes, further contributing to the chronic constriction of the nerve (Schon 1994). Long-standing compression causes damage to the myelin sheath, axonal degeneration and fibrosis. As already mentioned the
sympathetic fibers are located along with the other fibers, in the peripheral nerves and they may also be damaged when the nerve is compressed.

**Joint injury**

The joints, cartilage, and spinal discs are also easily injured. Overloading with too high forces and repetition of movements can cause injury and consequent inflammation and degeneration of joints, cartilage and spinal discs, and accelerate joint aging, which then evokes joint pain. When joint dislocation or semi-dislocation occurs, the symptoms may become aggravated. (Allan 1998; Cromie, Robertson et al. 2000). As an example the first carpometacarpal joint arthritis may be caused by thumb over-use (e.g. excessive texting on a mobile phone).

**2.7. Clinical Manifestations of ULMSDs**

Pain is the most common symptom associated with UMSDs. In some cases, there may also be joint stiffness, muscle tightness as well as, redness and swelling of the affected area. Some patients may also experience sensations of "pins and needles," numbness, skin colour changes, and decreased sweating of the hands. The details of different disorders are listed in Table 2.
Table 2. Identified disorders, work related risk factors and symptoms in ULMSDs, modified, (Canadian Centre for Occupational Health and Safety 1999; Yassi 2000)

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Work related risk factors</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendonitis /tenosynovitis</td>
<td>Repetitive wrist motions</td>
<td>Pain, weakness, swelling, burning or dull ache over affected area</td>
</tr>
<tr>
<td></td>
<td>Repetitive shoulder motions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sustained hyper-extension of arms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prolonged load on shoulders</td>
<td></td>
</tr>
<tr>
<td>Epicondylitis (elbow tendonitis)</td>
<td>Repeated or forceful rotation of the forearm and bending of the</td>
<td>Same symptoms as tendonitis</td>
</tr>
<tr>
<td></td>
<td>wrist at the same time</td>
<td></td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>Repetitive wrist motions</td>
<td>Pain, numbness, tingling, burning sensations, wasting of muscles at</td>
</tr>
<tr>
<td></td>
<td></td>
<td>base of thumb, dry palm</td>
</tr>
<tr>
<td>De Quervain's disease</td>
<td>Repetitive hand twisting and forceful gripping</td>
<td>Pain at the base of thumb</td>
</tr>
<tr>
<td>Non-specific neck shoulder pain</td>
<td>Prolonged restricted posture</td>
<td>Pain at neck and shoulder which may radiate to the whole upper limb</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.8. Diagnosis of ULMSDs

If increasing pain and symptoms such as weakness, numbness, tingling, and stiffness in the neck, shoulder and upper limbs continue following long period of intensive repetitive work, ULMSDs should be suspected (Hutson 1997). The diagnosis is confirmed by performing a physical examination supplemented with laboratory and neurophysiologic tests e.g. ENMG, that can reveal nerve or muscle damage. The physical assessment must include the evaluation of the motion range of the joint, hyperlaxity, muscle tenderness, pain and strength, and side to side differences (Pryse-Phillips 1984; D'Arcy and McGee 2000). Specific tests such as Finkelstein's test for deQuervain's tenosynovitis, Tinel's sign and Phalen's test for carpal tunnel
syndrome, and tests for thoracic outlet syndrome also need to be performed (Pryse-Phillips 1984; D'Arcy and McGee 2000; Herbert, Gerr et al. 2000).

Electroneuromyography (ENMG) includes two areas: electromyography (EMG) and nerve conduction velocity measurement (NCV). These are considered to be the golden standards for the diagnosis of certain disorders such as CTS. They can help in the differential diagnosis from other muscular or motor neuron diseases and also assist to locate and grade the neural damage (Dumoulin and Clauses 1981; Nathan, Keniston et al. 1995; Stevens 1997; Stevens, Smith et al. 1999; D'Arcy and McGee 2000; Fuller 2004). CT and/or MRI, an alternative to x-rays, provide images of tendons, ligaments, and muscles and improve the quality of the diagnostic information (Tong, Barest et al. 2003). They are helpful diagnostic tools in many cases. However, in some individuals, even though the patients are experiencing clear clinical symptoms, the results of the above examinations have been negative. For example, about 10% of all CTS patients with typical clinical symptoms may present with normal motor and sensory nerve conduction values (Redmond and Rivner 1988; White, Hansen et al. 1988; Rosen 1993; Nathan, Keniston et al. 1995; Padua, LoMonaco et al. 1997; Lew, Date et al. 2005; Prakash, Fook-Chong et al. 2006).

Moreover, in a number of chronic neck and shoulder pain patients with clear clinical symptoms, even CT and MRI findings can be negative and thus do not help in confirming any clear diagnosis. Furthermore, these procedures are expensive (CT and MRI) and, sometimes, even discomforting for the patient (ENMG). Therefore, many
researchers have tried to develop some new non-invasive and less expensive techniques, which would be easy to perform and also be helpful in coming to appropriate diagnosis. For example, high resolution ultrasonography (Newman and Adler 1998; Teh 2006), sympathetic skin responses (SSRs) (Arunodaya and Taly 1995; Mondelli, Vecchiarelli et al. 2001) and infrared thermography (Meyers, Cros et al. 1989; Silverstein, Silverstein et al. 1996; Sharma, Smith et al. 1997; Ming, Zaproudina et al. 2005) have been examined as ways of revealing sympathetic pathology in the musculoskeletal disorders; some of these techniques seem to achieve good results e.g. high resolution ultrasonography nowadays is considered as a good diagnostic method in certain diseases in clinical practice (Newman and Adler 1998; Teh 2006). Also, the technique of microneurography has been improved and permits recording of the sympathetic neural outflow directly from postganglionic axons in conscious human subjects (Macefield, Elam et al. 2002). Some researchers have reported new methods to measure focal recordings from even a single C-fibre (Macefield and Wallin 1999; Elam, McKenzie et al. 2002; Macefield, Elam et al. 2002).

