# POST-TRAUMATIC COLD INTOLERANCE IN MEDIAN AND ULNAR NERVE INJURY PATIENTS

## SUBJECTIVE & OBJECTIVE FINDINGS

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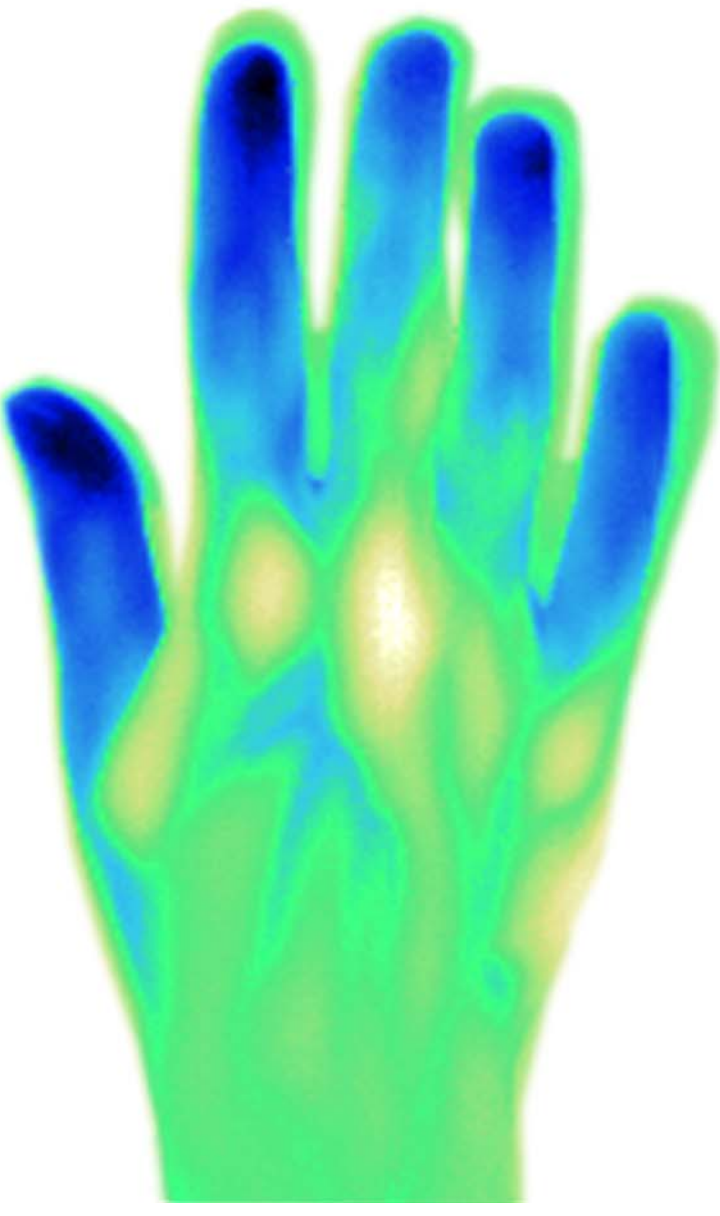
ALEID C.J. RUIJS, M.D.



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## Subjective and Objective findings

Aleid C.J. Ruijs

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# Post-Traumatic Cold Intolerance in Median and Ulnar Nerve Injury Patients

## Subjective and Objective findings

# Post-Traumatische Koude Intolerantie na Letsel van de Nervus Medianus of de Nervus Ulnaris

## Subjectieve en Objectieve Bevindingen

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# Chapter 1

## Case and General Introduction

## 1.1 General introduction and case.

The objective of this thesis was to investigate the pathophysiology and consequences of cold intolerance following peripheral nerve injury. The reasons for choosing this topic were the frequent questions and complaints made by patients during their follow-up visits and the lack of understanding thereof. The following case will illustrate the clinical problems that are the main theme of this thesis. They are frequently encountered after a peripheral nerve injury or upper extremity injury and include specific problems occurring during or after cold exposure:

> While out with his friends on a Saturday night, a thirty year old man suffers a knife wound to his right forearm after a fight. He is brought in by ambulance, paramedics having bandaged his severely bleeding wound, with a length of approximately 3 centimetres. The hand surgeon on call performs a physical examination of the hand. She finds a severely bleeding wound and impaired sensibility in the ring and little fingers and weakness of sideways movement of the fingers and thumb, suggesting transection injury of both the ulnar nerve and ulnar artery. He is taken to the operating theatre and the same day both structures are microsurgically repaired and the wound is closed.
>
> After awakening from surgery, still slightly hung over, he realizes what has happened and worries about his future. He informs the surgeon that he works as a carpenter, making design furniture for a local shop. In his spare time, he enjoys mountaineering and has recently climbed Mont Blanc. He is intending to go to the Himalayas next year to climb a 7000 meter high peak, and is worried about the risks of frostbite.

To answer her patient's questions and address his concerns, specifically for his work and mountaineering activities, the surgeon needs to know, amongst others:

- The incidence and severity following a specific nerve injury when taking into account the specific patient characteristics (age, gender, co-morbidity, number of severed structures, psychological stress, and compliance to hand therapy, etc.). *[Introduction, Chapters 3 & 4]*
- The incidence and severity of post-traumatic cold intolerance after different types of injuries to the upper extremity (nerve injury, digital re-plantation, fractures, soft tissue injury). *[Introduction, Chapters 2, 3, 4 & 5]*

As this thesis concentrates on cold intolerance, emphasis will be placed on questions concerning this subject, such as its signs and symptoms, pathophysiology and changes in thermo-regulation:

- How can the severity of subjective symptoms of cold intolerance be measured in a patient and followed over time? *[Introduction, Chapters 3, 4 & 5]*
- How can symptoms of cold intolerance be measured objectively and followed over time? *[Chapters 6, 7 & 8]*
- Are changes in thermoregulation of the hands after nerve injury responsible for the subjective symptoms of cold intolerance? *[Chapters 6 & 7]*
- Do changes in thermoregulation of hands after nerve injury normalize over time? Is there a correlation with the degree of sensory recovery? *[Chapters 6 & 7]*
- Is cold induced vasodilation (CIVD, Hunting reaction) upon prolonged cold exposure altered in peripheral nerve injury patients? *[Chapter 8]*
- How is protection against frostbite altered after peripheral nerve injury? Should additional protective measurements against frostbite be undertaken when exposed to cold environments? *[Chapter 8]*

This thesis is devoted to post-traumatic cold intolerance in peripheral nerve injury patients and seeks to answer the questions set out above.

### 1.2 Post-traumatic Cold Intolerance: signs and symptoms.

Cold intolerance may be defined as an exaggerated or abnormal reaction to mild to severe cold exposure of hands and fingers with signs, symptoms or a change in behaviour. Symptoms include discomfort, avoidance of cold and protection against cold. It is manifested as pain, discolouration (white/blue), numbness, weakness or stiffness of the fingers[(1-5)]. Signs can be discoloration (white/blue) of the fingers or slower re-warming after returning into a warm environment. Change in behaviour may include the avoidance of cold or protection against cold.

Several names have been used to describe this pattern of cold related symptoms following upper extremity injury, such as cold sensitivity[(6-11)], cold hypersensitivity[(12, 13)], cold allodynia[(14)] and Trauma Induced Cold Associated Symptoms (TICAS)[(1)]. The term Cold Intolerance seems to be the most frequently used[(2-4, 15-22)]. In this thesis, we choose to use the term post-traumatic cold intolerance, as it covers the three main properties of cold intolerance: it is abnormal (intolerance), occurs during and after exposure to cold and we will study cold intolerance as a complication after trauma to a peripheral nerve of the upper extremity. It is important to differentiate from non post-traumatic disorders such as Raynaud's phenomenon, scleroderma, thoracic outlet syndrome or Buerger's disease, which can have similar signs and symptoms.

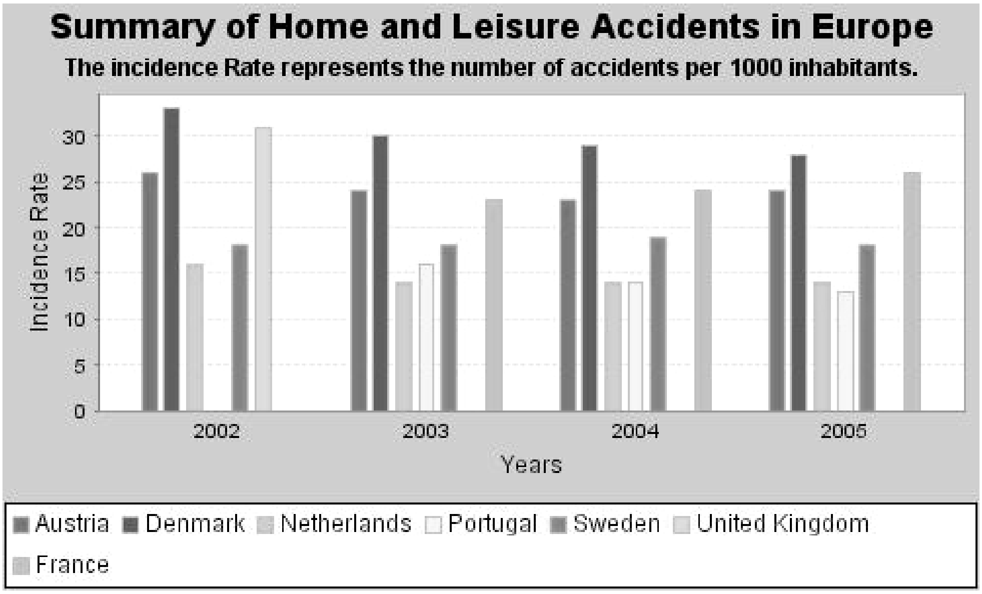
Post-traumatic cold intolerance is a frequent sequel of upper extremity trauma to the soft tissues, nerves, arteries and bones (wounds, lesions, fractures). It can also occur after chronic repetitive trauma during vibration exposure in workers[(23, 24)]. The incidence of post-traumatic cold intolerance is particularly high following upper extremity nerve injury. In the majority of peripheral nerve-injured patients, cold intolerance is reported to be the most bothersome, prolonged and disabling symptom, affecting both work and leisure activities[(4, 8, 16, 17, 19, 20, 25)]. The signs and symptoms of cold intolerance do not present directly post-injury[(26)], but typically develop in the first four months after injury, with a peak level during the first year after injury[(9, 27)]. Several studies have shown that in the majority of patients these symptoms do not improve over time[(17, 20, 25)]. Median and ulnar nerve injuries have been found to have a significantly higher severity of cold intolerance than other upper extremity nerve injuries. Associated vessel injury, smoking, crush injury, level of the nerve lesion and early post-operative pain have all been recorded as predicting variables[(5, 6, 15, 28-30)]. An inverse relationship with sensory recovery has also been observed[(31)], directing towards a neural pathophysiology.

Our purpose was to examine the signs, symptoms and behavioural changes of peripheral nerve injury patients with post-traumatic cold intolerance, both subjectively and objectively. We started with subjective testing of their signs, symptoms and behaviour using a validated questionnaire. Then we proceeded to objective testing of thermo-physiologic signs using both cold-stress testing and a newly developed instrument that tests the CIVD reaction. These methods of testing will be further explained in the following sections.

### 1.3 Incidence of upper extremity injuries and impact on society.

To stress the impact on society of post-traumatic cold intolerance and to estimate how many people are involved, data are presented on the incidence of upper extremity injuries and more specific peripheral nerve injuries. The Injury Database (IDB) is a database controlled by the European Commission on non-fatal home, leisure and sports accidents in Austria, Denmark, France, The Netherlands, Portugal, Sweden and the United Kingdom.(32, 33). It is an Internet database set up by DG SANCO (Directorate General for Health and Consumer Affairs of the European Commission) under the Injury Prevention Programme in 1999, in order to provide central access to the data collected in the Member States under the EHLASS Programme (European Home and Leisure Accident Surveillance System). Annually, more than 50 million people in the European Union receive medical treatment for an injury, from which an estimated 6.8 million are admitted to hospital (Table 1). Almost 50% of these injuries concern the upper extremity, including arms, wrists and hands. In The Netherlands, 633.250 injuries per year occurred during 2002-2005. Of these, 264.500 injuries were injuries to the upper extremity (incidence rate 14.5/1000). In The Netherlands and Denmark, the rate of injury to the hand or wrist was 29% of all injuries, respectively 18 or 36 per 1000 inhabitants per year(34-39). The majority of patients with upper extremity injury are males between 16 and 35 years old(33, 39), while the highest incidence in girls is around 10 years of age(32, 33, 40). The causes of injury in decreasing order of frequency are: home and leisure accidents (including suicide attempts and alcohol or drug abuse related injuries), occupational accidents, sports injuries and motor vehicle accidents(34, 41). Peripheral nerve injuries occur typically in men (70-80%) during transport (motor vehicle crash, motorcycle crash) or as a result of aggression (deliberate breakage of windows, stab wounds, gunshot wounds). The agents causing peripheral nerve injury were glass (55.2%) sharp metal objects (predominantly knives or other tools) (29.0%), machinery (9.2%), and 6.5%(42) of other or unspecified nature. In a Polish study of 1199 consecutive hand injuries, 26.6% of patients had used alcohol, contributing to the accident(31).

Table 1. The incidence of upper extremity injuries in Europe during 2002-2005.




*Summary of home and leisure accidents in Europe from 2002- 2005 regarding the upper extremity. © European Injury Database[39]*

**1.4 Costs of upper extremity injuries.**

From a public health point of view, upper extremity injuries, due to their impact on hand function, have major implications for patients, employers, the economy, the health service and both personal and corporate insurance[43]. The cost of upper extremity injuries is made up by both direct medical costs (hospital stay, diagnostic procedures, surgery, pharmaceutical treatment, post-operative hand therapy and follow-up hospital visits) and indirect costs due to lost production (sick leave, time off for treatment and rehabilitation, loss of Gross National Product (GNP) during treatments, and disability).

Direct medical costs differ according to the extent of the injury and the health care system of each country. In a study from the United States (1987), direct medical costs were calculated between $3.000 for simple cases requiring a single procedure and $22.000 for complex cases requiring replantation or multiple surgical procedures[40, 44]. In 1980 in France, direct cost of treatment was FF5223 (€796) for digital amputations and FF2316 (€353) for patients who had a stiff digit as a result of their injury. This was 20-30% of indirect costs[37]. In 2003 in Sweden, healthcare costs for minor injuries were less than €2500, but €8.000 for severe injuries and €15.000 for major hand and fore-arm trauma (30% of total costs)[45]. Direct costs were also calculated for 170 patients treated between 1999 and 2000 in Poland[42]. Direct costs made up 3-5% of the total costs and were €93 for sober patients and €129 for patients with alcohol intake[45]. Upper extremity injuries cause up to 20% of sick leaves[40]. In France in 2001, hand injuries accounted for 27% of work accidents causing loss of work of at least 1 day[40, 44], with an average of 22 lost working days[46, 47]. In a Dutch study on median and ulnar nerve injury patients, 59% returned to work within 1 year after injury and mean time off work was 31.3 weeks [48, 49].

The rehabilitation period after upper extremity injury is long and the injury frequently leads to disability. This disability is caused by a loss of hand function due to pain, tissue loss, loss of articulation, cicatrisation, loss of muscular movement, loss of normal sensibility, and can be accompanied by post-traumatic cold intolerance in temperate, continental and polar climates. Furthermore, a high level of early post-traumatic psychological stress accompanies forearm and wrist nerve injuries, negatively influencing functional outcome and work resumption[37, 40, 42, 44, 45]. Long time impairment and loss of productivity are reflected in the indirect costs, which are estimated to be 4 to 20 times the direct medical costs for hand injuries [40]. In France, 29.8% of work related accidents injuring the hands caused permanent partial impairment. About one-fifth of the total costs of permanent impairment were found to be due to hand injuries[4, 8, 13, 16, 17, 19, 20, 25]. These figures are averages, and when the rehabilitation period is prolonged by complications, the actual figures are significantly higher.

Consequences of post-traumatic cold intolerance as a complication of upper extremity injury often include a change of work and sometimes re-education is necessary, such as changing manual outdoor labour to indoor deskwork. Transportation is also affected, as riding a bicycle or waiting in the cold for public transport are painful. Jobs in and around the house that were easily done before the injury (such as cleaning outside windows, removing snow, or washing the car) now have to be done by another (hired) person. Although not directly having an economic impact, the change in leisure activities (from outdoor sports to indoor sports) has a considerable impact on the patient’s family and social life [25, 30, 50, 51].

### 1.5 Subjective testing of post-traumatic Cold Intolerance.

In this thesis, we start with subjective testing of post-traumatic cold intolerance. This gives us an insight into the severity and the natural history of post-traumatic Cold Intolerance and it's predicting factors. In recent literature, an array of subjective tools, such as the VAS scale, single questions [4, 16, 27], or multiple questions [10], have been used both clinically and experimentally. Furthermore, a validated questionnaire consisting of 4 questions has been developed by McCabe et al.[18] in 1991 and that was modified by Irwin et al. in 1997 [9, 11, 20, 25] into the Blond McIndoe Cold Intolerance Symptom Severity (CISS) questionnaire.

Studies subjectively investigating the incidence and severity of cold intolerance in a patient population with peripheral nerve injuries are listed in table 2A. Table 2B shows studies concerning cold intolerance in amputations, replantations and revascularizations of the upper extremity, and Table 2C studies on upper extremity trauma in general. Depending on definition, patient group, follow-up and testing method, the incidence of cold intolerance ranges between 42 and 100%.

Several studies tested patients on two or three instances over time [4, 8, 16, 18, 52] and found that despite an improvement of symptoms, cold intolerance did not disappear. Other studies found a presence of post-traumatic cold intolerance after a follow-up of more then 10 years[6, 30, 52]. It might be possible that patients develop strategies for better protection of their extremities from a cold stimulus and therefore report fewer symptoms, while an abnormal reaction to a cold environment remains. However, to our knowledge, this has not been studied in sufficient detail yet.

When the results of subjective testing were compared to the injury characteristics, both a correlation with sensory recovery[3, 9, 13] and a correlation with the presence or absence of bone injury[8] was found. Chapters 3, 4 and 5 describe subjective testing performed in respectively a control group, a median and ulnar nerve injury patients group and a group of patients with a neuroma of the upper extremity.