2.9. Treatments and Prevention

The treatment of ULMSDs involves several approaches including the following:

- Cessation of performance of the injury-inducing activity
- Physical therapy and alternative methods
- Medication and surgery

The initial approach to treatment of ULMSDs is to avoid the activities causing the injury.
This often requires work restrictions. In some cases, transfer to a different job needs to be considered. A splint can also be used to restrict movements or to immobilize the injured joint. However, the use of splints in occupational situations requires extreme caution. If used inappropriately, splints can cause more damage than their non-use. Splints are usually used for two reasons: to mechanically support a joint where an excessive load is anticipated, or to restrict the movement of the injured joint. (Brigham and Women's Hospital 2003; Novak, Barr et al. 2004)

Heat increases the blood flow and increases swelling but cold can reduce both swelling and pain. Application of heat or cold seems to be able to relieve pain and may accelerate the repair process. Heat is recommended for pain relief of minor injuries but not for injuries with significant inflammation and swelling. (Brigham and Women's Hospital 2003)

Stretching is beneficial because it promotes improvements in blood circulation and reduces muscle tension. However, people suffering from ULMSDs should consult a physiotherapist before exercising. Stretching or exercise programs can aggravate the existing condition if not properly designed. (Rempel, Harrison et al. 1992)

If the symptoms still remain despite the above methods, further treatments are needed. Non-steroidal anti-inflammatory drugs and injection of corticosteroids can reduce inflammation and pain. More elaborate treatments or even surgery may be required if all other approaches fail. For the neuropathic pain, the first step is to apply a topical local anesthetic patch. If local treatments fail to achieve the desired results, then the next
consideration is the use of some systemic medications e.g. tricyclic antidepressants (TCAs), pregabalin, gabapentin or antiarrythmics (Galer, Harle et al. 1996; Galer, Twilling et al. 2000). In some severe cases, i.e., some severe CTS patients, the final treatment option is surgery (Helwig 2000).

The fundamental principles of prevention ULMSDs are 1) avoidance of the risk factors, 2) provision of an ergonomic workstation, 3) re-designing of the task and 4) use of proper tools; all of these can be considered as preventive measures. However, the actual performance of the tasks may depend on the individuals. Training should be provided for those workers who are exposed to the risks. Workers need to know how to adjust their workstations appropriately to the task to be done as well as to their individual needs. Training should also emphasize the importance of rest periods and instruct how to take advantage of short periods of time between tasks to relax the muscles, and how to consciously control muscle tension throughout the whole work shift. (Cailliet 1991; Koh, Ong et al. 1994; Hagberg 1996; Tittiranonda, Rempel et al. 1999; Dowler, Kappes et al. 2001; Lintula, Nevala-Puranen et al. 2001)
3. AIMS OF THE STUDY

The purpose of the present study was to examine the skin temperature, evaporation and tactile sensation changes as signs of abnormal nerve function in ULMSDs, especially in CTS but also in NS-NSP. Also the efficacy of the carpal tunnel release (CTR) operation in the alleviation of those signs and symptoms of CTS was examined.

Furthermore, possible abnormalities in the peripheral vasoregulation responses to a cold provocation test were examined. Moreover, the usefulness of several non-invasive techniques i.e. the infrared thermography, skin surface evaporation and tactile sensation measurements in the diagnosis of ULMSDs was clarified.

The specific aims were:

1. To examine the skin temperature and possible underlying abnormalities in the blood flow regulation in the CTS hands.
2. To study the efficacy of CTR in the alleviation of the CTS signs and symptoms.
3. To examine the vasoregulatory responses to a cold provocation test in peripheral nerve disorders.
4. To explore the possible sensory and sympathetic nerve dysfunctions in NS-NSP by using DIRT, skin evaporation and tactile threshold measurements.
5. To critically evaluate the usefulness of the above methods in the diagnostics of ULMSDs and follow up of the development of functional abnormalities in the vasoregulation and tactile sensations as well as their recovery after treatment.
4. SUBJECTS AND METHODS

4.1. Subjects

**Exclusion criteria:** Subjects who had a history or physical examination suggestive of diabetes mellitus, Raynaud syndrome, hyperthyroidism, hypothyroidism, hypertension and excessive alcohol consumption, or exposure to toxins were excluded. Subjects who had acute symptoms e.g. fever and wounds or acute infection on their hands were also excluded from the measurements.

**Healthy control subjects** consisted of 22 volunteers (8 men and 14 women, with a mean age of 49.2, range of 22-64) without any symptoms in their upper limbs. They were the staff of our university and hospital and our students. Altogether 41 hands (3 hands with wounds were excluded, n=41) were investigated.

**CTS patients:** Fifty six CTS hands of forty two patients (19 men and 23 women, with a mean age of 45.74 yrs, range 24 – 67) were referred to the study. All CTS hands (n=56) were diagnosed by a hand surgeon and the diagnosis was confirmed by nerve conduction studies (NCS).

**CTR patients:** Twenty two CTS hands of sixteen patients of the above CTS group (6 men and 10 women, with a mean age of 44.75 yrs, range 31 – 67) underwent the CTR operation and participated in the follow-up study. All patients had more than three of the following indicators of CTS (Kaplan, Glickel et al. 1990; Kouyoumdjian, Morita et al. 2003): 1) duration of the symptoms more than ten months, 2) constant paraesthesiae, 3) stenosing flexor tenosynovitis, 4) a Phalen's test positive in less than 30 seconds and 5)
age over 50 years. The CTR operations were conducted in a standard way in Kuopio University Hospital or Kaajani Central Hospital (Fig. 5).

Fig. 5. Carpal tunnel syndrome: operation view.

Twenty **NS-NSP patients** (8 men, 12 women with mean age of 49.8, range 26 - 76) participated in the study. The diagnoses were confirmed by one neurologist and one physiotherapist. The criteria for NCS were established as follows: patients with problems e.g. pain originating from the neck and shoulder area and lasting for more than three months and no neck and shoulder surgery, no malignancies or rheumatoid arthritis. The patients who with a specific diagnosis e.g. cervical radiculopathy, ankylosing spondylitis, rotator cuff tear were all excluded.

The differences of the mean age of the subjects in the study groups were not significant (all p values >0.20).
4.2. Methods

Subjective Symptoms

All the subjects of CTS, CTR and NS-NSP groups were asked to complete a questionnaire regarding his/her general information, subjective symptoms and past history.

Nerve Conduction Studies (NCS):

The NCS were performed in order to: 1) confirm the diagnosis of CTS, 2) follow the neural dysfunction of CTS after the CTR operation. All studies were performed with surface electrodes and standard ENMG recording equipment (SIERRA LT E NMG Recorder, Cadwell Ltd, Co, USA) by a member of the research group who is neurophysiologist (J.S.) working in the Department of Clinical Neurophysiology of Kajaani Central Hospital. If the hand skin temperature (middle of the palm) was lower than 32 °C, the hand was warmed up by soaking it in warm water.