Table 2a: Subjective testing of post-traumatic Cold Intolerance in peripheral nerve injuries of the upper extremity.

| **Author** | **N & type of injury** | **Mean FU (months)** | **Method** | **% CI** | **Comments** |
|---|---|---|---|---|---|
| Collins[18] | 50 UE NI | 120*<br>(60-504) | Questionnaire + McCabe | 76% | No improvement |
| Irwin[30] | 398 UE NI | < 120* | CISS | 83% | Mean score 41 |
| Kilinc[6] | 20 MN<br>7 UN<br>13 MN and UN | 23* | Single question | 50%<br>42%<br>70% | Wrist-level<br>Correlation with sensory recovery |
| Lenoble[26] | 82 MN or UN | 42 | Single question | MN 50%<br>UN 73% | Correlation with 2PD |
| Ruch[27] | 9 MN or UN | (7-81 days) | McCabe | Absent | Similar average score as controls |

*N= number. FU= Follow-up period. Method= testing method.*
*UE= upper extremity. NI= nerve injury. MN= median nerve. UN= ulnar nerve.*
** retrospective study*

Table 2b: replantations, amputations and revascularizations.

| **Author** | **N & type of injury** | **FU (months)** | **Method** | **% CI** | **Comments** |
|---|---|---|---|---|---|
| Backman[20] | 19 replant. | (9-95)* | 4 questions | 100% | Improvement 60% |
| Backman[13] | 10 replant. | 1/2+12+ 36 | 4 questions | 100% | Sympt. improved |
| Vaksvik[53] | 81 replant./ revasc. | 96* (72-120) | McCabe, PWES, DASH | 80% | Replantation more severe CI |
| Gelberman[5] | 29 replant. | < 36* | Single question | 90% | |
| Kay[29] | 14 replant./ revasc. | 33* (7-53) | Questionnaire | 93% | 50% improved |
| Koman[4, 16] | 4 fore-arm replant. | 24 | Interview | 75% | |
| Lithell[11] | 20 replant.<br>8 amput.<br>8 revasc.<br>4 ORIF | (24-144)* | Interview^ | 100% | No difference between groups |
| Nylander[25] | 8 replant.† | 18-21 | Questionnaire# | 88% | |
| & Povslen[54] | 8 replant.† | 144 | Questionnaire# | 63% | Pain improved |
| Schlenker[1] | 26 thumb replant. | > 6* | Interview | 85% | Correlation with age |

*FU= Folluw-up period. Method= testing method. CI= Cold Intolerance.*
*^ During the interview patients were asked if they had the following symptoms: coldness, white fingers, painful fingers, numbness, stiffness or malaise.*
*# Degree of cold-induced comfort experienced indoors, outdoors, in summer, and in winter. Change in occupational or leisure activities?*
*McCabe= the McCabe Cold Sensitivity Severity Scale, PWES= Potential Work-Exposure scale. DASH= Disabilities of the Arm, Shoulder and Hand.*
** Retrospective study. † Same patient group.*

Table 2c: upper extremity injuries in general (e.g. fractures and soft tissue injuries).

| Author | N & type of injury | FU (months) | Method | % CI | Comments |
|---|---|---|---|---|---|
| Campbell[9] | 176 hand | 24 | Open and closed questions | 73% | |
| Craigen[3] | 123 hand / forearm | 11 and 36 | McCabe<br>At 3 y the 25 worst cases | 85% at 11 m | Correlated to fracture<br>At 3 y score ↓ |
| Koman[10] | 261 UE * | - | McCabe, Levine, DASH, McGill, SF12 | 63% | Shoulder less CI, correlated to fracture |
| McCabe[17] | 35 hand<br>20 nerve<br>57 control | >12 | McCabe (CSS) score 0-400 | <br>Average 171<br>Average 80 | |
| Nancarrow[55, 56] | 65 hand # | 60- 84 | Questionnaire | 69% | Pain first week correlated to CI |

*FU= Folluw-up period. Method= testing method. CI= Cold Intolerance.*
*# Surgically treated lacerations of nerves, vessels and tendons, fractures and soft tissue damage. * Soft tissue or soft tissue and bone injuries, requiring treatment. ^ Acute trauma requiring surgery after crush, laceration, amputation, puncture and injection injuries.*

## 1.6 Thermophysiological testing in patients with post-traumatic Cold Intolerance.

As symptoms of post-traumatic Cold Intolerance, in addition to pain, include blue or white fingers, stiff fingers and numb fingers, it has been assumed that the thermo-physiological reaction to cold is disturbed, resulting in a lower arterial digital blood flow in the injured hand. In a thermo-neutral situation, the body exhibits a thermal symmetry of <0.5ºC [(57, 58)]. Although temperatures of fingers and toes are not as stable as that of other parts of the body and fluctuate between individuals and in any one individual from day to day, both sides should still be symmetric in a healthy situation [(59)].

Skin temperature in digits, palm and toes can be considered an indirect measurement of skin blood flow[(2, 14, 19, 21, 27, 29, 55, 60-77)]. Therefore, differences in skin temperature between the injured and uninjured hand are suggestive of disturbances in thermo-physiology. To analyze these thermo-physiological reactions to cold exposure, a range of tools have been used to objectivate and investigate post-traumatic cold intolerance in volunteers, patients and animal models [(78)].

It is important to distinguish between short term cooling (less than 5 minutes) and cooling for a prolonged period of time (more than 20-30 minutes). The first method is called isolated cold stress testing, where the hand or foot is cooled for a short, fixed period of time (1 to 5 minutes) and then allowed to re-warm at room temperature. When cooling for a prolonged period of time, however, the fingers will show Cold Induced Vasodilatation (CIVD), which is thought to protect the hands against frostbite [(20)]. This CIVD reaction is further described in the next chapter.

In cold stress testing, the thermo-physiological response of the fingers is measured during the short cooling period and also during the subsequent re-warming period (approximately 5-30 minutes). The cold stimulus can range between 0 to 30ºC and has been applied to the digits or hands using a water bath, a cold air chamber or a cuff containing cold water around the base of the finger (Table 3). Changes in skin temperature of the hand and fingers have been measured either using thermocouples (small fast-response thermometers) attached to the skin or infrared (video)thermography. Laser Doppler flowmetry, digital systolic blood pressures, cappilaroscopy and plethysmography have been used to investigate vascular responses. An overview of investigators that have used cold stress testing in patients with replantations or nerve injury is presented in Table 3. In Chapters 6 and 7 we used isolated cold stress testing to objectivate symptoms of post-traumatic Cold Intolerance in median or ulnar nerve injury patients.

Table 3: cold stress testing after upper extremity injury.

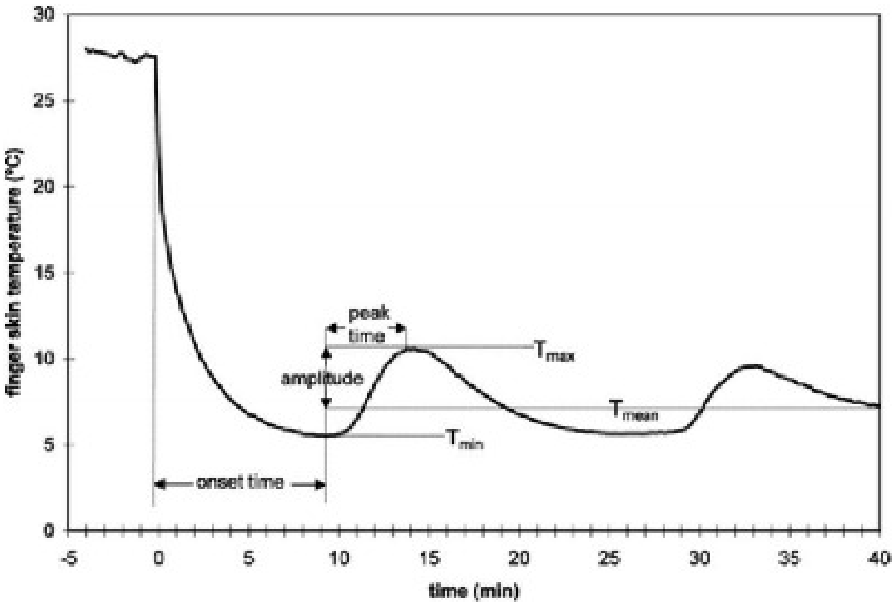
| Author | N & type of injury | FU | Method and location | | Tsk | Vasc resp | Results |
|---|---|---|---|---|---|---|---|
| Backman [20] 1993 | 10 dig replant. | 2w/1y/ 2y | cuff 30/15/10ºC | Digit | No | DSBP | B 60% |
| Backman [27] 1995 | 29 dig replant. | 9-46m | cuff 30/15/10ºC | Digit | No | DSBP | B 40% |
| Cankar[79] 2000 | 10 replant. | 2-3w | water 15ºC 6 minutes | Hand | No | LDF | D |
| Freedlander [19] 1986 | 21 replant. | <1y- 10y | Water RT/10ºC 1 minute | Hand | No | LDF | B 52% |
| Isogai[15] 1995 | 12 thumb replant. | 2-5y | Water 0ºC 1 minute | Hand | No | Pleth DSBP | C |
| Kay[5] 1985 | 14 dig replant / revasc. | | Water 15ºC | Hands | No | Pleth Art inflow DSBP | A |
| Koman[68] 1984 | 96 UE injury 24 control | | air 6-10ºC 20 minutes | Hands | TC | DSBP | C |
| Koman[29] 1986 | 4 forearm replant. | 6w, 3m, 6m, 1y, 2y | air 6-10ºC 20 minutes | Hands | TC | DSBP | A |
| Nylander[11] Povlsen[25] 1987/1995 | 8 replant. | 2, 12 y | Cuff 30/10ºC | Digit | No | DSBP | B 88% |
| Nystrom[70] | 10 replant. | 2 w | Cuff 30º/15º/10ºC | Digit | TC | DSBP | D |
| Pulst[73] 1981 | 23 high nerve lesion | 1-19 m | water 0ºC 30 sec | Hands | THG | No | < 5 m B > 6 m D |
| Ruch[26] 2003 | 9 MN or UN | 7-81 d | air 5-8ºC 20 minutes | Hands | TC | LDF | B |
| Suominen[69, 80] 1996 | 18 forearm flap | 13 m (3-24) | Water 15ºC 5 min | Hands | THG | No | C |

*FU= Folluw-up period. Method= cooling method. CI= Cold Intolerance.*
*Tsk= finger skin temperature measured.Vasc resp= analysis of vascular response.*
*LDF laser Doppler flowmetry, DSBP digital systolic blood pressure, TC thermocouples, Pleth plethysmograph, THG infrared thermographyy.*
*Dig digital, RT room temperature.*
*Digit: one digit was tested. Hand: one hand was tested. Hands: both hands were tested simultaneously.*
*Results: A= correlation with sensory recovery was found.B= percentage of patients with arterial vasospasm/ vasoconstriction. C= correlation with vasoconstriction and cold intolerance. D= vasodilatation.*

## 1.7 Continuous cooling and Cold Induced Vasodilatation (CIVD) or Hunting reaction.

In Chapter 8, the disturbance of the peripheral blood flow regulation mechanism in peripheral nerve injury patients is further studied by provoking a cold induced vasodilatation (CIVD). Cold Induced Vasodilatation (CIVD), first described by Lewis et al. in 1930 [69] as Hunting reaction, is a cyclic regulation of blood flow that is initiated when protruding body parts, such as the hands, feet, chin and nose, are continuously cooled to less than 15ºC for a period of more than 5 minutes [64, 81]. In healthy volunteers the CIVD reaction starts after 5 to 10 minutes of cooling, and is characterized by a quick rise in temperature of the fingertips, then a slow fall to almost environmental temperature. This cycle is then repeated 2 to 4 times per hour as long as the cooling continues (Figure 1).

Figure 1: CIVD reaction in the fingertip.




*Parameters derived from a temperature profile of a fingertip immersed in cold water. The onset time is the time from immersion to the minimum temperature. The amplitude is the difference between Tmin and Tmax. The peak time is the time interval between Tmin and Tmax Figure reproduced with permission from the author* [78].

To quantify the CIVD reaction, several parameters are defined. Common parameters include both minimum and maximum temperature of fingertip temperature, amplitude of the CIVD reaction (Tmax-Tmin) and peak to peak time (duration of the cycles) [78].

The common method of provoking the CIVD reaction is to immerse the hands or fingers in cold water, measuring fingertip temperature with thermocouples and blood flow with, for example, a Laser Doppler flow device. Table 4 shows an overview of experiments on CIVD since 1980. It seems that a lower temperature (less than 4°C) gives a more reliable CIVD reaction and a better synchronicity between the fingers than cooling to 5-15°C, although a lower temperature is much more painful [71, 78, 81, 82]. Cooling in water yields better results than cooling in air [82].

The amplitude of the CIVD reaction and finger skin temperature are under the influence of the body core temperature and food intake, with a higher body core temperature or food intake leading to a stronger and faster CIVD reaction [78, 83, 84]. The CIVD reaction is also characteristic for each individual, and Mekjavic et al. [85] have described seven different patterns of the CIVD reaction. As natives of cold climates in general have better CIVD reaction [86-89], it was assumed that the CIVD response can be trained by acclimatisation to cold and repeated immersions of the hands in cold water. However, previous studies have not find a benefit of cold acclimation by repeated immersion of the hands in cold water during 2 or 3 weeks [85, 90] or during a two-week stay in the arctic or other cold climate [91].

Until now, the majority of studies focused on covariates influencing the shape of the CIVD reaction in healthy subjects and elucidating aspects of the mechanism responsible for the CIVD reaction. According to Daanen et al. 2003 [78], these factors can be grouped in experimental factors and individual factors. Experimental factors include ambient temperature, body temperature, cooling medium, surface area cooled, and altitude. Individual factors include, age, gender, physical fitness, mental stress, acclimatization to cold, adaptation to cold, cold resistance training, diet, alcohol ingestion, tobacco smoking, and vascular pathology.

Several hypotheses on the mechanisms responsible for the CIVD reaction have been described, but none have yet been generally accepted. It is most likely a protection mechanism against frostbite, although recently Flouris et al. [92] suggested that it is a mechanism to lose excessive heat from the body for example during exercise as the CIVD reaction significantly diminishes body core temperature (Tc). A diminished neuromuscular function during cold exposure (manual dexterity) seems not to benefit from the raise in finger skin temperature during a CIVD reaction. [64]

To be able to measure thermo-physiological responses using infrared videothermography, a novel method was developed at our institute. This exists of a continuously cooled metal plate that effectively cools the palmar sides of the hands while measuring the thermo-physiological response of the dorsal sides of the hands with infrared videothermography. This method was used in Chapter 8 to provoke a CIVD reaction in median or nerve injury patients and to give us insight in thermo-physiological disturbances in peripheral nerve injury patients during their follow-up.

Table 4: Literature review of experiments on the CIVD reaction since 1980.

| Author | N | T test | Time (min) | Site | Test | Conclusion |
|---|---|---|---|---|---|---|
| Bergersen [93] 1999 | 10F<br>11M | 3°C | 30-45 | D3 right | T<br>LDF | I |
| Chen[94] 1996 | 4M<br>4F | 0°C air | 60 | D2 L | T | |
| Cheung[81] 2007 | 10M | 8°C | 30 | LH | T | A |
| Daanen[95] Ch6 | 12M | 5°C | 40 | LH | T | A |
| Daanen[95] Ch7 | 8M | 10°C | 47 | BH | T | A<br>B |
| Daanen[95] Ch8 | 7M: High + low Tc | 6°C | 40 | RH | T<br>LDF | B |
| Daanen[95] Ch9 | 8M: high + low Tc | 5+<br>8.5°C | Max<br>40 | BH | T | B |
| Daanen[95] Ch10 | 9M: warm, neutral, cool Tc | 8°C | 30 | DH | T | B |
| Daanen[95] Ch11 | 8M | 6°C | 40x | BH | T<br>LDF | A |
| Flouris[92] 2008 | 6M4F | -20°C air | 130 | D4 ND, body | CC | B |
| Geurts[64] 2005 | 8M4F | 9°C | 30 | D2 R<br>FDI | CC | C |
| Geurts[90] 2005 | 7M3F | 8°C | 30 | RH | CC | D |
| Jobe[96] 1985 | 8 Raynaud<br>9 control | 5 + 10+<br>15°C | 15 | D3 right | T | F |
| Livingstone [98] 1991 | 4M | 0°C | 30 | D3 ND | Tm | E |
| Livingstone [91] 1996 | 3 arctic 14d<br>3 Ottawa | 0°C | 30 | D3 ND | T | D |
| Mekjavic[85] 2008 | 9M | 8°C | 30 | RH | T | D |

| | | | | | | |
|---|---|---|---|---|---|---|
| Moriya[97] 1990 | 14F | | | | | |
| O'Brien[71] 2005 | 19M 2F | 4°C | 30 | D3 | T LDF | A |
| Purkayastha [98] 1992 | 10 control 10 arctic 6 migrant 6 arctic natives | 4°C | 30 | RH | TP | E Arctic natives best CIVD |
| Sendowski[99] 2000 | 12M | 5°C | 30 | D2R or RH or LH+D2R | T LDF | E |
| Sendowski [100] 1997 | 20 M volunteer | 5°C | 30 | D2 dh Hand Forearm | T LDF | G |
| Takano[84] 1989 | 12F before + after 700 kcal | 0°C | 10 | D3 left | T O2 | CIVD index increased |
| Van der Struijs[82] 2008 | 11M | 5°C -18°C air | 30 | D2-D4 R | | H |

*Test temperature in degrees Celsius, cooling medium water or air. Time in minutes. Body part: D3 is third digit, RH is right hand, LH is left hand, BH is both hands, ND is non-dominant hand, body= whole body cooling. Test method: T is thermocouples attached to the skin, CC is ceramic chip thermistor attached to the skin, LDF is laser Doppler flowmetry.*
*Results: A= the CIVD reaction is not homogenous and highly variable between subjects. B= CIVD reaction is correlated to Tcore, a higher Tcore gives a better CIVD reaction. C= no benefit o neuromuscular function during CIVD reaction. D= decreased CIVD reaction on cold acclimatization. E= better CIVDreaction after acclimatization. F= cooling at lower temperatures gives a stronger CIVDreaction. G= Index finger cooling earlier and faster CIVD without cardiovascular changes and less pain then hand or forearm cooling. H= Water cooling gives more frequent CIVD. I= Paralysis smooth muscle AVA causes CIVD*

## 1.8 Infrared thermography.

In Chapters 6 and 8 we chose infrared (video-)thermography to analyze re-warming patterns of the hand and cold induced vasodilatation during exposure to cold. Because skin temperature correlates highly with skin blood flow and skin sympathetic nerve activity, changes in central and peripheral mechanisms of blood flow regulation are represented by changes in skin temperature [(101)]. Videothermography is therefore able to capture the temperature of a whole extremity in a sequence of thermal (temperature) images, without contact and with a high level of accuracy and repeatability [(102)].
An infrared video camera is able to photograph infrared waves and store the acquired pictures digitally [Figure 2]. All objects with a temperature above absolute zero (-273.15ºC) emit thermal energy in the form of infrared waves. Digital infrared thermography is able to measure this emission two-dimensionally. Since the emissive factor of the skin is approximately 0.98, the measured temperature values can be interpreted as the surface temperature of the skin. The improvement of thermal and spatial resolutions in modern digital infrared cameras to a sensitivity of <0.1ºC, driven by advances in military and industrial use has provided new options for the use of infrared imaging in health care fields. The improved resolution, sampling with a speed of 1 frame/second, the ample storage and analysis methods of the digital data, and the flexibility in the experimental setup made infrared thermography our first choice for acquiring data in Chapters 6, 7 and 8. However, the infrared camera is not able to capture temperatures of an object submerged under water. Therefore, in Chapter 6, data of the (pre-) cooling period are only available where we used thermocouples in addition to infrared thermography.

## 1.9 Therapy and treatment options for cold intolerance.

Other then external protection of hands to cold exposure by using protective clothing to protect hands from exposure to cold, there is no standard treatment available. In experimental settings, relief of cold intolerance has been sought by pharmaceutical, surgical and behavioural treatments. Pharmaceutical treatment is aimed at improving peripheral vasodilatation. In a study by Isogai et al. [(66)], Beraprost, a prostacyclin analogue with a stable vasodilatatory effect, has been used in 11 patients with cold intolerance 6 to 24 months after digital revascularization or replantation. Treatment for two weeks resulted in a reduction of pain 2 weeks post-treatment in 9 of the patients, and improved skin temperature in 8 patients. No side effects were observed. Nifedipine has also been shown to be helpful in the relief of cold intolerance, but it is not suitable for long-term treatment due to the systemic effects[(103, 104)]. The effects of one to five regional intravenous guanethidine blocks were measured in 24 patients with cold intolerance. Signs of vasodilatation lasted a few days in all patients and nine patients (30%) were free of cold intolerance for at least two and up to twelve weeks after the block. Administration of the block is painful for several minutes, and one patient had a slight headache for two days [(2)]. A peripheral sympathectomy at the level of the wrist and palm has been performed in 6 patients with Raynaud's disease secondary to scleroderma and arteriographically proven occlusive distal arterial disease. Six-month follow-up showed no improvement of digital temperature, but did show diminished pain and ulcer healing in all patients[(105)].
As cold intolerance is strongly correlated to the degree of sensory recovery, improvement of sensory recovery should be pursued. Recent studies show that not only classical sensory re-education, starting when perception of touch/pressure (SWM 4.56) could be detected in the affected area is beneficial to sensory recovery, but early sensory re-learning using cortical audio-tactile interaction could further improve sensory recovery. For example, using a Sensor Glove System with incorporated microphones, Shape-Texture-Identification (STI) was improved after 1 year follow-up in the experimental group (n=14) compared to the control group (n=12)[(7)].
Using classical conditioning, the hands being submerged in a warm water bath while exposing the whole body to cold (0ºC) three times a day, three days a week for six weeks, cold intolerance improved in eight out of ten patients, and this improvement lasted up to one year in 67% of patients[(21)]. More recently, Carlsson et al. repeated this experimental setup and found an improvement in 15 of 18 hand injury patients after 12 months, but no subjective improvement in nine patients with vibration induced cold intolerance [(7)]. The search for improvement of cold

intolerance could be sought in further research on classical conditioning and prevention of symptoms by protecting the hands against cold exposure.

### 1.10 Outline and aim of this thesis:

The objective of this thesis was to analyze the signs, symptoms and behavioural changes of peripheral nerve injury patients with or without post-traumatic cold intolerance, both subjectively and objectively. To achieve these goals, we have evaluated an existing questionnaire on signs and symptoms of cold intolerance in a control group, median or ulnar nerve injury patients and patients with painful neuromas. Furthermore, to measure changes in the thermo-physiologic responses, we used infrared thermography to examine re-warming patterns of the hands and fingers during and after cold stress testing and we tested the absence or presence of Cold Induced Vasodilatation (CIVD) during continuing cold exposure to the hands.

In ***Chapter 2*** we performed a meta-analysis of 23 articles (608 nerve injuries) on the outcome of median and ulnar nerve repair after traumatic transection injury, using modern microsurgical techniques.

***Chapters 3, 4 and 5*** describe a subjective testing method for the presence of cold intolerance in a control group, a median and/or ulnar nerve injury group and a painful neuroma group. The questionnaire used was the Cold Intolerance Severity Score (CISS) by Irwin et al.[(18)].

In ***Chapter 3*** the CISS questionnaire was validated using 107 healthy volunteers. The average CISS score in a healthy population without previous upper extremity injury was calculated and the limit for abnormal cold intolerance was defined.

In ***Chapter 4*** the CISS questionnaire was used to assess the degree of cold intolerance in 108 median and/or ulnar nerve injured patients. The incidence of post-traumatic cold intolerance was calculated and predictors for the presence of abnormal cold intolerance were found.

In ***Chapter 5*** we analyzed the presence of cold intolerance in post-traumatic neuroma patients, who are characterized by a disturbance of peripheral nerve regeneration and severe pains.

In ***Chapter 6*** the use of infrared thermography as an assessment tool of the signs of cold intolerance in nerve injury patients was evaluated. In this pilot study, the results of 4 median nerve and 4 ulnar nerve injury patients after cold stress testing are described. The results encouraged us to proceed with the experiments of Chapters 7 and 8.

In ***Chapter 7*** Infrared videothermography was used to continuously monitor re-warming patterns of the hands and fingers after short term (5 minutes) cooling in healthy volunteers and median or ulnar nerve injury patients. This study gave us insight into the thermophysiology of the hands following cold stress testing.

***Chapter 8*** analyzes the internal protection against cold in healthy volunteers and nerve injury patients, using an experimental setup to test the presence or absence of the CIVD (cold induced vasodilatation) reaction.

***Chapter 9*** presents the overall discussion, conclusions and research perspectives and ***Chapter 10*** the summary of this thesis in both English and Dutch.

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# Chapter 2

## Median and ulnar nerve injuries: A Meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair.


Aleid C.J. Ruijs MD[1,2]
Jean-Bart Jaquet[2] MD
Sandra Kalmijn[3] MD PhD
Henk Giele[1] FRCS
Steven E.R. Hovius MD PhD[2].

1 Department of Plastic and Reconstructive Surgery, Radcliffe Infirmary, Oxford University Medical School, Oxford, United Kingdom.
2 Department of Plastic and Reconstructive Surgery, University Hospital Rotterdam "Dijkzigt" and Erasmus University Medical School, Rotterdam, The Netherlands.
3 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands



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## SUMMARY

**Background** – The aim of this study is to quantify variables that influence outcome after median and ulnar nerve transection injuries. We present a meta-analysis based on individual patient data on motor and sensory recovery after microsurgical nerve repair.
**Methods** – Twenty-three articles were ultimately included, giving individual data for 623 median or ulnar nerve injuries. The variables age, gender, nerve, site of injury, type of repair, use of grafts, delay between injury and repair, follow-up period and outcome were extracted. Satisfactory motor recovery was defined as MRC grade 4 and 5, satisfactory sensory recovery as MRC grade 3+ and 4. For motor and sensory recovery, complete data were available for 281 and 380 nerve injuries respectively.
**Results** – Motor and sensory recovery were significantly associated (Spearman r = 0.62, p<0.001). Multivariate logistic regression analysis showed that age (< 16 years versus > 40 years OR = 4.3, 95% CI 1.6-11.2), site (proximal versus distal OR = 0.46, 95% CI 0.20-1.10) and delay (per month OR = 0.94 95% CI 0.90-0.98) were significant predictors of successful motor recovery. In ulnar nerve injuries the chance of motor recovery was 71% lower than in median nerve injuries (OR = 0.29, 95% CI 0.15-0.55). For sensory recovery age (OR = 27.0, 95% CI 9.4-77.6), and delay (per month OR = 0.92, 95% CI 0.87-0.98) were found to be significant predictors.
**Conclusions –** In this individual patient data meta-analysis age, site, injured nerve and delay significantly influenced prognosis after microsurgical repair of median and ulnar nerve injuries.

## INTRODUCTION

Peripheral nerve injuries in general have a great impact on the patient's life. The amount of posttraumatic stress accompanying traumatic hand and forearm injuries is equal on the IES scale to the amount of stress experienced by survivors of the disaster with the cruise ship Estonia[1]. When motor and sensory function in the hand are altered, return to work activity may be jeopardized. Despite improvements in treatment, recovery after peripheral nerve injuries is not only often disappointing, but also difficult to predict. For both patient and doctor it is necessary to prognosticate the chances of recovery, so that treatment expectations can be realistic and appropriate rehabilitation measures can be taken. In previous literature, a number of factors have been found to predict motor and sensory recovery after peripheral nerve injury. These include age, delay between injury and repair and surgical technique. However, despite numerous published reports on peripheral nerve repair there is no agreement on which variables are independent predictors of a successful prognosis and the effect of the predictors is not quantified. Although some excellent reviews have been published on nerve grafting[2,3], only Frykman performed a meta-analysis[4]. In 114 median nerve injuries and 98 ulnar nerve injuries it was found that type of nerve, age, gap length and level of injury affected outcome. He based his results on 10 studies published between 1972 and 1988.

At present, a larger number of studies with detailed individual data are available, which enabled us to do an individual patient data meta-analysis[5] examining independent predictors of motor and sensory recovery. Predictors that could be investigated included age, gender, site of injury, median or ulnar nerve, combined median and ulnar nerve injuries, delay between injury and repair, the use of grafts, gap length and follow-up period. This is the largest meta-analysis with individual data on outcome after repair of median and ulnar nerve injuries undertaken so far.

## MATERIAL AND METHODS

A literature review up to April 2004 was performed to collect publications on outcome of median or ulnar nerve repair after transection injury. Studies were found by using the following search strategy: (Median Nerve/surgery [MAJR] OR Ulnar Nerve/surgery [MAJR]) AND (nerve repair (text word) OR outcome (text word)) with the limits English and human in the Pubmed database. With this strategy 122 articles were found. Additionally, the text word "spaghetti wrist" was entered, which gave 8 hits. A reference check was performed and the Cochrane database was searched. No effort was made to find unpublished reports or fugitive literature. Abstracts were screened by AR to select qualifying studies according to the in- and exclusion criteria. Included are studies that use microsurgical techniques for median or ulnar nerve repair and give individual data on sensory and/or motor recovery outcome scores using the British Medical Research Committee scale[6-28]. In a number of studies the assessment method was not the BMRC motor or sensory scale[29-35], or the individual data were not given[36-61]. Furthermore, case reports[62-68], iatrogenic injuries[69-73], partial nerve injuries[74,75], war or gunshot injuries[76-78], non-microsurgical repair[79-89] and repair with the aid of experimental techniques[90-94] were excluded.
Ultimately, 23 studies were suitable for inclusion in this individual patient data meta-analysis. The following data were extracted from the studies: age at time of injury, gender, injured nerve, type and site of injury, adjacent injuries, delay between injury and repair, type of repair, use of grafts, length of gap, follow-up period and motor and sensory BMRC-scores. The British Medical Research Council introduced in 1954 scales for motor and sensory testing of peripheral nerve function[95] Part of the sensory scale consists of two-point discrimination measurement. This has been demonstrated to be a widespread, often used measurement of sensibility in the hand[96-100]. Manual muscle testing is a widespread method for the testing of motor function and has adequate intra and interobserver reliability[98, 101].
Groups were classified as follows. Age: <16 years, 16-25 years, 26-40 years and >40 years. Injured nerve: median, ulnar or combined median and ulnar nerve injury. Delay between injury and repair was counted in months. Site of injury: low (wrist and distal two third of the forearm), intermediate (proximal one third of the forearm and the elbow) and high (upper arm). The use of autologous nerve grafts was also noted. The remaining gap after removal of injured nerve ends was grouped as ≤ 50 mm or > 50 mm.

Follow-up time was counted in years: < 1 year, 1 to ≤ 2 years, 2 to ≤ 3 years and > 3 years. Although various classifications have been made previously, we choose to classify satisfactory motor recovery as BMRC grade M4 or M5 and unsatisfactory as BMRC grades M0 to M3. Based on clinical experience, we classified satisfactory sensory recovery as BMRC grade S3+ and S4 and unsatisfactory as BMRC grades S0 to S3.

Table 1: Description of included studies.

| **Author and year of publication** | | **n** | **Nerve** | **Age (yrs)** Mean/ range | | **FU (months)** Mean/ range | | **Delay(months)** Mean/ range | |
|---|---|---|---|---|---|---|---|---|---|
| Hakistan[12] | 1968 | 13 | M/U/C | - | - | - | - | 0 | 0-0 |
| Millesi[17] | 1972 | 65 | M/U | 33 | 7-67 | 22 | 6-48 | 9.2 | 0-56 |
| Walton & Finseth[10,27] | 1977 | 8 | M/U | 27 | 16-51 | 23 | 10-31 | 17.6 | 3-84 |
| Ito[13] | 1976 | 20 | M/U | 28 | 2 -68 | 48 | - | - | - |
| Millesi[18] | 1976 | 22 | M/U | 30 | 11-69 | 35 | 9-48 | 12.4 | 1-49 |
| Moneim[19] | 1982 | 20 | M/U | 33 | 14-79 | 25 | 10-36 | 14.3 | 0.5-48 |
| Stellini[22] | 1982 | 39 | M/U | - | 15-65 | 31 | 18-52 | - | - |
| Tackmann[25] | 1983 | 41 | M/U | 34 | 7-72 | 20 | 4-59 | 0 | 0-0 |
| Puckett[20] | 1985 | 46 | M/U/C | 22 | 1-61 | 40 | 12-84 | 0 | 0-0 |
| Stevenson[23] | 1986 | 10 | C | 5 | 3-9 | - | >15 | 0 | 0-0 |
| Jongen[15] | 1987 | 22 | M/U | 20 | 4-58 | 24 | 12-60 | 0 | 0-0 |
| Frykman[11] | 1988 | 13 | M/U | 27 | 3-51 | 60 | 18-120 | 6.1 | 1-30 |
| Barrios[7] | 1989 | 44 | U | 29 | 6-69 | 24 | >6 | 5.2 | 0-23 |
| Rogers[24] | 1990 | 8 | C | 26 | 17-47 | 74 | 24-132 | 0 | 0-0 |
| Widgerow[28] | 1990 | 30 | M/U/C | 34 | 13-63 | 36 | 20-60 | 0 | 0-0 |
| Barrios[8] | 1991 | 31 | M/U | 9.5 | 4-15 | 24 | 12-60 | 8.2 | 0-70 |
| Daoutis[9] | 1994 | 88 | M/U | 31 | 8-52 | 26 | >24 | 4.6 | 1-24 |
| Trumble[26] | 1995 | 13 | M/U | 29 | 7-61 | 33 | 23-66 | 2.7 | 0.5-6 |
| Kato[16] | 1998 | 51 | M/U | 28 | 12-61 | 37 | 25-65 | 1.7 | 0-9 |
| Selma[21] | 1998 | 28 | M | 26 | 4-45 | 25 | 14-48 | 0.1 | 0-1 |
| Amillo[6] | 1999 | 6 | M/U | 11 | 6-16 | 24 | 18-60 | 9.3 | 2.5-16 |
| Jerosch-Herold[14] | 2000 | 41 | M | 33 | 12-72 | 34 | 9-90 | 0.1 | 0-3 |

Table 2: Large studies not included in meta-analysis due to lack of individual patient data.

| Study | Nerve Injuries | Follow-up methods | Predictors | Not predictors |
|---|---|---|---|---|
| Birch[37] | 56 MN + 52 UN | BMRC motor & sensory, questions | Age (child vs adult)*<br>Primary repair<br>Distal injury | |
| Kalomiri[46] | 73 MN + 85 UN + 27 C | BMRC motor & sensory | Age (child vs adult)*<br>Delay | |
| Kalomiri[47] | 118 UN | BMRC motor & sensory | Age<br>Delay | Length of graft |
| Merle[54] | 150 MN + UN | Chanson's method | Age<br>Type of accident**<br>Type of trauma***<br>Level of injury<br>Type of repair | Gender |
| Vastamaki[60] | 110 UN | 2PD<br>Ridge sensitometer<br>BMRC | Age (sensory)<br>Level of injury (motor)<br>Length of contusion<br>Sharp injuries<br>Delay (motor)<br>Length of graft (motor) | Additional injuries<br>Microscope vs loupe<br>Graft<br>Nerve |

** There was no clear relation between age and outcome in later decades.*
*** Industrial, suicide attempt, housework.*
**** Sharp versus crush injury.*
*MN= median nerve, UN= ulnar nerve, C= combined median and ulnar nerve injury.*

**Data analysis**

All data analyses were performed using SPSS for windows, release 10.1. Data analyses were separately performed for sensory recovery and motor recovery. In the final model, only subjects with complete data on all risk factors were included, resulting in 380 cases for sensory recovery and 281 cases for motor recovery. The association between each predictor and recovery was first assessed by univariate logistic regression analyses, with the odds ratio (OR) and 95% confidence interval (95%CI) as measure of association. The above-described risk factors were all tested. Additionally, we adjusted for study, since heterogeneity of the studies may affect the relation between risk factors and outcome. Variables that were univariately associated with motor or sensory recovery ($p<0.10$) were then included in a multivariate logistic regression model to evaluate the independent contribution in the prediction of recovery. Model reduction was performed by excluding variables that were not borderline significantly related with recovery (OR with $p<0.10$) from the overall model. To assess the predictive or discriminative ability of the models we calculated the area under the receiver operating characteristics curve (ROC area) with 95% CI. The ROC curve of a multivariate logistic model plots the sensitivity and 1-specificity at each consecutive threshold in the range of predicted probabilities of the model. The area under this curve, i.e. the ROC area, can range from 0.5 (no discrimination between subjects with and without recovery) to 1.0 (perfect discrimination).

Table 3: Description of study population.

| Characteristic | Number |
|---|---|
| Nerves | 623 |
| Median | 322 (51.7%) |
| Ulnar | 301 (48.3%) |
| Of which combined | 138 (23.7%) |
| Age group | 520 |
| Child (<16 y) | 113 (21.7%) |
| Adolescent (16-25y) | 151 (29.0%) |
| Young adult (26-40y) | 145 (27.9%) |
| Adult (>40y) | 111 (21.3%) |
| Site | 538 |
| Low | 442 (82.2%) |
| Intermediate & high | 96 (17.8%) |
| Graft used | 582 |
| Yes | 331 (56.9%) |
| Gap | 268 |
| < 50 mm | 110 (38.5%) |
| 50 mm and over | 176 (61.5%) |
| Follow-up time | 500 |
| < 1 year | 72 (14.4%) |
| 1-2 year | 124 (24.8%) |
| 2-3 year | 200 (40.0%) |
| >3 year | 104 (20.8%) |
| BMRC Sensory | 608 |
| Satisfactory | 259 (42.6%) |
| BMRC Motor | 432 |
| Satisfactory | 223 (51.6%) |

## RESULTS

Of the collected studies, 23 gave appropriate individual data and were included in our meta-analysis (Table 1). Of the studies that could not be included in our meta-analysis due to lack of individual data, the ones with more than 100 nerve repairs (n= 5) are described in Table 2[37,46,47,54,60]. All studies were retrospective observational studies. The number of nerve injuries included per study ranged from 6-88, and a total of 623 nerve injuries were available. In the final model, only subjects with complete data on all risk factors were included, resulting in 380 cases for sensory recovery and 281 cases for motor recovery. A description of the study population is given in Table 3.