The motor conduction velocity (MCV) of the median nerve was measured between the elbow and wrist. The distal motor latency measurement was performed from the wrist to the thenar muscle on the maximal muscle mass (abductor pollicis brevis) as near to the end-plate area as possible. The absolute distance between the stimulating and recording point was not relatively since it dependent on the size of the hand.

The sensory conduction velocity (SCV) of the median nerve was measured from the wrist to the 2nd finger (index finger).
The MCV of the ulnar nerve was measured between the wrist and elbow (just upwards from the ulnar sulcus). The distal motor latency was measured between the wrist and the hypothenar muscle. The SCV was measured from the wrist to the fifth finger. Orthodromic technique was used in the measurements of median and ulnar SCVs.

The criteria for NCS of CTS were the same as used in our previous study (Ming, Zaproudina et al. 2005), and established as follows: the distal latency of median nerve (motor) was more than 4.6 msec. and/or it was 1.6 msec. more than that of the ulnar nerve; distal latency of the ulnar nerve was less than 3.7 msec; correspondingly the sensory conduction velocity (SCV) of the median nerve was 10 m/sec less than that of the ulnar nerve.

**Infrared Thermography and Cold Provocation Test**

All subjects rested in a warm room with the temperature maintained at 22-24°C for at least 15 minutes before the measurements. Then a series of photos of the hands were taken from a 2 meter distance by using digital infrared video camera (sensitivity at 0.05°C; IRTIS Ltd, Moscow, Russia) which provides thermographic images as a way of measuring the temperatures without any contact with the subject. All the data were collected in a computer. Subsequently, the pictures were analyzed with DIRT software without knowledge of the NCS status. If a hand’s thermo-picture showed that the temperatures in the median nerve distribution area (1st to 3rd and half of 4th finger and thenar eminence (Th) innervated by the median nerve, see Fig.1) were significantly different (difference > 0.5 °C) from the ulnar nerve distribution area (half of fourth
finger, fifth finger and hypothenar eminence (Ht), see Fig. 2), the finding was considered abnormal. The appropriate software calculated the average temperatures of a determined skin area of the finger-tips from digit 1 (D1) to digit 5 (D5) (*30 mm² spot in the middle of finger-tips*), and that of the central parts (100 mm²) of Th and Ht were also determined. Then the difference between Th and Ht and every two of five fingers (absolute value) were calculated, the median index (MI): (D1−D2) + (D2−D3) + (D1−D3) was also computed. The MI and the equation were originally used by Dr. Stuart Meyers et al (1989) in their paper *Liquid crystal thermography: quantitative studies of abnormalities in carpal tunnel syndrome*. The higher MI, the more variable the skin temperature in the median nerve distribution area; this may reflect a malfunction in vasoregulation.

The 1st to 3rd finger-tips are innervated by median nerve, so the MI can be used as an indicator of the median nerve distribution area. The temperature differences between the median and the ulnar nerve distribution areas MED.ULN = (D1-D5) + (D2-D5) + (D3-D5) + (Th-Ht) were also evaluated.

A cold provocation test was performed in 9 subjects (4 CTS patients (7 CTS hands) and 5 healthy control subjects (10 hands). A series of infrared pictures of hands were taken with the DIRT equipment before and after the cold provocation with both feet kept in ice water for 45 sec (Yamamoto, Iwase et al. 1992).

The follow-up of the CTR operation was done in 22 hands of 16 CTS patients (6 men and 10 women, with a mean age of 44.75 yrs, range 31 – 67). All these patients had
been operated at least 6 months before the infrared thermography procedure was repeated.

**Skin Surface Evaporation**

The skin surface evaporation of each finger-tip (in the middle of the tip) was measured in each subject of the NS-NSP group and the healthy controls with an evapometer (Vapometer, Delfin, Kuopio, Finland). All of the subjects were acclimated to the environment in a warm room of temperature 22-24°C and humidity 22-25% for more than 15 minutes before the measurements were performed.

**Tactile threshold measurement**

The perception threshold of each finger tip was measured in subjects of the NS-NSP and the healthy groups by using the 'Aesthesiometer', a set of monofilaments (Somedic Sales AB, Sweden) in the same room with the same environment as the DIRT measurements. To assess the tactile sensation, the hairs were applied in an ascending and descending order of magnitude and both the appearance and disappearance of the sensation was recorded. The lower value was chosen as the tactile threshold.

**4.3. Statistical analysis**

The statistical analyses were conducted by the SPSS-PC statistical package, version 14.0. $X^2$ test was used to compare the difference between CTS and control group as regards to the percentage of abnormal temperature differences based on the infrared thermographic pictures, and was also used to compare the difference of subjective
symptoms prevalence in the operated CTS subjects before and after CTR operation. Paired-samples t-test was used to compare the differences of the measured mean values in the CTR follow up group before and after CTR, and independent-samples t-test for all the other statistical comparisons. If the p value was lower than 0.05, the difference was considered as statistically significant.

4.4. Ethical considerations

This research work was performed in the Department of Physiology, University of Kuopio, the Department of Hand Surgery, Kuopio University Hospital and the Department of Neurophysiology, Kajaani Central Hospital in Finland with the approval of the regional ethical committee (No. 142/2003). All subjects were thoroughly informed by personal instruction and written informed consent was obtained at inclusion. They were allowed to withdraw from the study at any stage.
5. RESULTS

5.1. Carpal Tunnel Syndrome

Typically a temperature difference existed between the skin areas innervated by the median and ulnar nerves in the CTS hands (Fig. 6B, C) but not in the healthy controls (Fig. 6A). In the CTS group, in 31 of 38 hands, the temperature in the median nerve distribution area was significantly different (>0.5 °C) from that of the ulnar nerve. The temperature of median nerve distribution area was higher in 32 and lower (Fig. 6B) in 24 CTS hands (see Fig. 6C). In the control group, only 4 of 41 hands indicated that the temperature of median nerve distribution area was higher. The difference between CTS and control groups as regards to the percentage of abnormal temperature differences between median and ulnar nerve distribution areas based on the infrared thermographic pictures was significant ($p < 0.01$).
Fig. 6. The infrared pictures of a healthy hand and two CTS hands: (A) normal hand showing no thermal differences between the median and ulnar nerve distribution areas; (B) CTS hand, showing warmer median nerve distribution area than that of the ulnar nerve; (C) CTS hand, showing lower temperatures in the median than in the ulnar nerve distribution area and.