A satisfactory sensory outcome was achieved in 42.6% of the patients and a satisfactory motor outcome in 51.6%. Motor and sensory recovery outcome scores were significantly correlated (Spearman correlation coefficient 0.62, P= <0.001, n= 417). Table 4 shows the crude association between the predictors and satisfactory motor and sensory recovery. Table 5 presents the multivariate logistic regression analysis and shows several independent predictors.

Patients under 16 years of age were four times more likely to have a satisfactory motor recovery (OR 4.3 95% CI 1.6-11.2, p< 0.05) than patients over 40 years of age. Intermediate or high lesions compared to low lesions (OR 0.46 95% CI 0.20-1.1, p< 0.10) and a longer delay between injury and repair were associated with a lower chance of motor recovery (per month OR 0.94, 95% CI 0.90-0.98, p< 0.05). Ulnar nerve injuries gave a 71% lower chance of motor recovery than median nerve injuries (OR=0.29, 95% CI 0.15-0.55, p< 0.05). Since there were too many missing values on gap width, this predictor was not included in the final model, even though a gap of ≥50 mm was significantly and independently associated with a 17% lower chance of motor recovery compared to a gap of <50 mm.

For sensory recovery, younger age was predictive of satisfactory recovery, whereas longer delay between injury and repair was again associated with a lower chance of recovery, i.e. for each month of extra delay the chance of recovery was reduced by 8%. After grouping the delay period into primary repair (0 days delay), delayed primary repair (1 day- 1 month), early secondary repair (1 – 3 months) and secondary repair (3-6 months, 6-12 months and more than 1 year delay), there seemed to be a tendency for the early secondary repair (1- 3 months) to achieve slightly better results (OR = 4.66, 95%CI 0.81-26.83 ) compared to delayed primary repair (1 day- 1 month, OR = 2.38, 95% CI 0.58-9.82) and no delay (0 days, reference group), although this was not significant (p= 0.08). There was no

Table 4: Crude association of predictors with satisfactory outcome.

| Predictor | Groups | Satisfactory Sensory recovery % (n) | Satisfactory Motor recovery % (n) |
|---|---|---|---|
| **Age** | <16 years | 69 (74/108) | 60 (55/92) |
| | 16-25 years | 44 (65/149) | 66 (69/104) |
| | 26-40 years | 38 (54/142) | 49 (47/96) |
| | >40 years | 20 (21/106) | 34 (26/77) |
| | Total: | n= 505 | n= 369 |
| **Gender** | Male | 39 (57/148) | 53 (73/137) |
| | Female | 38 (21/55) | 55 (29/53) |
| | Total: | n= 203 | n= 190 |
| **Nerve** | Median | 44 (138/315) | 61 (111/182) |
| | Ulnar | 41 (121/293) | 45 (112/250) |
| | Total: | n= 608 | n= 432 |
| **Combined** | Yes | 41 (56/138) | 54 (53/98) |
| | No | 43 (183/430) | 51 (170/334) |
| | Total: | n= 568 | n= 432 |
| **Site** | Low | 43 (185/433) | 54 (136/253) |
| | Intermed. & high | 34 (31/90) | 36 (34/94) |
| | Total: | n= 523 | n= 347 |
| **Delay** | No delay | 47 (96/206) | 67 (46/69) |
| | 1 day- 1 month | 39 (19/49) | 60 (18/30) |
| | 1 - 3 months | 66 (38/58) | 79 (46/58) |
| | 3- 6 months | 47 (51/109) | 56 (62/111) |
| | 6-12 months | 25 (15/59) | 26 (15/58) |
| | > 12 months | 16 (7/44) | 23 (9/40) |
| | Total: | n= 525 | n=366 |
| **Graft used** | No | 53 (133/251) | 64 (80/126) |
| | Yes | 40 (125/316) | 47 (143/306) |
| | Total: | n= 567 | n= 432 |
| **Gap** | <50 mm | 39 (41/105) | 51 (52/102) |
| | 50 mm and over | 37 (62/166) | 43 (73/171) |
| | Total: | n= 271 | n= 273 |
| **Follow up** | < 1 years | 24 (17/72) | 40 (19/47) |
| | 1-2 years | 43 (52/121) | 48 (36/75) |
| | 2-3 years | 48 (92/193) | 51 (90/177) |
| | > 3 years | 33 (33/99) | 47 (37/79) |
| | Total: | n= 485 | n= 378 |

significant difference between median and ulnar nerve injuries in relation to sensory recovery. For patients >40 years old and a delay of >3 months the predicted probability of a satisfactory sensory outcome was 0.14 compared to 0.43 in all other patients; for motor recovery these probabilities were 0.25 versus 0.55. In the prediction of sensory recovery, the ROC area was 0.82 (95%CI: 0.77-0.87), whereas for the prediction of motor recovery it was 0.87 (95%CI: 0.84-0.91). Although the ROC area is not very informative for clinical purposes it is a measure of discriminative power and >0.80 can be considered as good.

Table 5: Results of multivariate logistic regression analysis for satisfactory sensory and motor recovery and ROC area.

| Predictor | Categories | Satisfactory Sensory Recovery OR (95% CI), n= 380 | Satisfactory Motor Recovery OR (95% CI), n= 283 |
|---|---|---|---|
| Age | <16 yrs | 27.0 (9.4-77.6) * | 4.3 (1.6-11.2)* |
| | 16-25 yrs | 6.6 (2.8-15.3) * | 2.8 (1.2-6.9) * |
| | 25-40 yrs | 1.9 (0.9-4.3) | 1.4 (0.5-3.6) |
| | >40 yrs | Reference | Reference |
| Delay | per month | 0.92 (0.87-0.98) * | 0.94 (0.90-0.98)* |
| Follow-up | < 1y | Reference | - |
| | 1-2 yrs | 1.2 (0.-3.1) | |
| | 2-3 yrs | 3.0 (1.0- 8.8)* | |
| | >3 yrs | 1.2 (0.4-3.9) | |
| Site | intermed/high vs low | - | 0.46 (0.20-1.1)** |
| Nerve | Ulnar vs Median | - | 0.29 (0.15-0.55)* |
| ROC Area (95% CI) | | 0.82 (0.77-0.87) | 0.87 (0.84-0.91) |

** Significant at the p < 0.05 level, ** Significant at the p < 0.10 level.*
*OR = odds ratio, 95% CI = 95% confidence interval.*
*ROC area = Area under the Receiver Operating Characteristics curve.*

## DISCUSSION

Due to the considerable variety of factors influencing nerve regeneration and outcome, final recovery after peripheral nerve injury is a complex matter. In numerous studies in the past decades, several variables have been proposed to influence outcome. However, many of these publications were based on small patient numbers and due to the wide range of patient and injury characteristics, different parameters were found to be of prognostic importance. In this individual patient data meta-analysis we seek to find conclusive evidence for independent predictors of a satisfactory outcome.

Although several authors have proposed new assessment methods to evaluate functional recovery of the hand after nerve repair no conclusive test battery is available. Recently, Rosen published a rationale for the evaluation of functional recovery following nerve injuries[102]. We used the MRC scale for both motor and sensory function testing, as it is the most widely accepted classification to score the outcome of peripheral nerve injuries[103]. Since the introduction of microsurgical techniques in the sixties, the repair of peripheral nerve injuries has not changed considerably. Therefore it seems not likely that the operation techniques have influenced our results. It is known that experience of the surgeon plays an important role, however it was not possible to take this into consideration. Not all variables were known for every patient, so it was not possible to include all patients in the data analysis. Furthermore, only studies that gave individual data could be included in our meta-analysis. This could have lead to selection bias if other predictors of recovery were present in the patients that were excluded from our analyses, especially for the larger studies. To reduce this, we evaluated the results of the studies that did not meet our inclusion criteria and had more than 100 nerve injuries. (Table 2) It showed that mainly the same predictors were found. To prevent further selection bias we also excluded case reports.

The significant prognostic factors influencing outcome found in this meta-analysis differed for motor and sensory recovery. For motor recovery age, delay, site and type of injured nerve were found to predict outcome, for sensory recovery age and delay were significant prognostic factors. Younger patients were more likely to have a satisfactory motor and sensory outcome, and the longer the delay between injury and repair the smaller the chance of a favorable outcome. Combined median and ulnar nerve injuries and the use of autologous nerve grafts did not significantly predict motor and sensory recovery.

From previous research, several factors have been pointed out to influence final recovery. In general age was found to be a main factor for recovery[6-8,15, 20,21, 23, 31, 34, 52, 80, 83, 104]. This can be explained by factors like shorter regeneration distance and greater regeneration potential, but recent research in primates shows also that in children there is probably a higher potential for brain plasticity compared to adults[105, 106]. Some authors mentioned that especially sensory recovery benefits from a younger age, which is in accordance with our findings[58]. Barrios did not find a better outcome in children after nerve grafting[7].

We found that delay is associated with outcome. This confirms the results of many earlier studies that found an unfavorable prognosis after more than six or twelve months delay[6-9, 15, 23, 26, 52, 83, 107, 108]. Others advocated the use of an early secondary repair for all injuries[109]. Merle found, in a small group of patients, a higher percentage of failures after nerve repair performed on an emergency basis than after secondary repair[54].

In the past, several authors[110-113] advocated the use of primary repair for clean-cut injuries and early secondary repair (4-6 weeks) for blunt or extensive injuries. We found a similar tendency for sensory recovery, but this was not significant ($p=0.08$). Our results favor a primary repair, although when contra-indicated an early secondary repair can be considered as a safe option. Unfortunately, we did not have individual information on the type of injury (blunt or clean-cut).

It is important for both doctor and patient to know when the end point of recovery has been reached. This information can provide the patient a realistic prognosis especially regarding the possibility of returning to work[114]. Furthermore this data can be used to predict at an earlier stage the need for other treatment options, such as tendon transfer. According to the literature, significant improvements can be found for up to 5 years after nerve repair[58]. This meta-analysis indicated that there seems to be significant improvement for at least a follow-up period of 3 years.

Site has been mentioned[80] as the most important determinant of outcome; our conclusion is that it is a significant predictor only for motor recovery. A muscle can become atrophic and irreversibly damaged in one and a half to two years. Nerve regeneration occurs with a speed of approximately 1 mm a day, and if in the meantime innervation is not restored, motor recovery will be poor[115].

As in this meta-analysis, several authors found a better motor recovery in median nerve injuries compared to ulnar nerve injuries[6, 19, 25, 42, 58, 107], and no difference for sensory recovery[26] Combined ulnar and median nerve injury has been identified as a predictor for worse prognosis due to the associated extensive soft tissue damage[13, 28, 78]. Although combined nerve injuries are usually accompanied by extensive tissue damage[80], they do not necessarily imply a poor result[107]. In this meta-analysis we did not find a significant effect on outcome either. Unfortunately, information on the number of injured structures was lacking in our study. As shown in earlier studies[11, 17, 18, 27, 104], we found no difference between direct repair and interfascicular grafting. However, it was not possible to measure the influence of the graft length with our data. It has been noticed that long grafts are more likely to give unfavorable results[6-8, 42]. A number of other factors were found in previous research to influence recovery but could not be investigated in this meta-analyses due to missing data. These factors are the effect of the type and severity of the initial injury[116], good cooperation and motivation of the patient[15, 28], specialized hand therapy[23, 58, 117], cognitive capacity[33], early psychological stress experienced due to the trauma[1] and comorbidity such as diabetes and alcoholism[46, 47]. Since it is not possible to influence the factors regarding the injury, except sometimes for delay, effort should be made to intervene with the postoperative parameters such as optimized hand therapy and psychological intervention.

Improvement of the results may be sought in refinement of the surgical procedure, hand therapy in specialized centers and experimental techniques[118], such as silicone tubes[90, 92, 93] or biodegradable nerve guides[119]. It would be advisable to follow a large cohort of patients prospectively with detailed measuring of possible predictors. Also the use of a more extended test battery besides motor and sensory testing, such as ADL, quality of life, cold intolerance and psychosocial factors, could give a better insight in the outcome of peripheral nerve repair and regeneration.

## CONCLUSION

In this individual patient data meta-analysis several predictors have been found influencing outcome after peripheral nerve repair. Age, site, injured nerve and delay significantly influenced prognosis after microsurgical repair of median and ulnar nerve injuries. In patients younger than 16 year with no delay, the chances of satisfactory sensory recovery are the highest, whereas for motor recovery a patient under 16 years, with a distal median nerve injury and no delay will give the best results. A follow-up time of at least 3 years is necessary to evaluate the final outcome. On the basis of the figures from this meta-analysis, it is possible to estimate which patients have a high or low chance of successful motor and sensory recovery after median or ulnar nerve injury.

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# Chapter 3

## Cold Intolerance of the hand measured by the CISS questionnaire in a normative study population.

Aleid CJ Ruijs[1]
Jean-Bart Jaquet[1]
Hein AM Daanen[2, 3]
Steven ER Hovius[1]

[1] Department of Plastic and Reconstructive Surgery, Erasmus Medical Center
Rotterdam and Erasmus University Medical School, Rotterdam, The Netherlands.
[2] TNO Human Factors, Thermal Physiology Group, Soesterberg, The Netherlands.
[3] Faculty of Human Movement Sciences, Vrije Universiteit, Amsterdam

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## SUMMARY

**Background** - Cold intolerance has been recognized as one of the most disabling sequelae of upper extremity trauma, especially when neurovascular structures are involved. In this study, we aimed to describe cold intolerance in a normative study population, validate the Cold Intolerance Symptom Severity (CISS) questionnaire and define the threshold for abnormal cold intolerance.

**Methods** - One hundred and eight volunteers participated in our study. In addition to the CISS score, information about age, gender and previous surgery or trauma to the upper extremity was obtained. There were no volunteers with previous peripheral nerve injury and subjects with a history of Raynaud's disease, upper extremity injury or surgery were excluded (n=40).

**Results** - The CISS scores of the study population (n=68) averaged 12.9 (SD 8.2). Age and gender were not correlated with CISS score. The upper 95% confidence interval of the CISS scores for healthy subjects is about 30.

**Conclusions** - We suggest this value of 30 on the CISS scale as a threshold for pathological Cold Intolerance.


## INTRODUCTION

Post-traumatic cold intolerance, defined as abnormal pain with or without discoloration and/or stiffness to the hand after exposure to cold, is a frequent[1-7] and persistent[3, 7-9] sequela of upper extremity injury, especially when neurovascular structures are involved[1, 4, 6, 9-12]. The effects are often disabling to the patient[7] (Nancarrow et al. 1996), leading to occupational changes, or to the discontinuation of favourable leisure activities[6] (Lithell et al. 1997). It has been shown that the symptoms of cold intolerance develop in the first months after the injury[1, 7] (Backman et al. 1993; Nancarrow et al. 1996) and generally do not improve over time[1, 7, 9]. To assess the severity of cold intolerance in a patient population with surgical repair of peripheral nerve lesions in the upper limb, the Cold Intolerance Symptom Severity (CISS) questionnaire was developed by Irwin et al.[13] (Table 1). In this study, we aimed to evaluate the CISS questionnaire in a normative study population and to define the threshold for abnormal cold intolerance.

## MATERIAL AND METHODS

One hundred and eight healthy volunteers, representing the average patient population, were recruited to fill-out the CISS questionnaire[13] (Table 2). Average age was 33.3 (range 16 to 62) years old. There were 59 men and 49 women. The volunteers were given a brief explanation of cold intolerance and of the purpose of this study. All participants provided informed consent. Detailed information on their general health status, previous surgery and trauma of the upper extremity were also recorded. None of the volunteers had suffered upper extremity nerve injury or had undergone elective peripheral nerve surgery and none were treated for diabetes or vascular disease. Excluded were thirteen subjects with a history of surgery on the upper extremity, not including nerve injury, for trauma or elective reasons and twenty-six who had sustained a non-surgical injury to the upper extremity, such as a fracture, fingertip injury, sprain, ulnar collateral injury of the MCP joint of the thumb or burn wound. Additionally one subject with Raynaud's disease was excluded.
Each volunteer completed the CISS questionnaire, which takes approximately 5 minutes to fill out. This consists of six questions. The first question involves the occurrence of the following symptoms: pain, numbness, stiffness, weakness, aching, swelling and skin colour change to white or blue. This question gives insight into the pattern of cold intolerance. However, because the questionnaire focuses on the impact of cold intolerance on activities of daily life, the answers to this first question are not counted towards the final CISS test-score. (Irwin et al. 1997) Questions two to six relate to the frequency, duration, severity and impact of cold intolerance symptoms on activities of daily living. Question 5 consists of the earlier McCabe Cold Sensitivity Test (Craigen et al., 1999; Koman et al., 1998; McCabe et al., 1991). The questionnaire was translated into Dutch, following the recommendations for the cross-cultural adaptation of health status measures, supported by the American Academy of Orthopaedic Surgeons (AAOS) and the Institute for Work & Health (IWH). The possible CISS test-score ranges between a minimum of 4 and a maximum of 100. In addition to the CISS questionnaire, we recorded information about the age and gender of the subjects.

All data analyses were performed using SPSS for windows, release 12 (SPSS, Inc., Chicago, Ill). Student's T-test analyses were performed to find the influence of the variables gender and past surgery to the upper extremity on CISS test-score. A multivariate linear regression analysis was performed with the independent variables age and gender to determine predictors of CISS-score. Spearman's rank test was used to determine the correlation between the questions and the total CISS test-score.