The result also showed that the mean of Th-Ht ($p < 0.001$), MI ($p < 0.001$) and MED.ULN ($p < 0.001$) were significantly higher in the CTS group compared to the control groups (Fig. 7 and Table 3).

![Fig. 7. The temperature difference of thenar and hypothenar (Th−Ht), the median index (MI) and the temperature differences between the median and the ulnar nerve distribution areas (MED.ULN) in the CTS and control groups (all examined cases are presented).](image)

Table 3 The mean temperature differences of thenar and hypothenar (Th−Ht), median index (MI) and the temperature differences between the median and the ulnar nerve distribution areas (MED.ULN) in the CTS and control groups. The table shows the
same data as Figure 7. The difference between the groups was significant.

<table>
<thead>
<tr>
<th></th>
<th>Th-Ht mean ± SE</th>
<th>MI mean ± SE</th>
<th>MED.ULN mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTS</td>
<td>0.89 ± 0.10</td>
<td>2.84 ± 0.43</td>
<td>4.0 ± 0.39</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>0.32 ± 0.05</td>
<td>0.84 ± 0.10</td>
<td>1.59 ± 0.17</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

5.2. Follow-up of CTR operation

Six months after CTR, the NCS results of all the operated hands (n=22) were back to normal and the clinical subjective symptoms i.e. numbness, swelling and pain of the CTS patients were also relieved except for 2 CTS hands in which numbness, weakness and thenar atrophy were still present (see Table 4).

Table 4 Symptoms of and NCS results in CTS patients before and after CTR

<table>
<thead>
<tr>
<th></th>
<th>Numbness or Tingling</th>
<th>Weakness in thumb</th>
<th>Swelling and / or dryness</th>
<th>Thenar atrophy</th>
<th>NCS abnormal</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before CTR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=22)</td>
<td>22</td>
<td>18</td>
<td>14</td>
<td>2</td>
<td>22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After CTR</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(N=22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The median nerve index MI and the MED.ULN were significantly higher in the CTS patients compared to the healthy controls (MI: p<0.001, MED.ULN: p<0.005) before the CTR operation. After CTR, no significant differences were found in the above values between the groups, and in the CTR group, the MI and MED.ULN were significantly lower than the corresponding values found before operation (p<0.005 for
both parameters, see Table 5 and Fig. 8).

**Table 5** Median nerve index and temperature difference between areas innervated by the median nerve and the ulnar nerve (MED.ULN) before and after the CTR operation in CTS hands and non CTS hands compared with healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>MI +- 2SE</th>
<th>MED.ULN +- 2SE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CTS hand</td>
<td>Non CTS hand</td>
</tr>
<tr>
<td>Before operation</td>
<td>2.39 +- 0.49</td>
<td>1.69+-0.34</td>
</tr>
<tr>
<td>After operation</td>
<td>1.04 +- 0.18</td>
<td>1.25+-0.25</td>
</tr>
<tr>
<td>Healthy control</td>
<td>0.84 +- 0.10</td>
<td>1.59 +- 0.18</td>
</tr>
</tbody>
</table>

**p value**

- CTS hands before CTR VS healthy controls: < 0.001 NS. < 0.005 NS.
- CTS hands before CTR VS the same hands after CTR: < 0.005 NS. < 0.005 NS.
- CTS hands after CTR VS healthy controls: N.S. NS. N.S. NS.
Fig. 8. Median nerve index and temperature difference between areas innervated by the median nerve and the ulnar nerve (MED.ULN) before and after the CTR operation in CTS hands and non-CTS hands compared with healthy controls.

All of the finger-tips of the affected hand including those fingers innervated by the ulnar nerve were cooler than in the healthy controls before but warmer after the operation (see Table 7). Remarkably, the temperature of the fingers innervated by the median nerve was significantly higher after than that measured before the operation (D1, D2, D3, P < 0.05, see Table 6 and Fig. 9).

Before the operation, the non-CTS hands of the CTS patients were also colder than the hands of the healthy controls although the difference was not statistically significant.
The values approached those of the healthy controls after CTR. (see Table 6 and Fig. 9).

**Table 6** The mean finger-tip temperatures (°C) of healthy controls and CTS patients before and 6 months after CTR operation

<table>
<thead>
<tr>
<th></th>
<th>D1 ±</th>
<th>D2 ±</th>
<th>D3 ±</th>
<th>D4 ±</th>
<th>D5 ±</th>
<th>Th ±</th>
<th>Ht ±</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2SE</td>
<td>2SE</td>
<td>2SE</td>
<td>2SE</td>
<td>2SE</td>
<td>2SE</td>
<td>2SE</td>
</tr>
<tr>
<td>Non CTS before</td>
<td>30.13±</td>
<td>29.92±</td>
<td>29.70±</td>
<td>29.64±</td>
<td>29.52±</td>
<td>31.93±</td>
<td>31.49±</td>
</tr>
<tr>
<td>CTR</td>
<td>± 1.29</td>
<td>1.23</td>
<td>1.35</td>
<td>1.37</td>
<td>1.36</td>
<td>0.76</td>
<td>0.92</td>
</tr>
<tr>
<td>Non CTS after CTR</td>
<td>31.85±</td>
<td>32.09±</td>
<td>31.68±</td>
<td>31.90±</td>
<td>31.74±</td>
<td>32.91±</td>
<td>32.91±</td>
</tr>
<tr>
<td></td>
<td>± 0.74</td>
<td>0.68</td>
<td>0.70</td>
<td>0.70</td>
<td>0.69</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>CTS before</td>
<td>29.74±</td>
<td>29.21±</td>
<td>28.91±</td>
<td>28.84±</td>
<td>28.77±</td>
<td>31.32±</td>
<td>31.31±</td>
</tr>
<tr>
<td>CTR</td>
<td>0.80</td>
<td>0.92</td>
<td>0.93</td>
<td>0.94</td>
<td>0.94</td>
<td>0.43</td>
<td>0.50</td>
</tr>
<tr>
<td>CTS after CTR</td>
<td>32.10±</td>
<td>32.17±</td>
<td>32.04±</td>
<td>31.95±</td>
<td>32.07±</td>
<td>33.17±</td>
<td>33.12±</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.51</td>
<td>0.53</td>
<td>0.56</td>
<td>0.54</td>
<td>0.30</td>
<td>0.33</td>
</tr>
<tr>
<td>Healthy control</td>
<td>30.31±</td>
<td>30.14±</td>
<td>30.08±</td>
<td>29.97±</td>
<td>30.00±</td>
<td>31.98±</td>
<td>31.78±</td>
</tr>
<tr>
<td></td>
<td>± 0.61</td>
<td>0.63</td>
<td>0.64</td>
<td>0.65</td>
<td>0.64</td>
<td>0.37</td>
<td>0.40</td>
</tr>
</tbody>
</table>

D1, D2, D3 significantly higher after CTR at 0.05 level

N.S.
Fig. 9 The mean finger-tip temperatures (°C) of healthy controls and CTS patients before and after CTR.

5.3. Non-Specific Neck & Shoulder Pain Syndrome

DIRT, skin surface evaporation and tactile threshold measurements were all performed in the NS-NSP patients.

The tactile thresholds (in nominal force, g) of all the fingers were significantly higher in NS-NSP group (n=34) than in the control group (n=30) (P1, P2, P3, P4 and P5: p<0.01, see Table 7).

Table 7 Finger-tip tactile thresholds in NS-NSP and control subjects. P: finger-tip tactile threshold (nominal force, g)

<table>
<thead>
<tr>
<th></th>
<th>#P1 ± 2SD</th>
<th>#P2+2SD</th>
<th>#P3+2SD</th>
<th>#P4+2SD</th>
<th>#P5+2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (N=30)</td>
<td>29.03±1.99</td>
<td>26.53±0.37</td>
<td>28.77±1.99</td>
<td>26.53±0.37</td>
<td>26.53±0.37</td>
</tr>
<tr>
<td>NS-NSP (N=34)</td>
<td>168.03±50.90</td>
<td>182.56±51.51</td>
<td>176.58±52.11</td>
<td>171.56±52.08</td>
<td>170.62±52.09</td>
</tr>
</tbody>
</table>

#: p<0.01

The infrared thermography showed that all the finger-tip temperatures (average temperature of 30 mm² spot in the middle of each finger-tip) were lower) in NS-NSP (n=38) group than in the control group (n=30) although the differences were not statistically significant (see Fig. 10).
Fig. 10. Mean of finger-tip temperatures (°C) of the digits 1 to 5 (D1 - D5) in control, NS-NSP and CTS subjects. The differences in the mean temperatures between the groups were not statistically significant.

The skin surface evaporation (V) was significantly lower in the fingers of NS-NSP patients (n=38) compared to the corresponding values in the healthy controls (n=32) (V1, V3 and V4: p<0.001; V2 and V5: p<0.005. see Table 8).

Table 8 Finger-tip evaporation in the control and NS-NSP subjects. V: finger-tip evaporation (g/m²/h)

<table>
<thead>
<tr>
<th></th>
<th><strong>V1+2SD</strong></th>
<th>*V2+2SD</th>
<th>**V3+2SD</th>
<th>**V4+2SD</th>
<th>*V5+2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>125.80±8.80</td>
<td>97.03±9.89</td>
<td>102.32±10.12</td>
<td>94.57±9.76</td>
<td>71.97±7.11</td>
</tr>
<tr>
<td>(n=32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS-NSP</td>
<td>72.45±5.75</td>
<td>61.66±6.20</td>
<td>55.59±5.49</td>
<td>49.94±3.68</td>
<td>47.72±4.46</td>
</tr>
<tr>
<td>(n=38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: p<0.005, **: p<0.001
**5.4. Cold Provocation Test**

In the control group (10 hands of 5 subjects), the immersion of the feet into the ice water for 45 seconds evoked temperature changes in their hands. At first, the hands turned colder and after 2-8 minutes, they started to warm up. They turned and stayed warmer than before the cold provocation for more than 15 minutes except for both hands of one subject. These hands turned cold and became even colder after the provocation. In the CTS patients, the reactions were delayed or absent in the affected nerve distribution area (Fig. 11 - 12).

![Image](image.png)

**Fig. 11.** The skin temperature responses to the cold provocation test (immersion of the feet into ice water for 45 seconds) in the hands of a healthy subject, male, 22 yrs, as recorded by DIRT. (A): Before cold provocation; (B): 2 min. after cold provocation, the fingers were colder than before the provocation; (C): 10 min. after provocation, the fingers turned even warmer than before cold provocation.
Fig. 12. The skin temperature responses to the cold provocation test (immersion the feet in the ice water for 45 seconds) of a male, 47yrs, with CTS in both hands, (A): Before cold provocation the 2nd, 3rd, 4th fingers of both hands were colder than other fingers; (B): 4 min. after the cold provocation, the fingers became even warmer than before cold provocation except for the 2nd, 3rd, 4th fingers which stayed cold. (C): 5 min. after provocation, the fingers became even warmer than before cold provocation except for the 2nd, 3rd, 4th fingers of the right hand and the 2nd, 3rd fingers of the left hand which stayed cold. (D): 12 min. after the cold provocation the fingers became even warmer than before the cold provocation except for the 2nd, 3rd, 4th fingers of the right hand and 2nd, 3rd fingers of the left hand which remained cold.
6. DISCUSSION

6.1. Carpal Tunnel Syndrome and Sympathetic Pathophysiology

In CTS patients, the temperatures of the affected hands showed abnormalities. The means of MI and MED.ULN of the CTS subjects were significantly different from those of the healthy controls. The MI was computed by \((D1-D2) + (D2-D3) + (D1-D3)\), and MED.ULN was computed by \((D1-D5) + (D2-D5) + (D3-D5) + (Th-Ht)\). As stated previously, digits D1, D2 and D3 are innervated by the median nerve. The higher MI, the more variable the skin temperature in the median nerve distribution area, and it may reflect the malfunction of vasoregulation (Meyers, Cros et al. 1989). Therefore a different MI and MED.ULN mean that the temperatures of the median nerve distribution area of the CTS were significantly different from the control group. Accordingly, it can be concluded that in CTS there is a temperature difference between the areas innervated by the median and ulnar nerves and it was accordance with earlier reports (Meyers, Cros et al. 1989; Tchou, Costich et al. 1992).