## RESULTS

The normative study population consisted of 68 healthy volunteers after applying the exclusion criteria. The CISS score of the normative study population, i.e. volunteers with no medical history of upper extremity surgery or injury, averaged 12.9 (SD 8.2, range 4-38.4). The upper limit of the 95% confidence interval (calculated as the mean + 2 times the standard deviation) is a CISS-score of 29.3. The median and mean scores per question are given in Table 3. Spearman's Rank correlation test revealed correlation coefficients between the separate questions and the total test-score ranging between 0.42 for question 3 and 0.90 for question 5, all significant at the 0.01 level (2-tailed). Gender did not influence the CISS score significantly (male 11.7 versus female 14.2, p=0.22). Multivariate linear regression analysis failed to show age as a significant predictor for cold intolerance. When comparing the included study population and the excluded subjects who underwent surgery to the upper extremity in the past, we found a significant difference in mean CISS score (12.9 versus 20.1, p=0.16). (Table 4)

[#] *In question one, patients are asked to score their symptoms as follows: "Please give each symptom a score between 0 and 10, where 0= no symptoms at all and 10= the most severe symptoms you can possibly imagine." However, the scores given in this question do not count towards the final CISS test-score.*
** For our normative population, we replaced question one by the following sentence: Cold Intolerance is a painful reaction of mostly the fingers to a low temperature, such as during cold weather. Several symptoms can occur, such as painful, numb, stiff and swollen fingers, weakness of the fingers or the hand, an aching feeling and a white or blue discoloration of the fingers or hand.*
*The texts in italic are our suggestions as to how to improve the scoring.*
*** These are the questions of the McCabe Cold Sensitivity Test[12].*

Table 1: CISS Questionnaire[13].

| Question # | Score |
|---|---|
| 1. Which of the following symptoms of cold intolerance do you experience in your injured limb on **exposure to cold? *** **Pain, numbness, stiffness, weakness, aching, swelling, skin colour change (white/ bluish white/ blue)** | Not scored # |
| 2. How often do you experience these symptoms? (please tick) | |
| Continuously/ all the time | 10 |
| Several times a day | 8 |
| Once a day | 6 |
| Once a week | 4 |
| Once a month or less | 2 |
| (Suggestion to add: never) | 0 |
| 3. When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved (please tick): | |
| (Suggestion to add: not applicable) | 0 |
| Within a few minutes | 2 |
| Within 30 minutes | 6 |
| After more than 30 minutes | 10 |
| 4. What do you do to ease or prevent your symptoms occurring? (please tick) | |
| Take no special action | 0 |
| Keep hand in pocket | 2 |
| Wear gloves in cold weather | 4 |
| Wear gloves all the time | 6 |
| Avoid cold weather/stay indoors | 8 |
| Other (please specify) | 10 |
| 5. How much does cold bother your injured hand in the following situations (please score 0-10) | |
| Holding a glass of ice water** | 10 |
| Holding a frozen package from the freezer** | 10 |
| Washing in cold water** | 10 |
| When you get out of a hot bath/shower with air at room temperature** | 10 |
| During cold wintry weather | 10 |
| 6. Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each | |
| Domestic chores | 4 |
| Hobbies and interests | 4 |
| Dressing and undressing | 4 |
| Tying your shoe laces | 4 |
| Your job | 4 |

Table 2: Description of the Normative Study Population (108 subjects):

| | **Included** | **Excluded *** |
|---|---|---|
| Number | 68 (63%) | 40 (37%)<br>26 (previous injury)<br>13 (previous surgery)<br>1 (Raynaud's disease) |
| Mean age (range) | 35 year (16-62) | 31 year (17-61) |
| Male (%) | 37 (54%) | 22 (55%) |

** 40 subjects showed upper extremity injury (such as fractures, fingertip injuries, sprains etc), surgery (e.g. for fractures or tendon repair) or Raynaud's disease in their past medical history and were excluded from the study population. None of the volunteers had peripheral nerve injury in their past medical history.*

Table 3: total CISS test-score and scores per question.

| | **Median** | **Mean (SD)** | **Range** |
|---|---|---|---|
| **Total CISS test-score** | **11.8** | **14.1 (10.1)** | **4 - 49** |
| Question 2 | 2 | 2.5 (1.46) | 2 - 10 |
| Question 3 | 2 | 2.8 (1.73) | 2 - 10 |
| Question 4 | 2 | 2.1 (2.08) | 0 - 10 |
| Question 5 | 4 | 5.5 (5.81) | 0 - 27 |
| Question 6 | 0 | 1.1 (2.31) | 0 - 10 |

Table 4: Influence of Variables on CISS score (student's T-test):

| **Variable** | | | |
|---|---|---|---|
| Study population (n=68) | CISS 12.9 | Range 4-38.4 | SD 8.2 |
| Gender | Male, n= 37 | Female, n=31 | p= 0.21 |
| Mean (SD) | 11.7 (8.1) | 14.2 (8.4) | |
| Previous Surgery | No, n= 68 | Yes, n= 13 | p= 0.016* |
| Mean (SD) | 12.9 (8.2) | 20.1 (15.5) | |

** Significant at the p< 0.05 level.*

## DISCUSSION

Interest in symptoms of cold intolerance or cold sensitivity after peripheral nerve injury has increased recently and it has now been recognized as one of the major complications following upper extremity trauma. Several ways to (indirectly) evaluate cold intolerance have been described. Clinical tools are aimed mainly at recording digital surface temperature, using thermography or thermometers[14]. Differences in skin temperature between the injured and uninjured limb are suggestive of cold intolerance. In a laboratory setting, this has been measured by isolated cold-stress testing, where the extremity is rapidly cooled for a fixed period of time and then allowed to re-warm at room temperature[15]. Also digital blood flow and digital blood pressure have been measured under normal conditions and after exposure to cold[9].

The symptoms and severity of cold intolerance have also been evaluated from the patient's perspective using a VAS scale, using single questions[9, 16, 17], multiple questions[6, 18, 19] or validated questionnaires[3, 8, 12, 13]. McCabe et al.[12] also developed a potential work exposure scale, measuring the potential exposure of the worker's hands to cold at the workplace. For further research and clinical purposes, a reliable, consistent and validated test is of great importance. We found the Cold Intolerance Symptom Severity (CISS) questionnaire[13] to be the most clear and extensive questionnaire currently available. To obtain a baseline value and define an average score for an uninjured and healthy person, we have tested it in a normative study population. Subjects without previous history of peripheral nerve injury or other upper extremity injury scored, on average, 12.9 points on the CISS questionnaire. Previous surgery to the hand or arm was predictive of a significantly higher score. CISS score was not influenced by age or gender. In a study by Koman et al.[5], using the modified McCabe scale, a higher percentage of women were found to have cold intolerance following upper extremity injury. In a study by Dahlin et al.[16], 50% of diabetic patients recorded cold intolerance following sural nerve biopsy, whereas only 5% of the control group, consisting of non-diabetic patients, reported cold intolerance following sural nerve biopsy.

We found the CISS questionnaire a reliable, clear and easy to use test, addressing the symptoms of cold intolerance and the influence of cold intolerance on the patient's daily life and activities. However, to improve the sensitivity of this test further, we suggest adding respectively "never" and "not applicable" to questions number 2 and 3, both with a score of zero.

Previously, CISS scores have been arbitrarily grouped in mild (4-25), moderate (26-50), severe (51-75) and extreme severe cold intolerance (76-100)[13]. Applying these groups, 63 subjects (93%) of our study population would have been classified as having mild cold intolerance and 5 subjects (7%) as having moderate cold intolerance. Based on our results in the normative study population, we suggest the upper limit of the 95% confidence interval of the subjects with no history of previous upper extremity injury or surgery (CISS score = 29.3) as the threshold for pathological cold intolerance. A score above this cut-off point (CISS - score 30 or higher) would be indicative of pathological cold intolerance. According to the method described above, the female threshold would be higher than the male threshold. However, since the thresholds are not sharply defined, and since an extra threshold would make application of the CISS test more complicated, we decided not to make a gender specific threshold. For the moment, we can use this questionnaire as a screening method. In the future, however, we hope to correlate the score to physiological parameters such as surface temperature of the digits after exposure to cold.

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# Chapter 4

## Cold Intolerance following median and ulnar nerve injuries: prognosis and predictors

Aleid C.J. Ruijs[1]
Jean-Bart Jaquet[1]
Willemijn G. van Riel[1]
Hein A.M. Daanen[2, 3]
Steven E.R. Hovius[1].

[1] Department of Plastic, Reconstructive and Hand Surgery, Erasmus MC, Rotterdam, The Netherlands.
[2] TNO Human Factors, Thermal Physiology Group, Soesterberg, The Netherlands.
[3] Faculty of Human Movement Sciences, Vrije Universiteit, Amsterdam, The Netherlands.

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## SUMMARY

**Background** - This study describes the predictors for cold intolerance and the relationship to sensory recovery after median and ulnar nerve injuries.
**Methods** - The study population consisted of 107 patients two to ten years after median, ulnar or combined median-ulnar nerve injuries. Patients were asked to fill out the Cold Intolerance Severity Score (CISS) questionnaire and sensory recovery was measured using Semmes-Weinstein monofilaments.
**Results** - Fifty-six percent of the patients with a single nerve injury and seventy percent with a combined nerve injury suffered abnormal cold intolerance. Patients with no return of sensation had dramatically higher CISS-scores than patients with normal sensory recovery. Females had higher CISS scores post-injury than males. Cold intolerance did not diminish over the years. Patients with higher CISS scores needed more time to return to their work. Age, additional arterial injury, site or type of the injury and dominance of the hand were not found to have a significant influence on cold intolerance.

## INTRODUCTION

Cold intolerance is defined as abnormal pain, with or without discoloration, numbness, weakness or stiffness of the hand and fingers after exposure to mild to severe cold[1-5]. Although this condition is a frequent sequel of upper extremity trauma, the incidence is particularly high following upper extremity nerve injury. In the majority of peripheral nerve-injured patients, Cold Intolerance is the most bothersome, prolonged and disabling symptom, affecting both work and leisure activities[5-10].

Previous studies defined various predictors for cold intolerance[4, 5, 7-15]. Median and ulnar nerve injuries have been found to have a significantly higher severity of cold intolerance than other upper extremity nerve injuries[12, 13]. Associated vessel injury[12, 16, 17], smoking[6, 12, 18], crush injury[12, 19], level of the nerve lesion[4, 20] and early post-operative pain[9] have all been recorded as predicting variables. An inverse relationship with sensory recovery has also been noted[17].

In this study, we examined the incidence and severity of cold intolerance after median and/or ulnar nerve injury, seeking predictors of cold intolerance, particularly the relationship to sensory recovery, and the changes in cold intolerance over time.

Table 1: The CISS Questionnaire[12].

| Question * | Score |
|---|---|
| 1. Which of the following symptoms of cold intolerance do you experience in your injured limb on **exposure to cold?** **Pain, numbness, stiffness, weakness, aching, swelling, skin colour change (white/ bluish white/ blue)** | Not scored * |
| 2. How often do you experience these symptoms? (please tick) | |
| Continuously/ all the time | 10 |
| Several times a day | 8 |
| Once a day | 6 |
| Once a week | 4 |
| Once a month or less | 2 |
| 3. When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved (please tick): | |
| Within a few minutes | 2 |
| Within 30 minutes | 6 |
| After more than 30 minutes | 10 |
| 4. What do you do to ease or prevent your symptoms occurring? (please tick) | |
| Take no special action | 0 |
| Keep hand in pocket | 2 |
| Wear gloves in cold weather | 4 |
| Wear gloves all the time | 6 |
| Avoid cold weather/stay indoors | 8 |
| Other (please specify) | 10 |
| 5. How much does cold bother your injured hand in the following situations (please score 0-10): | |
| Holding a glass of ice water** | 10 |
| Holding a frozen package from the freezer** | 10 |
| Washing in cold water** | 10 |
| When you get out of a hot bath/shower with air at room temperature** | 10 |
| During cold wintry weather | 10 |
| 6. Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (0-4): | |
| Domestic chores | 4 |
| Hobbies and interests | 4 |
| Dressing and undressing | 4 |
| Tying your shoe-laces | 4 |
| Your job | 4 |

* *In question one, patients are asked to score their symptoms as follows: “Please give each symptom a score between 0 and 10, where 0 = no symptoms at all and*

*10 = the most severe symptoms you can possibly imagine." However, the scores given in this question do not count towards the final CISS test-score.*
*** These are the questions of the McCabe Cold Sensitivity Test[14].*

## PATIENTS AND METHODS

The study population was defined as all subjects admitted to the Department of Plastic and Reconstructive Surgery at the Erasmus Medical Centre, Rotterdam, the Netherlands, for surgical treatment of a median, ulnar or combined median and ulnar nerve injury between January 1990 and December 1998. A peripheral nerve injury chart was designed to score retrospectively baseline data regarding aetiology, nerve and associated injury, treatment, complications and work status. To participate in this study, patients were required to meet three entrance criteria: 1) The patient had suffered an injury of at least a single ulnar or single median nerve located within the area between the wrist crease (distal border) and the flexor elbow crease (proximal border). 2) The patient was aged 12 years or older on the day of injury. 3) The patient had no amputation of the hand or fingers and no hand and/or forearm fractures. A total of 138 patients met the inclusion criteria.

Hospital medical, general practitioners and municipal records were consulted to trace the included patients. In 2000 and 2001, the Blond McIndoe Cold Intolerance Symptom Severity (CISS) questionnaire[12] and a covering letter requesting participation in this study was sent to these 138 patients. The patients were invited to undergo sensory testing, either at our outpatient clinic or in their home. Three follow-up mailings, including the CISS, were sent to non-responders at a two-month interval. Fifteen subjects declined to participate and sixteen subjects were not traceable leaving a final population of 107 patients in the study (a response rate of 78%). The Medical Ethics Committee of the Erasmus MC approved the protocol of this study. All participants provided informed consent.
The severity of cold intolerance was measured using the self-administered CISS questionnaire (Table 1), which has been validated in both a peripheral nerve injury group and a normative control group[12, 21]. The CISS questionnaire consists of 6 questions. The first question details the occurrence of the following symptoms: pain, numbness, stiffness, weakness, aching, swelling and skin color change to white or blue. Answers to this first question are not included in the final CISS score. Questions two to six relate to the frequency, duration, severity and impact of cold intolerance symptoms on activities of daily live. Question 5 consists of the earlier McCabe Cold Sensitivity Test[4, 14, 16]. The questionnaire was translated into Dutch, following the recommendations for the cross-cultural adaptation of health status

measures, supported by the American Academy of Orthopaedic Surgeons and the Institute for Work and Health. Summation of the answers to questions two to six allow a minimum score of 4 and a maximum score of 100. A score of 30 can be regarded as the cut-off point for abnormal cold intolerance, as tested in a normative study population[21]. Sensory recovery was tested with Semmes-Weinstein monofilaments (North Coast Medical Inc, Morgan Hill, California, USA). The monofilaments 2.83, 3.61, 4.31, 4.56 and 6.10 were used according to the procedure described by Bell-Krotosky[22-24]. Ten zones in the hand were tested, 6 in the territory of the median nerve and 4 in the territory of the ulnar nerve. The scores were interpreted as suggested by Imai[25] (Table 2). A score of 6.10 was interpreted as having no sensation.

## STATISTICAL METHODS

Detailed information on cold intolerance was available for 107 patients. For 85 of these patients sensory recovery was also measured. Student t-tests were used to compare continuous variables and chi-square tests to compare categorical data. All tests are two sided and a p-value of less than 0.05 was considered statistically significant. When multiple groups were compared, ANOVA tests were performed (two-sided, $p<0.05$). The Pearson Correlation was used to calculate bivariate correlation. All data analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 11.0.

Table 3: Characteristics of responders (n=107) and non-responders (n=29).

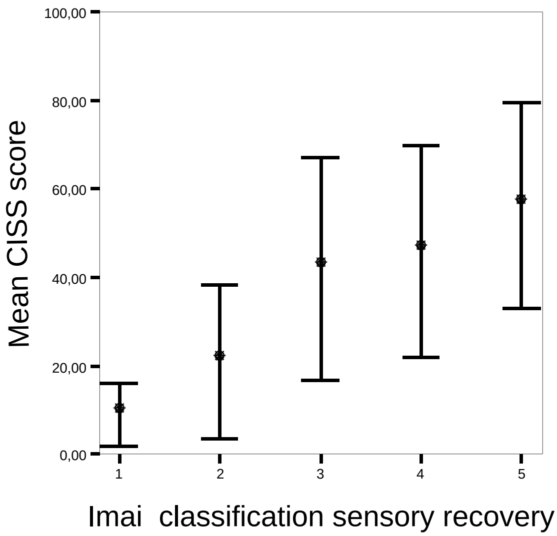
| **Characteristic** | **Responders (%)** | **Non-responders (%)** |
|---|---|---|
| Age | | |
| Mean ± SD | 30.7 (SD 12.0) | 28.9 (SD 12.0) |
| Range | 14 - 67 | 15 – 61 |
| Gender (%) | | |
| Male | 85 (79) | 20 (69) |
| Female | 22 (21) | 9 (31) |
| Type of injury (%) | | |
| Median | 44 (41) | 15 (52) |
| Ulnar | 41 (38) | 11 (38) |
| Combined | 22 (21) | 3 (10) |
| Dominant hand affected | | |
| Yes (%) | 64 (59) | 13 (45) |
| No | 36 (35) | 10 (34) |
| Unknown (%) | 7 (6) | 6 (21) |
| Structures affected | | |
| Mean ± SD | 5.8 ± 4.1 | 5.5 ± 4.1 |
| Range | 1 – 15 | 1 – 15 |
| Lesion (%) | | |
| Sharp | 73 (68) | 23 (79) |
| Crush | 16 (15) | 3 (10) |
| Avulsion | 13 (12) | 2 (7) |
| Unknown | 5 (5) | 1 (3) |

*SD = standard deviation.*
*The differences in percentage are shown between parentheses.*
*None of the percentages showed a significant difference between responders and non-responders.*

Table 2: Imai classification of sensory recovery[25].

| **Quality of Sensation (range 1-5)** | **Filament Marking** |
|---|---|
| 1: Normal | 2.83 |
| 2: Diminished light touch | 3.61 |
| 3: Diminished protective sensation | 4.31 |
| 4: Loss of protective sensation | 4.56 |
| 5: Anaesthetic | 6.10 |

Figure 1: CISS score versus sensory recovery (n=85).




*The error bars represent 1 Standard Deviation, ANOVA p=0.02. CISS = Cold Intolerance Severity Score, ranging from 4 (no CI) to 100 (maximum CI).*

## RESULTS

The characteristics of responders and non-responders are presented in Table 3. The responders and non-responders had similar age and gender distributions and no statistical difference between them was found for severity, affected nerve and type of injury. Data are reported for the 107 patients who filled out the CISS questionnaire. Eighty-five of these patients also returned for sensory testing using Semmes-Weinstein monofilaments. The study population consists of 85 males and 22 females, with an average age of 30.7 (SD 12.0) (range 14-67) years on the day of repair. Accidental injuries at work were the primary cause of trauma (32%), followed by activities at home (29%), nightlife (13%), victims of violence (8%), suicide attempt (5%) and other (e.g. sports and traffic accidents, 8%). In 59% of the cases, the dominant hand was affected. An isolated median nerve injury occurred in 44 patients (41%). Forty-one patients (38%) had an isolated ulnar nerve injury and 22 (21%) had injured both the median and the ulnar nerves. The types of injury included 73 (68%) sharp lacerations, 16 (15%) crush injuries and 13 (12%) avulsion injuries.