The skin temperature is dependent on the local circulation and the vasomotor activity, which is regulated by the sympathetic nervous system (Breivik, Cousins et al. 1998). In CTS patients, the median nerve became compressed at the wrist, as the condition progresses, sympathetic denervation may occur, and they may cause initially paralytic vasodilation and accordingly an increase of the blood flow and temperature to the affected area (Aminoff 1979; Gautherie, Jesel et al. 1995). After the initial period of vasodilation in the first 5 to 8 months, a vasoconstrictive phase develops, when the temperature of the affected area became reduced (Pulst and Haller 1981). This may be...
due to postdenervation hypersensitivity of the blood vessels to circulating catecholamines (Pulst and Haller 1981). These changes may be the reason for the variable skin temperature in the areas innervated by the median nerve. Another potential underlying mechanism could be an antidromic activation of the afferent thin Aδ and C-fibers. It has been shown that activation of nociceptive afferents results in local warming of the area where the pain is felt (Comstock, Ochoa et al. 1986). This may be due to the release of sensory neuropeptides e.g. substance P and CGRP, both of which are vasodilators, from the nerve endings (Comstock, Ochoa et al. 1986). In addition, a lesion in the median nerve may generate plastic changes in the afferent sensory and sympathetic postganglionic neurons. This may lead to chemical coupling between the sympathetic and sensory afferent neurons. Such coupling may cause activation and/or sensitization of the primary afferents and may affect the reactivity of the blood vessels. (Baron, Janig et al. 1988; Michaelis and Janig 1998).

Also, at the beginning of CTS, the tendons and soft tissues at the wrist and nearby areas are inflamed, and this may also increase the temperature (Lu and Tang 1995; Franzblau, Salerno et al. 1997). There were a few CTS subjects in present study with normal temperatures in the median nerve distribution area and it is possible that in those cases the vasoregulation had not yet been affected.

The cold provocation test, however, proved that in CTS, there was evidence of abnormal vasoregulation in the area innervated by the median nerve. In healthy subjects, the 45 seconds cold provocation (with the feet placed into ice-water) caused a decrease
in the skin temperature indicating that vasoconstriction of the hands had occurred resulting in decreased blood flow. This response must have been induced by reflex activation of the sympathetic nervous system mediated by the CNS. In response to the cold provocation, the heart rate and muscle activity also increase and result in an elevated heat production to maintain body temperature (Salerno, Corrao et al. 1990). When the cold stimulus ended after 45 seconds this heat generation system was still active. This may be the reason why the healthy hands first turned colder and warmed up later on. Because of the dysfunction of the sympathetic fibres in the median nerve in the CTS hands, the above mentioned reflex had become disrupted, and the temperature changes in the distribution area of the median nerve were absent or considerably impaired. (Salerno, Corrao et al. 1990; Dishman, Nakamura et al. 2003) As far as I know that there are no such findings were reported.

Thus, DIRT may be useful for revealing the integrity or dysfunction of vasoregulation. In combination with the cold provocation test or maybe with some other provocations which activate the sympathetic system, it may be helpful in the diagnosis of CTS.

However, in this study, only those CTS patients who were diagnosed by a hand surgeon and who fulfilled our NCS criteria were studied, which means that those very mild CTS hands were not included in this study. As mentioned in § 2.8, there are about 10% CTS patients who could have been considered as having normal NCS results, especially had we used the index finger to measure the SCV, since it has been reported the index finger might be less sensitive than middle finger (Macdonell, Schwartz et al. 1990). Accordingly, a study with several subgroups differentiated by NCS grading and duration
and severity of the symptoms would be needed in order to control the methodology in more detail.

6.2 Carpal Tunnel Release: Recovery of Vasoregulation

Six months after the CTR operation, most of the patients no longer were experiencing the subjective symptoms of CTS such as numbness, pain and swelling and the results of NCS were back to normal, reflecting the good capacity for functional recovery of the compressed nerves after CTR. However, in two hands (9%) numbness and weakness were still present. This may be due to delayed recovery of some nerve fibers even though this was not evident in NCS.

The hand temperatures also approached the normal values. In particular, the temperature difference between the finger-tips innervated by the median and ulnar nerves was lower compared to that before the CTR operation.

Altogether these findings indicate that the function of the motor, sensory and sympathetic nerve fibers of median nerve are capable of recovery and the vasomotor-activity may revert to normal after the decompression of the median nerve as a result of the operation.

One interesting question is why the temperatures in the area innervated by the ulnar nerve were also lower before CTR and increased after the CTR operation. This may be due to the fact that most of the operated patients had suffered severe and/or long lasting pain. It is possible that in such cases, changes take place in the pain regulatory
mechanisms in the central nervous system (CNS). As a result, the function of the nerves adjacent to the injured area may also be affected. It has been reported that noxious stimuli can elicit extensive sympathetically mediated constriction of the cutaneous vascular bed (Blessing and Nalivaiko 2000; Blessing 2003). Such changes could explain why the vasoconstriction also occurred outside the territory of the affected nerve e.g. in the area innervated by the ulnar nerve. In some patients, the damage of the nerve fibers due to compression may have been too severe. These fibers may have lost their function, and the pain had disappeared. The number of the subjects of this study was too limited, but a new study is underway with subgroups which have been differentiated by NCS grading, duration and severity of symptoms.

In conclusion, altered function of the pain regulation and reflex responses mediated via CNS could explain why the temperature of the whole CTS hand was lower than in normal subjects. However, another explanation for the restoration of the temperature back to normal may be due to the intimate relationship between the transverse and the volar carpal ligament. As a result, the ulnar nerve may also be affected in CTS. In fact, an increase in the volume of the Guyon's canal and a decrease in the pressure both in the carpal tunnel and Guyon's canal after CTR have been reported (Ablove, Moy et al. 1996). Accordingly a release of the compression of the ulnar nerve may also occur. Moreover, some of the preganglionic sympathetic fibers are ascending or descending within the sympathetic trunk. The signals may be transmitted up - and/or downwards (see Fig. 13). This could also explain why vasoconstriction occurred outside the territory of the affected nerve. Also, some afferents and efferents of the median nerve
and the ulnar nerve may connect to the same spinal segment (see Fig. 14), and they may interfere with each other (Snell 2004). In fact, it has been reported that a widespread reduction in the blood circulation is associated with the upper extremity musculoskeletal disorders such as trapezius myalgia (Larsson, Öberg et al. 1999), the cervicobrachial syndrome (Larsson, Cai et al. 1998), nerve compression syndromes (Lundborg, Rydevik et al. 1988; Mackinnon and Dellon 1988; Novak and Mackinnon 1999) and tendon disorders (Benjamin and Ralphs 1994).