Numbness was the most frequent cold-induced symptom, being present in 80% of the participants (Question 1). Other symptoms were pain (63%), stiffness (77%), weakness (72%), aching (67%), skin color change (50%) and swelling (33%). The mean CISS score was 38.4 (SD 25.6) with a minimum of 4 and a maximum of 88. Fifty-nine percent of the patients obtained a cold intolerance score of 30 or higher, 30 being the cut-off point for abnormal cold intolerance(21). This percentage was significantly higher in the combined group (70%) than in the median nerve alone (57%) or in the ulnar nerve alone (56%, p= 0.004) group. ANOVA analysis showed a statistical significant association between cold intolerance and the level of sensory recovery, as tested with Semmes Weinstein monofilaments and classified according to the Imai classification (n=85, p=0.002) (Imai et al., 1989). Patients who regained normal sensation (n = 2) scored, on average, 9 points (SD 7.1, patients with diminished light touch (n = 16) scored, on average, 20.9 points (SD 17.4), patients with diminished protective sensation (n= 25) scored, on average, 42 points (SD 25.3), patients with loss of protective sensation (n = 38) scored, on average, 46 points (SD 23.9) and the worst group, with no return of sensation (n = 4), scored, on average, 56.4 points (SD 23.4) [Figure 1]. Women scored significantly higher on the CISS than men (50.7 SD 30.3 versus 35.2 SD 23.4; n=107, p=0.011). Sensory recovery however, did not differ between the sexes (Imai scores, respectively, 3.30 SD 0.87 and 3.32 SD 1.05; n=85, p=0.958). Patients who returned to work within the first year post-injury had, on average, a lower (near normal) CISS score (31.0 SD 22.9) than patients who needed more than one year to return to work (49.1 SD 24.2; n=80, p=0.001). Patients with cold intolerance were on average 32 years old (SD 11.8) and patients without cold intolerance were on average 29 years old (SD12.1). Age was not significantly correlated with cold intolerance (Pearson correlation 0.127, p=0.193). Other non-significant predictors for CISS score were: additional injury to the ulnar or radial artery; dominant hand affected; site at the distal, middle or proximal 1/3 of the forearm; sharp, crush or avulsion injury. The CISS score of each patient did not diminish significantly over the years for the period of assessment of a mean of 6.1 (range 2 - 10) years. Using analysis of variance (ANOVA), we found no statistical difference in average CISS-score between the groups with 2 to 10 years of follow-up (Fig 2).

## DISCUSSION

Our most significant finding was the correlation between CISS-score and return of sensory recovery, as tested with Semmes-Weinstein monofilaments (Fig 1). Patients with no return of sensation indicated dramatically higher CISS-scores than patients with normal sensory recovery. A normal return of sensation gives significantly less complaints of cold intolerance. This is in agreement with the findings of several previous studies[13, 15, 17]. However, not all previous studies have identified this relationship[7, 8].

Although men and women were found to have a similar level of sensory recovery, women scored significantly higher on the CISS-scale than men, with an average difference of 15 points. In our previous studies of the CISS-scores in a normative population, we found no difference between men and women (n = 108)[21]. Therefore, this difference does not seem to be pre-existent and manifests itself only after these nerve injuries.

An important feature of this study has been identification of the fact that patients with more severe cold intolerance need a longer time to return to their work. In earlier studies it was found that satisfactory motor and sensory recovery are predictors for return to work, amongst other predictors such as level of education, type of job and compliance to hand therapy[26, 27]. In our study sensory recovery and cold intolerance were highly correlated, and this could be the cause of our finding. However, patients with outside jobs and severe cold intolerance would clearly need an adjustment of their work environment, protection against cold or a change of jobs.

Between the two nerves compared in this study, no significant difference in CISS-score could be found (median nerve 57 % CI, ulnar nerve 56% CI). This is in contrast to the finding of Lenoble et al.[13]. In a study of 82 patients, it was found that cold sensitivity occurs after 50% of median nerve injuries and after 75% of ulnar nerve injuries. We found that the incidence of cold intolerance was significantly higher in the combined median and ulnar nerve injury group, possibly because of the more extensive tissue damage and the increase in number of injured structures in combined nerve injuries. This finding is in contrast to that of other studies[12, 15]. In contrast to previous studies finding significantly increased severity of cold intolerance associated with vessel injury[12, 28], our study did not show arterial injury as a predictor for cold intolerance. Additionally, Kay[3] found no correlation between cold intolerance and vascular inflow to replanted digits in a study of 14 patients investigated by venous occlusion plethysmography. This supports the case for a neural, instead of an arterial, origin of post-traumatic cold intolerance[2, 29].

As in previous studies[7, 12], we found no significant relationship between the incidence of cold intolerance and age. The affected hand, site of injury and type of injury were also not found to be predictors for more severe cold intolerance.

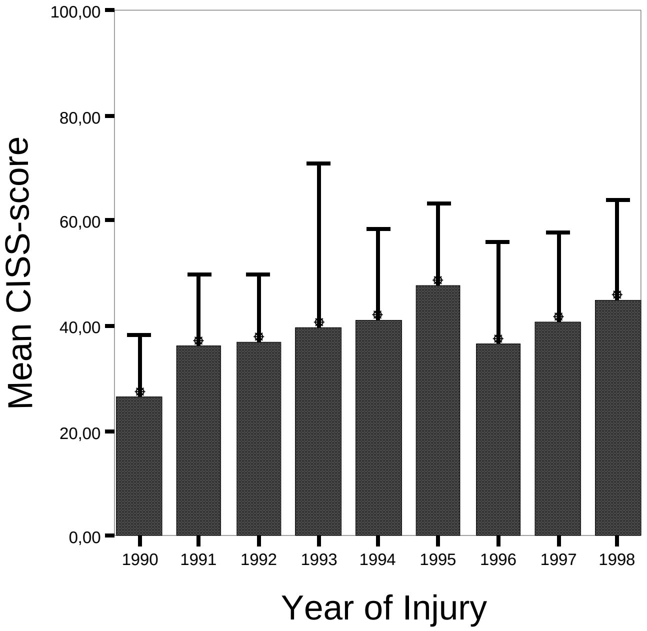
Gelberman et al.[11] postulated that the symptoms of cold intolerance are temporary following upper extremity injury and disappear over time. More recent studies have not confirmed this[5, 7, 20]. During our average follow-up time of 10 years, no significant improvement of symptoms was found.

This study did not allow us to identify cold intolerance present before the injury, nor to identify affected and unaffected digits. A more general criticism of the assessment method used is that, probably, too much emphasis is placed on question 5, which makes up half of the final CISS-score. Moreover, the minimum CISS score is four and not zero, as it is not possible to answer negatively to questions two and three.

Since there is, currently, no effective and reliable treatment available to relieve the symptoms, we believe that it is of importance to explain that this is a normal sequel of trauma and educate patients on cold intolerance, and simple methods of avoiding its painful sequelae at an early stage.

Additional research focusing on the thermophysiology of the hand and fingers is necessary to clarify the pathophysiology of the processes leading to post-traumatic cold intolerance. In the meantime, in respect of nerve injury patients, we should strive towards maximum sensory recovery with the aid of specialised hand therapy. For example, recent studies show that not only classical sensory re-education, starting when perception of touch/pressure (SWM 4.56) could be detected in the affected area is beneficial, but early sensory re-learning using cortical audio-tactile interaction could further improve sensory recovery. Using a Sensor Glove System with incorporated microphones, Shape-Texture-Identification (STI) was improved after 1 year follow-up in the experimental group (n=14) compared to the control group (n=12)[30, 31].

**Figure 2**: CISS score in 2000/2001 compared to CISS score in the year of injury.




*Analysis of variance (ANOVA) confirms that the means of the groups do not differ significantly.*

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# Chapter 5

## Cold intolerance in surgically treated neuroma patients: a prospective follow-up study.

Annemieke Stokvis, BSc
Aleid CJ Ruijs, MD
Johan W. van Neck, PhD
J Henk Coert, MD PhD

Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands.

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## SUMMARY

**Background** - Cold intolerance imposes great changes on patients' life-style, work and leisure activities and is often severely disabling. This study aims to investigate the incidence and severity of cold intolerance in patients with traumatic neuromas of the upper extremity, to point out predictors for cold intolerance and find correlations with other symptoms.

**Methods** - Between January and November 2006, 20 consecutive patients with surgically treated neuroma specific neuropathic pain of the upper extremities, were invited to participate in our study. 18 patients returned a questionnaire composed of both general questions concerning epidemiologic determinants and several specific validated questionnaires. To objectively estimate the incidence of cold intolerance in neuroma patients, we used the validated CISS (Cold Intolerance Symptom Severity) questionnaire with a pre-specified cut-off point.

**Results**- We found an incidence of cold intolerance of 100%, with a mean CISS score high above the cut-off point for abnormal cold intolerance. CISS scores were higher in patients with an avulsion injury of the peripheral nerve, extreme spontaneous pain, and sleep disturbances. A higher disability score, as well as increasing age were almost significantly correlated to a higher CISS score.

**Conclusions** - Cold intolerance is a difficult problem that has a high incidence in patients with a painful traumatic neuroma. There seems to be a relation between severity of cold intolerance and spontaneous pain, sleep disturbances, depression, age, and upper extremity function and it is unlikely that cold intolerance disappears with time.

## INTRODUCTION

Cold intolerance is defined as abnormal pain of the hand and fingers after exposure to mild or moderate cold, with or without discoloration, numbness, weakness or stiffness. It is also known as thermal hyperalgesia or cold sensitivity and affects all work and leisure activities taking place outdoors or in moderate cold. Therefore, cold intolerance may seriously influence patients' daily life[1, 2]. Cold intolerance is a common long-term sequel following upper extremity injury, with an estimated incidence up to 100%[3-6].

In a neuroma, abnormal connections between A- and C-fibers are made, causing cross-talk between nociceptive and non-nociceptive nerve fibers, resulting in mechanical and thermal hyperalgesia. There is abnormal sensitivity and spontaneous activity of injured axons, caused by sensitized C-nociceptors[7-12]. Therefore, a high incidence of cold intolerance is to be expected in neuroma patients. However, there is not much data available on the incidence of cold intolerance in patients with a painful traumatic neuroma, and the extent of this problem is currently unknown.

In addition, most studies focussing on peripheral nerve injuries have estimated the incidence of cold intolerance using only subjective symptoms mentioned by patients[3, 13], or did not specify the variable used to measure cold intolerance[14]. To objectively estimate the incidence of cold intolerance in neuroma patients, we used the validated CISS (Cold Intolerance Symptom Severity) questionnaire with a pre-specified cut-off point.

This study aims to investigate the incidence and severity of cold intolerance in patients with traumatic neuromas of the upper extremity, to point out predictors for cold intolerance and to find correlations with other symptoms.

## METHODS

### Study population

The patients who entered the study were on the waiting list for surgical neuroma treatment by author JHC in the Erasmus MC, Rotterdam. The diagnosis neuroma specific neuropathic pain was made based on the history and complaints of the patient, the presence of Tinel's sign and reduction of pain of at least 5 points on a visual analogue scale (VAS) after blockade of the injured nerve with 1% lidocaine.

Between January and November 2006, 20 consecutive patients, with surgically treated neuroma specific neuropathic pain of the upper extremities, were invited to participate in our study. This surgery entailed excision of the neuroma with relocation of the nerve end into muscle or bone. After obtaining their consent, the patients were sent a questionnaire when they were scheduled for surgery. The questionnaire was composed of both general questions concerning epidemiologic determinants and several specific validated questionnaires on pain, loss of upper extremity function, symptoms of psychopathology and cold intolerance. Patients were asked to return this questionnaire by mail prior to surgery. Non-responders were contacted by telephone, after 2 weeks, and requested to return the questionnaire. This study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center, Rotterdam.

** The answers given in this question do not count towards the final CISS test-score.*

*** These are the questions from the McCabe Cold Sensitivity Test[16].*

Table 1: The CISS Questionnaire[6].

| Question # | Score |
|---|---|
| 1. Which of the following symptoms of cold intolerance do you experience in your injured limb on exposure to cold? * | Not scored |
| Pain | |
| numbness | |
| stiffness | |
| swelling | |
| blue or white skin color change | |
| 2. How often do you experience these symptoms? (please tick) | |
| Continuously/ all the time | 10 |
| Several times a day | 8 |
| Once a day | 6 |
| Once a week | 4 |
| Once a month or less | 2 |
| 3. When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved (please tick): | |
| Within a few minutes | 2 |
| Within 30 minutes | 6 |
| After more than 30 minutes | 10 |
| 4. What do you do to ease or prevent your symptoms occurring? (please tick) | |
| Take no special action | 0 |
| Keep hand in pocket | 2 |
| Wear gloves in cold weather | 4 |
| Wear gloves all the time | 6 |
| Avoid cold weather/stay indoors | 8 |
| Other (please specify) | 10 |
| 5. How much does cold bother your injured hand in the following situations ( score 0-10): | |
| Holding a glass of ice water** | 10 |
| Holding a frozen package from the freezer** | 10 |
| Washing in cold water** | 10 |
| When you get out of a hot bath/shower with air at room temperature** | 10 |
| During cold winter weather | 10 |
| 6. Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (please score 0-4): | |
| Domestic chores | 4 |
| Hobbies and interests | 4 |
| Dressing and undressing | 4 |
| Tying your shoe-laces | 4 |
| Your job | 4 |

**Scoring methods**

The severity of cold intolerance was measured using the self-administered Blond McIndoe Cold Intolerance Symptom Severity (CISS) questionnaire which has been validated in both a peripheral nerve injury group and a normative control group[6, 15]. The CISS questionnaire consists of 6 questions (table 1). The first question involves the occurrence of the following symptoms: pain, numbness, stiffness, swelling and skin color change into white or blue. According to the official score guidelines, answers to this first question are not calculated towards the final CISS score. Questions two to six relate to the frequency, duration, severity and impact of cold intolerance symptoms on activities of daily live. Question 5 consists of the earlier McCabe Cold Sensitivity Test[4, 9, 16]. The CISS questionnaire was translated into Dutch, following the recommendations for the cross-cultural adaptation of health status measures, supported by the American Academy of Orthopaedic Surgeons (AAOS) and the Institute for Work & Health (IWH). All questions together allow a minimum score of 4 and a maximum score of 100.

The visual analogue scale (VAS) consists of a horizontal line of 10 cm, anchored with the words ‘no pain at all’ on the left side and ‘unbearable pain’ on the right. The patient has to place an x on the line representing the amount of pain felt. The VAS score ranges from 0 to 10. Additionally, four questions concerning the severity of different types of pain were asked. The types were: spontaneous pain, pain on pressure, pain on movement and painful hyperesthesia on light skin touch. The severity of the pain was scored as severe, moderate, mild or absent.

The disabilities of the arm, shoulder and hand (DASH) questionnaire is a self-administered outcome instrument developed as a measure of self-rated upper extremity disability and symptoms. It is the most widely used upper extremity-specific health-status measure[17]. The DASH consists mainly of a 30-item disability scale, scored 0 (no disability) to 100 (most severe disability). In this study we used the approved Dutch version of the DASH[18].

*SD = standard deviation.*

*CISS = Cold Intolerance Severity Scale, range 4-100, where 100 = most severe cold intolerance, cut-off point for abnormal cold intolerance is 30.*

*DASH = Disability of Arm Shoulder and Hand, range 0-100, where 0 = no disability and 100 = most severe disability.*

*VAS = Visual Analogue Scale, scale 0-10, where 0 = no pain at all and 10 = unbearable pain.*

Table 2: Characteristics of responding neuroma patients (n=18)

| **Characteristic** | |
|---|---|
| Age (years) | |
| Mean ± SD | 44.7 (SD 12.9) |
| Range | 18 - 74 |
| Gender | |
| Male | 10 (55.6%) |
| Female | 8 (44.4%) |
| Injured nerve | |
| Ulnar | 1 (5.6%) |
| Radial sensory branch | 8 (44.4%) |
| Digital | 7 (38.8%) |
| Lat. antebrachial cutaneus (LABCN) | 1 (5.6%) |
| LABCN and palmar median branch (combined) | 1 (5.6%) |
| Dominant hand affected | |
| Yes | 14 (77.8%) |
| No | 4 (22.2%) |
| Lesion | |
| Sharp | 11 (61.1%) |
| Crush | 4 (22.2%) |
| Avulsion | 2 (11.1%) |
| Unknown | 1 (5.6%) |
| Duration of pain (months) | |
| Mean | 45 (SD 36.7) |
| Range | 3 - 118 |

Table 3: Results of validated questionnaires

| **Variable** | **Score** |
|---|---|
| CISS | |
| Mean | 63.9 (SD 18.6) |
| Range | 38 - 96 |
| DASH | |
| Mean | 54.0 (SD 21.1) |
| Range | 14.2 – 81.7 |
| VAS pain score | |
| Mean | 7.5 (SD 1.7) |
| Range | 4.0 - 9.8 |

The Symptom Checklist-90 (SCL-90) is a self-rated scale that evaluates a broad range of psychological problems and psychopathological symptoms[19]. The Dutch SCL-90 consists of eight psychiatric symptom domains: somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility and sleep-disturbance[20]. Norms are available for a chronic pain population, which were used to adjust the SCL-90 scores[21].

Duration of pain was defined as time since the development of neuromatous pain in months.

### Statistical methods

Patient and injury characteristics were tested for association with the CISS score using Pearson's Correlation test for continuous variables. Analysis of variance (ANOVA) and student *t*-tests were used to compare categorical variables. All tests were two sided and a p-value of less than 0.05 was considered statistically significant. All data analyses were performed using Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA), version 12.0.

## RESULTS

### Study population

Of the 20 patients surgically treated by denervation, 18 returned the questionnaire. Of the two non-responders, one patient did not speak Dutch and the other did not want to cooperate. Demographics of the included neuroma patients are presented in table 2. The study population consists of 10 males and 8 females, with an average age of 44.7 years on the day of filling out the questionnaire. In 77.8% of the cases the dominant hand was affected. Types of injury included 11 (61.1%) sharp lacerations, 4 (22.2%) crush injuries, 2 (11.1 %) avulsion injuries and 1 (5.6 %) had an unknown cause. Only 5 patients had a partial digital amputation.