Fig. 13. The complexity of the reflex system of the sympathetic nervous system. Note that for simplicity only the left paravertebral ganglionic chain is shown. Modified from (Guyton and Hall 2001).
Fig. 14. Roots, trunks, cords and terminal branches of the brachial plexus, modified from (Snell 2004)

It is difficult to define exclusively by DIRT studies if the area innervated by median nerve was abnormal in the CTR group, because the area innervated by the ulnar nerve was also affected. Thus, DIRT may not be sufficiently accurate when studying severe CTS cases.

Another interesting finding was that the non-CTS hands of the CTS patients were also colder than those of the healthy controls before CTR but their temperatures approached the normal level after the operation. The mechanisms involved may be at least in part similar to those in the areas innervated by the ulnar nerve in the CTS hands as discussed above. Namely, they may reflect a contribution CNS inputs. In addition, it has been
reported that in CTS patients, both hands tend to be affected even when there are no symptoms such as changes in the nerve conduction and subjective symptoms in the non-CTS hands it was claimed that the symptoms may appear later (de Krom, Knipschild et al. 1992; Lu and Tang 1995; Bagatur and Zorer 2001; Mondelli, Giannini et al. 2002; Prick, Blaauw et al. 2003; Fuller 2004), this may well explain why we observed thermo-abnormalities in the non-CTS hand of the CTS patients. The results suggest that, at least in some cases, altered vasoregulation might be an earlier sign of CTS than the recorded changes in the nerve conduction or even the subjective symptoms. One possible mechanism is that the pain and other symptoms may elicit anxiety, and anxiety can activate the autonomic nervous system and be the cause of the impairment of vascular reactivity in both hands (Carter, Cooke et al. 2005).

Thus, DIRT may be useful as an additional tool for the follow-up of the development of functional abnormalities in the vasoregulation as well as for monitoring the functional recovery after the treatment in CTS.

6.3. Pathophysiology of the nerve fibers in NS-NSP

The present results showed that the tactile thresholds were elevated in NS-NSP patients. There were statistically significant threshold differences between NS-NSP and healthy groups in all finger-tips. This finding indicates that the tactile sensitivity was altered both in the median and the ulnar nerve distribution areas in the hands of NS-NSP patients. The causes of such a sensory deficit could be either peripheral or central in origin. The neck and shoulder pain is sensed in the central nervous system, and the
persistent pain may interfere with the tactile sensations at the same and nearby spinal levels or even at a higher level of the CNS. Positron emission tomography (PET) studies have demonstrated adaptive changes in the thalamus in complex regional pain syndrome (Fukumoto, Ushida et al. 1999), and a similar situation may also take place in NS-NSP. On the other hand, in the periphery, mild nerve compression may have existed even when the results of ENMG and MRI were still normal but the tactile thresholds of the finger-tips were already elevated. In this respect, also the finding that there was a large variation in the tactile thresholds of the affected hands also is interesting. This phenomenon may reflect the variability in the effect of the compression on the mechanosensitive afferents. It is also possible that some temporal variation may exist in the functional capacity of the nerve fibers which carry tactile somatosensory information. In this respect follow-up of the tactile thresholds in the same subjects would be worthwhile. However, these kinds of measurements were not performed in the present study.

The measurement of the tactile thresholds by using monofilaments is an old method in sensory physiology. Max von Frey (1895) developed this elegant way to measure the tactile sensation with carefully calibrated stimuli made from horse and human hairs (Freeman and Okun 2002). Nowadays, nylon monofilaments of varying diameters are used. The method can be considered as a golden standard for any other tactile perception test (Boivie, Hansson et al. 1994) and was applied not only in the NS-NSP study, but can also be used to evaluate CTS, LBP and other MSDs.
The finger-tip evaporation values were significantly lower in the NS-NSP group i.e. again both in median and ulnar nerve distribution areas. The results also showed that all of the finger-tip temperatures were lower in NS-NSP subjects than in the control group. The evaporation is related to the skin surface temperature and the function of sweat glands, the higher the temperature and the more sweating, the higher the evaporation. The extent of sweating is regulated by the sympathetic nervous system (Guyton and Hall 2001). The changes in the evaporation suggest that the microcirculation of the hands of the NS-NSP patients had been affected by the condition even though the temperature decline was too small to reach a statistically significant level. The lower finger-tip evaporation and temperature suggest that the blood circulation may have been reduced in the hands of the NS-NSP patients. (Guyton and Hall 2001)

As already mentioned, pain stimuli elicit a sympathetically mediated constriction of the cutaneous vascular bed (Blessing and Nalivaiko 2000; Blessing 2003) and reduce the blood flow to all of the fingers. Moreover, persistent pain may cause psychological stress which also can provoke vasoconstriction. In the present study, lower temperatures were recorded not only in affected median nerve distribution area, but also in the area innervated by the ulnar nerve in the CTS hand and even in the healthy hand of the opposite side. In addition, NS-NSP may damage the sympathetic nerve fibers and in this way affect the microcirculation and evoke dysfunction of the sweat glands (Breivik, Cousins et al. 1998; Ming, Zaproudina et al. 2005). As a consequence, the reduced blood flow and sweat gland impaired function may lower finger-tip evaporation and temperature in the NS-NSP. As evaporation requires both heat and blood flow also
usually an intact sympathetic regulation of the sweat glands, it seems to be a more sensitive indicator of the sympathetic dysfunction in NS-NSP than the temperature changes. Thus the evaporation recordings seem to offer an advantage over DIRT as an indicator of sympathetic dysfunction in NS-NSP.

With respect to the results obtained with the various imaging methods e.g. CT and MRI, the results obtained with these techniques can be negative in spite of the existence of peripheral nervous disorders such as nerve trunk compression in NS-NSP. However, these disorders can be revealed in the skin temperature, evaporation and tactile threshold measurements.

In conclusion, patients with NS-NSP may exhibit impairments of the function of the peripheral nervous system especially the function of vasoactive sympathetic fibers. Also, the tactile sensation may be affected and the mechanisms are still to be clarified but may involve either the modulation of the central nervous system function or direct compression of the peripheral nerves.

6.4. Thermal changes and other ULMSDs

Temperature changes have also been found in other musculoskeletal disorders. It has been reported that 27% of office workers with upper limb musculoskeletal disorders report that they have cold hands (Sluiter, Rest et al. 2000). Some researchers have reported that the reduced blood circulation is associated with the pathophysiology of upper limb musculoskeletal disorders (ULMSDs) such as trapezius myalgia (Larsson, Öberg et al. 1999), the cervicobrachial syndrome (Larsson, Cai et al. 1998), nerve
compression syndromes (Lundborg, Rydevik et al. 1988; Mackinnon and Dellon 1988; Novak and Mackinnon 1999), and tendon disorders (Benjamin and Ralphs 1994). One of our studies on LBP showed that there were significant temperature changes in the hands of some of these patients (Zaproudina, Ming et al. 2006). Accordingly, the results of the present study are in line with those reported previously.

6.5. Comments on the methodology

Some studies using thermography in CTS and other musculoskeletal disorders have been reported within the past 20 years (Pulst and Haller 1981; Meyers, Cros et al. 1989; Tchou, Costich et al. 1992; Sharma, Smith et al. 1997; Gold, Cherniack et al. 2004), but overall the success has been only limited. However, the present technology is far more advanced compared to that used before. The direct recording of the temperatures into a computer was convenient and also provided more information. The device used in the current study was much more sensitive (sensitivity 0.05°C) compared to those used previously, and it provided the possibility to record the temperatures on-line and subsequently to compute the data in several different ways. Digital infrared thermography seems to have potential as a diagnostic tool and may be represent in the future an additional approach for the differential diagnosis of CTS and other ULMSDs especially when combined with the cold provocation test. It is also a way to evaluate objectively the vasomotor activity of the sympathetic nerve fibers (Brelsford and Uematsu 1985; Elie and Guihenec 1990; Park, Park et al. 1994). Further follow-up studies are, however, needed to clarify the progress of neuropathophysiology, to differentiate the separate phases of neural injuries and to investigate the reversibility of
the functional abnormalities. Compared with other methods, DIRT is non-invasive, causes no uncomfortable experience and its costs are low.

The present results indicate that the thermography, tactile threshold and evaporation measurements in combination may be helpful in the examination of the neural pathophysiology in CTS and NS-NSP. It seems that these methods can be applied also in other musculoskeletal disorders. They are non-invasive and straightforward. The repeated measurements are, therefore, readily accepted by the patients. These methods provide a way to study the ULMSDs from a different perspective than that provided by CT, MRI and ENMG. However, many factors e.g. stress, fear, environmental temperature, moisture and background noise can affect the measurements. In order to minimize such confounding factors, all measurements in the present study were performed under standard conditions as described in the methods. Nonetheless, further studies on the reproducibility of the DIRT are needed before this technique can enter routine clinical practice.

The number of subjects in each group was limited in the present studies, but nonetheless statistically significant findings were obtained. It was difficult to obtain larger study groups because the local population is not large. It is likely that we had access to larger patient groups, the more statistically significant differences would have been found in the measured values.

6.6. Future directions

In the future, studies of ULMSDs using the digital infrared thermography, skin
evaporation and tactile thresholds should be continued. 1) The follow-up the changes of these parameters in different phases of the disorders and experimental pain models e.g. during capsaicin-induced pain in healthy controls may give more information on the sensory and sympathetic pathophysiology of ULMSDs as well as the mechanisms and role of secondary pain in the recorded vasoregulatory disorders. 2) Studies on other types of musculoskeletal disorders and peripheral nerve disorders would be needed for comparison to reveal the possible clinical applicability of the measurement techniques. 3) The methodological studies which can reveal and possibly improve the sensitivity and specificity of the applied methods will also be needed. 4) Also, more studies on the functional impairment of different types of nerve fibers in connection with nerve compression should be conducted. A combination of DIRT, NCS and tactile sensitivity testing could give information on the responses of the various fiber groups under such conditions. 5) Epidemiological studies in different working populations are needed to determine the morbidity and to define risk factors for ULMSDs. There are several new populations who complain of pain, possibly related to ULMSDs, which have never been studied. For instance, hardly any studies have been performed regarding the hand joint problems related to mobile phone use although they these disorders so seem to be increasingly common (BBC News 2005; Menz 2005; Ming, Pietikainen et al. 2006).
7. CONCLUSIONS

The novel findings of present study were: 1) there were significant temperature changes in the hands of CTS subjects before they were operated (CTR). After this procedure, the hand temperatures did not differ from control. The temperature changes also occurred in the territory of the ulnar nerve and opposite hand even in the hand that was considered healthy. 2) The present study also showed that the skin temperature, evaporation and tactile sensitivity were reduced in the hands of NS-NSP patients. 3) The findings in the cold provocation test in CTS hands revealed that the responses to the cold provocation were delayed or absent in the median nerve innervated area. As far as I am aware, this is the first time that such findings have been reported.

The findings of temperature changes in CTS hands (not only those hands undergoing the operation) are in accordance with some earlier reports. Also, the findings of thermo-abnormalities in the non-CTS hand of CTS patients are in agreement with some earlier reports which have claimed that the CTS may be very often bilateral.

These findings support the conclusion that the blood flow regulation in CTS and NS-NSP is abnormal, possibly because of disturbed sympathetic vasomotor regulation and that the circulation revert to normal at the same time as there is alleviation of the other symptoms of CTS i.e. when these are recorded six months after the CTR operation.

In NS-NSP patients, long lasting nerve pain may also affect tactile sensitivity.

The methods applied in the present study may be useful as additional tools in the differential diagnosis of CTS and NS-NSP and be helpful in the follow up of the
development as well as the recovery of functional abnormalities in these disorders. The
DIRT technique used in present study was superior to previously techniques and
provided detailed and multifaceted results.

Further studies are needed to clarify the progression and mechanisms behind the
neuropathophysiology in ULMSDs, to differentiate this disorder from the various phases and the
different types of nerve injuries and to investigate the reversibility of these changes.
REFERENCES:


sympathetic neurones recorded in awake human subjects." Autonomic Neuroscience 95(1-2): 146.


Upper limb musculoskeletal disorders in highly repetitive industries: precise anatomical physical findings.

Work-related cumulative trauma disorders of the upper extremity.


Kuopio University Publications D. Medical Sciences


D 393. Tuhkanen, Hanna. DNA copy number changes in the stromal and epithelial cells of ovarian and breast tumours. 2006. 112 p. Acad. Diss.