### Outcome variables

Pain was the most frequent cold-induced symptom in neuroma patients, indicated by 83.3% of the participants (table 1, question 1). Numbness was present in 33.3% of the neuroma patients. Other symptoms were stiffness (38.9%), skin color change (16.7 %,) and swelling (5.6%). The mean total CISS score of questions 2 to 6 was 63.9 (SD 18.6) with a minimum of 38 and a maximum of 96 (table 3). Therefore all patients (100%) exceeded the standardized cut-off point (CISS score 30) for abnormal cold intolerance[15].

Using ANOVA we found no statistical difference in CISS-scores between the different affected nerves. We found no significant correlation between CISS and VAS score or duration of pain. Other non-significant predictors for CISS score were: gender, smoking status, dominant hand affected, employment status, workers compensation and pending litigation (data not shown).

Age was nearly significantly correlated with cold intolerance (p = 0.077) (table 4). The DASH score showed an almost significant correlation with CISS score as well (p = 0.076).

ANOVA showed a statistically significant difference in mean CISS score between the different types of injuries (figure 1). This difference is created by the high mean CISS score for avulsion compared to other types of injuries (p = 0.004) (table 5), thereby identifying avulsion injury as a possible predictor for cold intolerance. The mean CISS score was significantly higher in patients with severe spontaneous pain compared to patients with no, mild or moderate spontaneous pain (p = 0.006). Patients with a high SCL-90 sleep-disturbance score had a significantly higher mean CISS score than patients with a below average sleep-disturbance score (p = 0.002). The unadjusted SCL-90 sleep-disturbance score also showed this correlation. Higher unadjusted SCL-90 depression score was almost significantly correlated to higher CISS-score (p = 0.078).

Table 4: Influence of continuous variables on CISS score (Pearson's correlation coefficient)

| **Variable** | **Correlation Coefficient** | **p-value** |
|---|---|---|
| SCL-90 Sleep-disturbance score (unadjusted) | 0.419 | 0.045* |
| DASH | 0.428 | 0.076 |
| Age | 0.427 | 0.077 |
| SCL-90 Depression score (unadjusted) | 0.438 | 0.078 |
| Duration of pain | 0.283 | 0.255 |

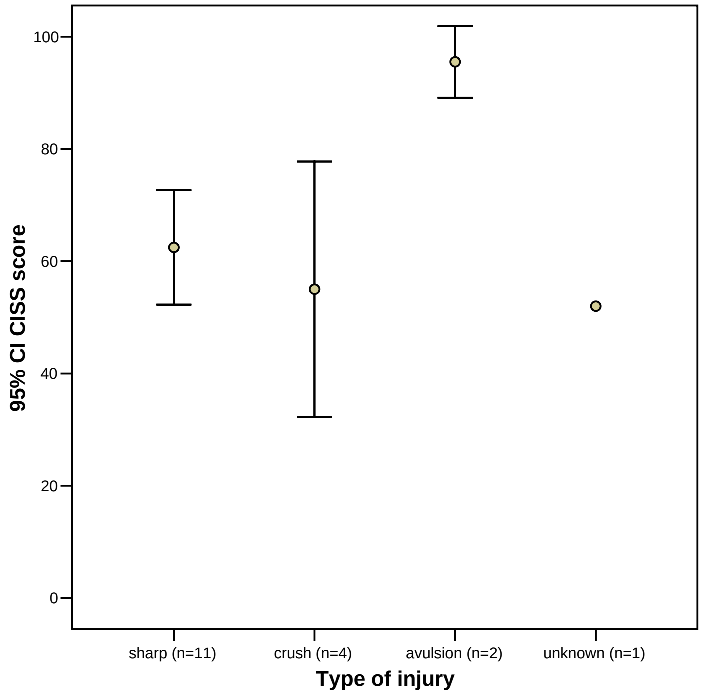
*DASH = Disability of Arm Shoulder and Hand, SCL-90 = Symptom Checklist-90 (unadjusted = unadjusted for chronic pain normative population).*
** = p-value significant at the 0.05 level.*

Table 5: Influence of categorical variables on CISS score (student's t-test)

| **Variable** | **p-value** |
|---|---|
| Type of injury | |
| Avulsion versus rest | 0.004** |
| Spontaneous pain | |
| Severe versus rest | 0.006** |
| SCL-90 Sleep-disturbance score | |
| High versus below average | 0.002** |

*** = p-value significant at the 0.01 level.*
*Type of injury, rest = sharp, crush, unknown.*
*Spontaneous pain, rest = moderate, mild, absent.*
*SCL-90 = Symptom Checklist-90.*

Figure 1. Mean CISS score versus type of injury (n=18)




*The error bars represent the 95% confidence interval, ANOVA p=0.03. CISS = Cold Intolerance Severity Score.*

## DISCUSSION

The present study was conducted to evaluate the incidence and severity of cold intolerance in patients with neuromatous pain. Using the CISS questionnaire we found an incidence of 100%, with a mean CISS score high above the cut-off point for abnormal cold intolerance[15]. Cold intolerance was higher in patients with an avulsion injury of the peripheral nerve, extreme spontaneous pain, and sleep disturbances (SCL-90). A higher disability score (DASH) and increasing age were almost significantly correlated to a higher CISS score.
To our knowledge, literature concerning cold intolerance in neuroma patients is lacking. Therefore, our data will be put into perspective using literature on peripheral nerve injury in general.

A high incidence of post-traumatic cold intolerance in the upper extremity has been reported by several authors, similar to the high incidence we found in neuroma patients[3-5, 14, 22-24]. The obtained mean CISS score in our study population is significantly higher than scores obtained in median and ulnar nerve injury patients, as found by Ruijs et al.[25]. Here, a mean CISS score of 38.4 was found for median and ulnar nerve injuries, with 59% of the 107 subjects being classified as having cold intolerance.
The estimated incidence of cold intolerance, as reported in literature, largely depends on the method of measuring and defining cold intolerance[13, 22]. In literature, this classification ranges from subjective symptoms mentioned by patients[3, 13], to the use of a validated questionnaire[6, 15]. Some articles do not even specify the variable used to measure cold intolerance[14], or do not describe any cut-off point for abnormal intolerance of cold or validation of the method used[26]. In our study, we used the validated CISS questionnaire with a specified cut-off point.

Pain was the most frequent cold-induced symptom in our study population. This is a common finding in literature where pain is often mentioned as the most troublesome symptom of cold intolerance[26, 27]. Although smoking is known to impair digital bloodflow and wound healing in the hand[28, 29], a relation between smoking and cold intolerance could not be observed. However, our findings are consistent with that of other authors[4, 30]. There was no significant relationship between duration of pain and CISS score, which implies that cold intolerance is independent of time after injury. This resembles the finding that cold intolerance is unlikely to disappear with time[5, 22, 23, 30-32].
Sleep disturbances are common in chronic pain patients. Surveys indicate that patients suffering from various pain conditions often report concomitant sleep disturbances[33-35]. Pain may interrupt or disturb sleep, but changes in sleep pattern

could also influence pain perception. Our results also showed a significant positive relation between CISS score and sleep-disturbance score. This might be explained by the fact that sleep deprivation has been proven to produce hyperalgesic effects[36-39]. In an experimental study by Onen et al.[36] a hyperalgesic effect related to sleep deprivation was demonstrated, as well as an analgesic effect related to recovery sleep. In addition to sleep disturbances, chronic pain patients often experience mood disturbances[34]. We also found a higher SCL-90 depression score that was almost significantly correlated to the higher CISS-score. This might be explained by the perpetuating cycle of depression, leading to sleep disruption, causing a decreased tolerance to cold[33]. In our study population depression was significantly correlated to sleep-disturbances.

Our data showed a significantly higher CISS score in patients with an avulsion injury. This finding is consistent with the finding of Irwin et al.[6] that sharp injuries are less likely to be associated with the severity cold intolerance. Sharp injuries lead to better revascularization and a higher success rate of replantation of amputated digits than do crush or avulsion injuries[6, 23, 40, 41]. An explanation for the higher CISS score in patients with an avulsion type injury may be the fact that adequate coaptation of the nerve ends is nearly impossible. This may cause several “micro-neuromas” at different levels. Another cause for the increased CISS score in avulsion injuries is the greater extent of the nerve injury.

Painful neuromas of the peripheral nerves may occur after (partial) nerve damage. Patients with a painful traumatic neuroma display intense pain, altered sensation and mechanical hyperalgesia and cold intolerance in the distribution of the injured nerve. Little is known about mechanisms of cold intolerance[42]. In the normal situation, lowering skin temperature evokes a painless cold sensation, which will ultimately become a cold and painful sensation after further cooling. In cold intolerant patients this process is disturbed. Cold sensation is mediated by small myelinated A-delta fibers and cold induced pain by unmyelinated C-nociceptors. The combination of the two inputs results in the blended sensation of cold and usually aching pain. In a neuroma, abnormal connections between A- and C-fibers are made, causing cross-talk between nociceptive and non-nociceptive nerve fibers, resulting in mechanical and thermal hyperalgesia. There is abnormal sensitivity and spontaneous activity of injured axons, caused by sensitized C-nociceptors[7-12]. In addition, loss of afferent A-fiber input may lead to disinhibition, creating a state of central sensitization of neural structures involved in pain perception[43, 44, 45]. These mechanisms possibly explain the significant relation between cold intolerance and severe spontaneous pain in neuroma patients: sensitized nociceptive C afferents in neuroma patients display exaggerated and unmodulated signals of pain after mild exposure to cold. In addition they may also fire spontaneously, leading to spontaneous pain.

Despite the relatively small number of patients, some relevant conclusions can be drawn from this study. Cold intolerance is a difficult problem that has a high incidence in patients with a painful traumatic neuroma. It imposes great changes on patients' life-style, work and leisure activities and is often severely disabling. Cold intolerance is more common after avulsion type injuries compared to sharp injuries. There seems to be a relation between severity of cold intolerance and spontaneous pain, sleep disturbances, depression, age, and upper extremity function and it is unlikely that cold intolerance disappears with time.

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# Chapter 6

## Application of infrared thermography for the analysis of rewarming in patients with cold intolerance.

Aleid CJ Ruijs[1]
Jean-Bart Jaquet[1]
Martine Brandsma[2]
Hein AM Daanen[2, 3]
Steven ER Hovius[1]

[1] Department of Plastic, Reconstructive and Hand Surgery, Erasmus MC, Rotterdam, The netherlands
[2] TNO Human Factors, Thermal Physiology Group, Soesterberg, The Netherlands
[3] Faculty of Human Movement Sciences, Vrije Universiteit, Amsterdam, The Netherlands.

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## SUMMARY

**Background** - Cold intolerance is a significant long-term problem after ulnar and median nerve injury. Unfortunately, the pathophysiology of cold intolerance is still unclear. The aim of this pilot study is to investigate the use of infrared thermography for the analysis of thermoregulation after peripheral nerve injury.
**Methods -** Four ulnar nerve injured patients and four median nerve injured patients (4-12 years after injury, six had symptoms of cold intolerance) immersed their hands in 15°C water for 5 minutes, after which infrared pictures were taken at 2 to 4-minute time-intervals.
**Results -** The regions supplied by the respective nerve could easily be identified in the patients with symptoms of cold intolerance. At baseline there was a symmetrical temperature distribution of the hand, however after cold stress testing the rewarming of the injured side was significantly slower.
**Conclusions** - The infrared temperature profile of the hand after immersion into cold water may be a helpful tool to assess thermoregulation after peripheral nerve injury.

## INTRODUCTION

Cold intolerance (CI) is a frequent result of upper extremity trauma and the incidence is especially high after upper extremity nerve injury. In the majority of peripheral nerve-injured patients, cold intolerance is the most bothersome, prolonged and disabling symptom, affecting both work and leisure activities[1-3]. In our series with 107 median and ulnar nerve injured patients we found that after a single nerve injury 56% of the patients were affected by CI and 70% of the combined nerve injured patients after a minimum follow-up period of 2 years[4]. It is defined as abnormal pain with or without discoloration, numbness, weakness or stiffness of the hand and fingers after exposure to mild to severe cold[2, 5-8]. Although cold intolerance can be measured subjectively using the Cold Intolerance Symptom Severity (CISS) questionnaire[4, 9], objective, validated test methods have not yet been made available for clinical use. All objects with a temperature above the absolute zero emit thermal energy in the form of infrared waves. Digital infrared thermography is able to measure this emission two-dimesionaly. Since the emissive factor of the skin is 0.98, the measured temperature values can be interpreted as the surface temperature of the skin.  The improvement of thermal and spatial resolutions in modern digital infrared cameras to a sensitivity of <0.1ºC, has lead to the advancement from military and industrial use into healthcare fields[10]. In this study we aim to look specifically at the application of infrared thermography in patients with complaints of cold intolerance after median and ulnar nerve injury. Our hypothesis is that infrared thermography is a useful diagnostic tool for post-traumatic cold intolerance.

## PATIENTS AND METHODS

### Patients

From our previously described study group of 107 ulnar or median nerve injured patients[11-12], eight were invited for the participation in this pilot study. A selection was made to get a representative sample of the nerve injury population, however patients with combined median and ulnar nerve injuries or ulnar or radial artery injury were excluded. Table I shows patient characteristics. The patients suffered a single nerve injury between the distal wrist crease and the elbow 4 to 12 years ago (mean 8.5 years, between 1990 and 1998) with no additional arterial injury. In four patients the ulnar nerve was injured and in another four patients the median nerve. Seven patients were male and one was female. The average age was 31.5 years (range 22-53). The patients completed the CISS questionnaire[4, 9], with a minimum score of 4 and a maximum score of 100. A score of thirty or higher can be regarded as abnormal cold intolerance[4].

### Cold stress

Both hands were immersed up to the ulnar styloids for five minutes in a water bath with a constant temperature of 15°C (range 14.7 to 15.6 °C). During immersion, the temperature of the palmar side of the distal phalanx of the index and little fingers was monitored at 1.5, 3 and 5 minutes using fine 40-gauge copper-constantan thermocouples (T-type) attached to the skin with adhesive tape. After removing the hands from the water bath, the hands were carefully dried using a towel and the thermocouples were removed. Then, infrared images were obtained using a FLIR ThermaCam SC2000 camera. Finger skin temperature was measured at least every 5 minutes, but more often when deemed necessary by the investigator, for instance when large fluctuations occurred. The thermographs were analysed using FLIR Thermoscan Researcher software.

## RESULTS

### Patients

In one patient (case 2), the cold stimulus was very painful. Therefore he removed both hands after three minutes of immersion instead of five minutes. The remainder of the procedure was according to protocol. The CISS scores ranged between 12 and 90. Applying the cut-off score of 30, six of the eight patients were identified as having abnormal cold-intolerance.

### Thermoregulation

In Figure 1, the baseline values of a typical subject are shown. Following the 30-minute acclimatisation period, all hands showed a symmetrical temperature distribution. Figure 2 shows the temperature charts during immersion into the 15°C water bath. There is a trend towards faster cooling of the injured side of the hand, however this was not statistically significant. In the ulnar-nerve injured hands, both index and little fingers reached approximately the temperature of the water bath after five minutes (Figure 2). Figure 3 shows typical examples of thermoregulation after cold stress testing. The first patient (Figure 3a) is a patient with an ulnar nerve injury and a CISS score of 90. The second patient (Figure 3b) is a patient with a median nerve injury and a CISS score of 51. We made thermographs of both palmar and dorsal sides of the hands; the results obtained on both sides were similar. In the four patients with median nerve injury, we found that the thumb, index, and middle fingers were significantly colder several minutes after rewarming than the ipsilateral ring and little finger and the contralateral hand. All uninjured digits were rewarmed after four to twelve minutes. However, in two of the median nerve injured patients the injured digits had not rewarmed at the end-point yet. In the four ulnar nerve injured patients, the ring and little finger of the affected hand were significantly colder several minutes after rewarming compared to the other ipsilateral fingers and the contralateral hand. In three of the ulnar nerve injured patients, the uninjured digits needed between five and eleven minutes to rewarm. In two of these patients the injured digits had not rewarmed at the end-point yet. In one ulnar nerve injury patient none of the digits had re-warmed at ten minutes.

Table I: Patient characteristics.

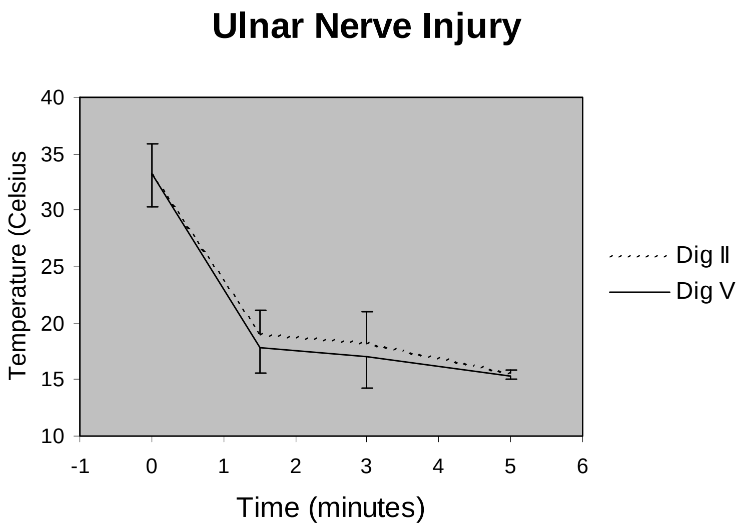
| Case No. | Age | Gender | FU (years) | Nerve | Side | CISS | CI |
|---|---|---|---|---|---|---|---|
| 1 | 23 | Male | 10 | Ulnar | Right | 12 | No |
| 2 | 25 | Male | 5 | Ulnar | Left | 60 | Yes |
| 3 | 28 | Male | 12 | Median | Right | 39 | Yes |
| 4 | 48 | Male | 9 | Ulnar | Right | 90 | Yes |
| 5 | 22 | Female | 12 | Median | Right | 49 | Yes |
| 6 | 25 | Male | 4 | Median | Right | 30 | Yes |
| 7 | 53 | Male | 8 | Median | Left | 51 | Yes |
| 8 | 28 | Male | 8 | Ulnar | Right | 19 | No |

*Legend: Age = age in years at time of injury. FU = follow-up time since surgery. Median= median nerve injury. Ulnar = ulnar nerve injury. CISS score is the total score of the CISS questionnaire, as filled out on the day of the experiment. The minimum CISS score is 4, the maximum score is 100. A score of 30 and higher is abnormal cold intolerance. CI = cold intolerance.*

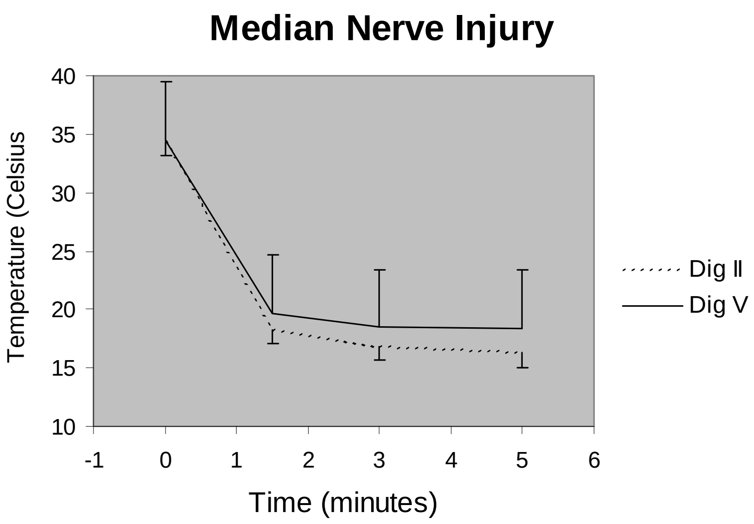
Figure 1. Example of baseline scan before cold stress.


*This figure shows a typical example of the pre-cold stress baseline scan. In none of the patients a left-right or ulnar-radial side difference was found after the 30-minute acclimatisation period.*

Figures 2a and 2b: Cooling phase of the experiment in respectively ulnar or median nerve injuries.




*The error bars represent one SD. Ulnar nerve injury patients (n=4). This chart shows the temperature of the palmar side of the fingertips of respectively digit II and digit V of the injured hand after immersion into the water bath. The temperature of the water bath was kept constant at 15.0°C (range 14.7 to 15.6 °C). Time = 0 minutes represents the baseline values before immersion.*

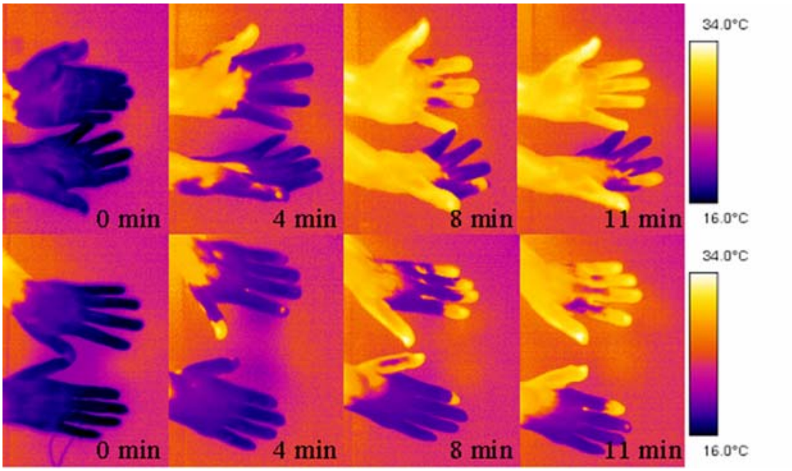



*Median nerve injury patients (n=4).*

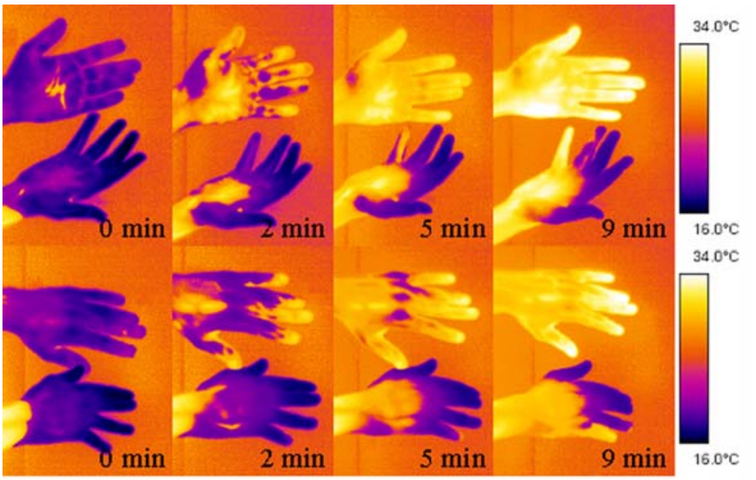
## DISCUSSION

This study indicates that infrared thermography might be a valuable tool in the assessment of the distribution of cold intolerance after traumatic median and ulnar nerve transection injury and repair. We did not find another study in which infrared thermography has been used to analyse the long-term results of upper extremity nerve injury on rewarming patterns in the hand following cold stress testing[13-18]. This study was designed as a pilot study, therefore the number of patients is small and we did not present control data at this moment. Several studies confirm that the skin temperature distribution of a healthy human body exhibits a contralateral symmetry and the maximum temperature difference between the two sides is less than 0.5°C[19-20]. The five minutes cooling phase at 15°C was well tolerated by seven of the eight patients. A longer immersion time is not recommended since cold induced vasodilatation might occur that may bias the results[21-24]. Ruch et al.[18] found a significant decrease in digital blood flow after cold stress testing of the fingers in a cold chamber in the acute phase of median and ulnar nerve injury. However, they did not find a significant difference in surface temperature between the injured and uninjured areas using a small surface thermistor on all fingers. This difference might be explained by regulatory changes in the acute phase and the long-term phase after peripheral nerve injury. As the temperature differences were clearly visible on the dorsum of the hand as well, the results of this pilot study might confirm the results of an anatomical study by Campero et al.[25]. In this study it was found that the ulnar nerve supplies vasomotor fibres to its cutaneous sensory territory and the median nerve normally provides supplementary vasomotor innervation to the skin of the radial aspect of the dorsum of the hand. This study also describes that the radial nerve does not normally contribute vasomotor sympathetic fibres to the skin of the hand, however we did not test radial nerve injured patients in this pilot study. This study confirms our hypothesis that infrared thermography can be a valuable tool in assessing cold intolerance in nerve injury patients and hopefully will be able to aid in the elucidation of the pathophysiology of cold intolerance. Future research will consist of measuring nerve-injured patients at multiple time-points after nerve injury continuously during the cooling down phase and rewarming phase.

Figures 3a and 3b. Thermography of dorsal and palmar aspect of the hands.




*(a) Thermographs of a patient eight year after ulnar nerve injury of the right forearm. The patient had a CISS-score of 60 and complained of cold intolerance. The scans at zero minutes (0 min) show the temperature of the hands after removal from the water bath (15℃). During the re-warming period, scans were taken at 4, 8, and 12 minutes. Top figures show the palmar side, the bottom figures the dorsal side.*




*(b) Thermographys twelve years after median nerve injury of the right forearm at 0, 2, 5 and 9 minutes after removing the hands from the water bath (15℃). The patient complained of cold intolerance and had a CISS-score of 39. Top figures show the palmar side, the bottom figures the dorsal side.*

## CONCLUSION

Based on the results of this pilot study, we conclude that the infrared temperature profile of the damaged hand after immersion into cold water may be a helpful tool to assess thermoregulation after peripheral nerve injury of the upper extremity.

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# Chapter 7

## Digital rewarming patterns after median and ulnar nerve injury.

Aleid CJ Ruijs[1]
Sjoerd P Niehof[2]
Ruud W Selles[3]
Jean-Bart Jaquet[1]
Hein AM Daanen[4, 5]
Steven ER Hovius[1]

[1] Department of Plastic, Reconstructive and Hand Surgery, Erasmus MC, Rotterdam, The Netherlands.
[2] Department of Anaesthesiology, Erasmus MC, Rotterdam, The Netherlands.
[3] Department of Rehabilitation, Erasmus MC, Rotterdam, The Netherlands
[4] TNO Human Factors, Thermal Physiology Group, Soesterberg, The Netherlands.
[5] Faculty of Human Movement Sciences, VU University, Amsterdam, The Netherlands.

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## SUMMARY

**Background -** Post-traumatic cold intolerance (CI) is a frequent and important sequel after peripheral nerve injury. In this study, it is hypothesized that altered re-warming patterns after peripheral nerve injury are related to the degree of post-traumatic CI. This hypothesis is tested by comparing re-warming patterns of the digits quantitatively in controls and in median or ulnar nerve injury patients and by investigating relationships between re-warming patterns, sensory recovery and CI.

**Methods -** Twelve median or ulnar nerve injury patients with a follow-up of 4 to 76 months after nerve repair and thirteen control subjects underwent isolated cold stress testing (CST) of the hands. Videothermography was used to analyze and compare re-warming patterns of the injured and uninjured digits after CST. Temperature curves were analyzed by calculating the Q value as an indicator of heat transfer (temperature added during the first 10 minutes after start active re-warming) and the maximum slope.

**Results -** Test-retest reliability was 0.64 and 0.79 respectively for the Q value and maximum slope. High Q-values and maximum slopes were interpreted as the presence of active re-warming. Patients with return of active re-warming had better sensory recovery (p=0.01) and lower CISS-scores (p=0.06). Better sensory recovery was correlated with lower CISS-scores (rho=0.642, p=0.024).

**Conclusions -** Test-retest reliability of CST was good and we found a difference in re-warming patterns between nerve injury patients and controls. The presence of active re-warming in the nerve injury patients was related to sensory recovery and less complaints of post-traumatic CI.

## INTRODUCTION

At low and high environmental temperatures, the body adapts blood flow to the extremities to maintain body core temperature at around 36.8ºC by increasing and decreasing heat exchange with the surroundings. When we enter a cold environment, vasoconstriction of the skin blood vessels prevents unnecessary heat loss, that could result in a lowering of the body core temperature[1, 2]. Skin temperature in the digits, palm and toes correlates highly with skin blood flow[3] and skin sympathetic nerve activity[4, 5]. Therefore, changes in central and/or peripheral mechanisms of blood flow regulation are, in part, represented by changes in skin temperature[6]. These changes in blood flow and therefore temperature of the skin can be measured accurately and continuously using video thermography[7]. In the absence of disease, there is thermal symmetry between opposite hands and body surface of less than 0.5 ºC in resting conditions after familiarization to room temperature[8, 9].

In the majority of upper extremity peripheral nerve injury patients, post-traumatic cold intolerance occurs (CI), defined as abnormal pain following exposure to mild cold[10-17]. Its incidence varies probably due to the variability in the method of testing between 56% and 83%[11, 15, 16, 18]. Cold intolerance has been found to be the most disabling symptom following peripheral nerve injury and it does not diminish over time[11, 13, 15, 18-21]. Cold intolerance has also been noticed frequently in patients with Raynaud's disease[22-25], upper extremity bone fractures[26], digital replantations[21, 27-35], and after raising a radial forearm flap[36, 37.]

The severity of CI has been studied subjectively using a single question[16, 30, 38], interviews[10, 17, 29, 39], questionnaires[13, 18, 32-34] and validated questionnaires such as the McCabe[12, 18-20, 40] and the Blond McIndoe Cold Intolerance Severity Scale (CISS) [11, 15].

In patients exposed to vibration tools (forestry workers, construction workers), Raynauds' disease, CRPS or digital re-plantations and amputations, several laboratory tests have been used to study digital blood flow and skin temperature, e.g. Laser Doppler flowmetry[31, 40-47], Plethysmography to measure the amount of blood inflow[27, 34, 43], finger systolic blood pressure[26, 33, 48-50], thermocouples on the skin[4, 44, 45, 51, 52] and infrared thermography[23, 36, 43, 53-59]. However, to our knowledge, re-warming has only been evaluated in nerve injury patients by Ruch[40] in very recent injuries (< 3 months old) using LDF and thermocouples and by Pulst[59] in recent injuries (1-19 months) using infrared thermography at 7 and 15 minutes after immersion of the hands in ice water. During the first six months after nerve repair, they observed vasodilatation of the area supplied by the nerve at room temperature and after cold stress testing because of loss of sympathetic activity[52, 59]. After approximately six months, compensatory changes provide vasoconstriction, and there is hypothermia at room temperature and after cold stress testing[59-61]. To test an experimental setup using thermography as a temperature measurement device in nerve-injury patients with a more than four years old nerve injury, we recently reported on a pilot study in eight peripheral nerve injury patients[14]. Although re-warming patterns were not measured continuously, we found that thermographic recordings following cold stress testing could be used to measure re-warming patterns in the hands and digits in peripheral nerve injury patients. It was shown that measuring the dorsal side of the hands resulted in a reliable temperature recording.

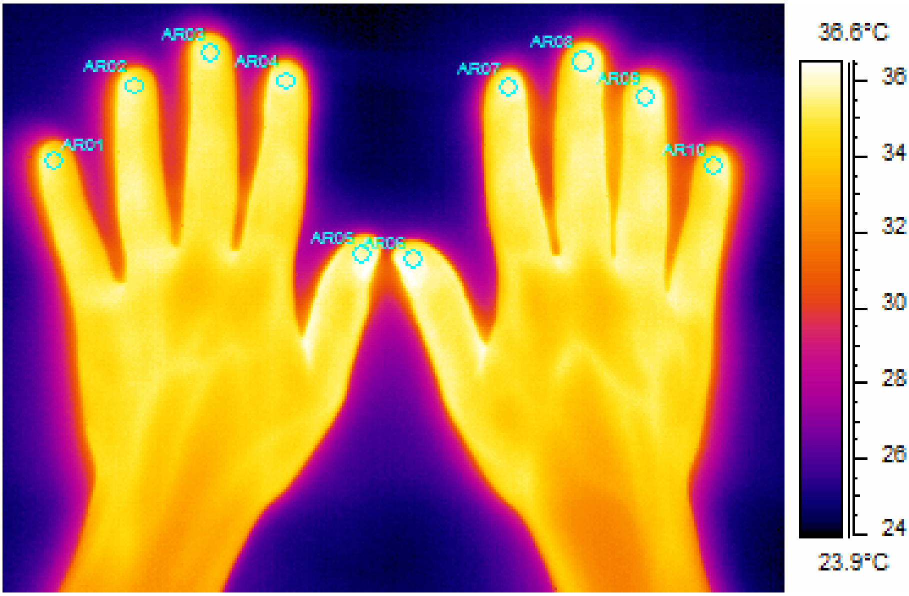
The aim of this study is to test the hypothesis that re-warming patterns of the digits are altered in peripheral nerve injury patients and that these patterns are related to the degree of post-traumatic CI. To achieve this goal, we describe the re-warming patterns quantitatively, compare control subjects with patients and investigate relationships between re-warming patterns, sensory recovery and CI. The experimental set-up involves continuous monitoring of re-warming patterns following cold stress testing with video thermography in control subjects and median or ulnar nerve injury patients.

## PATIENTS AND METHODS

### Control subjects

Thirteen control subjects (eight men and five women) participated in this study. They were recruited from the hospital staff and people living in the neighborhood of the hospital. Average age was 29 year (22-37y), three were left hand dominant, eleven right hand dominant. Three subjects smoked 2-10 cigarettes a day (average 6 /day), but were asked to refrain from smoking starting the evening before testing (Table 1a). One control subject was diagnosed with grand mal seizures and used carbamezepine 200 mg three times daily. Three of the four women used oral anticonceptives. The BMI ranged between 18.5 and 25.6 with an average of 22.8 (Table 1a). Mean CISS score was 10 with a range of 4-24, indicating that none had abnormal CI [(62)]. To screen for pathologies that might have an influence on the re-warming pattern, control subjects were asked about their current health status and past medical history. Four volunteers had a history of upper extremity injury. Two subjects had a clavicula fracture as a child, with no current complaints, and one had a capitatum and hamatum fracture 2 years ago, which healed without complaints. One subject had long-term symptoms of Repetitive Strain Injury (RSI). The Allen’s test was normal in all subjects. Sensory testing was performed using Semmes-Weinstein monofilaments numbers 2.83; 3.61; 4.31; 4.56; and 6.10. All volunteers had Imai score 1, indicating normal sensibility (Table 2). After exclusion of one volunteer who failed to return for the second test, a total of 13 volunteers were included for analysis.

Figure 1: example of thermograph with circles drawn for analysis.




*This figure shows a baseline thermograph of a male control subject. The circles represent the areas where average temperature was calculated. It was ensured that the circles were in the same location for every frame. The temperature scale is presented at the right side of this figure.*

Table 1a: Control group characteristics.

| Control | Gender | Age | BMI | Notes |
|---|---|---|---|---|
| 1 | F | 26 | 24.1 | OAC |
| 2 | M | 30 | 23.4 | Smoker |
| 3 | M | 27 | 23.5 | Smoker |
| 4 | F | 25 | 19.4 | OAC |
| 5 | M | 28 | 25.3 | Epilepsy |
| 6 | M | 31 | 25.6 | |
| 7 | M | 29 | 23.4 | |
| 8 | M | 32 | 18.5 | |
| 9 | F | 30 | 19.8 | |
| 10 | M | 33 | 25.3 | |
| 11 | F | 22 | 20.8 | OAC |
| 12 | F | 27 | 23.0 | OAC Smoker |
| 13 | M | 37 | 24.3 | Complaints of RSI |
| Mean (SD) | | 29 (3.7) | 22.8 (2.3) | |

*BMI= body mass index. OAC= oral anti-conceptives. RSI= repetitive strain injury.*

**Patients**

Twelve peripheral nerve injury patients (nine men and three women) participated in our study. (Table 1b) Six patients had a single ulnar nerve injury and six patients a single median nerve injury. All were sharp injuries between elbow and wrist level and were primary repaired using microsurgical techniques. Follow-up after injury was between 4 and 63 months. Injuries less than 24 months ago were considered recent nerve injuries without maximum recoveries. Patients with a longer follow-up were considered non-recent nerve injuries with potential sensory and motor recovery. Average age at injury was 29 year (15-62y) and four patients were left hand dominant. Five subjects smoked 2-20 cigarettes a day (average 11 cig/day), but also refrained from smoking starting the day before testing. One ulnar nerve injury patient had agoraphobia, treated with a serotonine re-uptake inhibitor, and one was treated for hypercholesterolemia with statines. One median nerve injury patient previous underwent surgery for an Arnold-Chiari malformation. In two ulnar nerve injury patients the ulnar artery was tied off during surgery. In all other patients both radial and ulnar arteries were patent, confirmed by the Allen’s test and Doppler test when necessary. Past medical histories showed burns and fractures of the upper extremity and one surgical removal of a dorsal wrist ganglion, with no current complaints. Average BMI was 25.0 (Table 1b). Seven patients had abnormal CI (CISS score >30). For sensory testing, the same set of Semmes-Weinstein monofilaments was used as in the control group. Three

patients had Imai scores of 5 in the affected area, one had a score of 4, seven had a score of 3 and one had a sensory recovery of 2. (Table 2)
All subjects completed the CISS questionnaire [11, 20, 62], which has a minimum score of 4 and a maximum score of 100. A score of thirty or higher is considered abnormal CI [62] (Table 1b). Sensory testing was performed using Semmes Weinstein monofilaments (North Coast Medical Inc, Morgan Hill, CA) and outcome was classified according to Imai et al.[63] Patency of both radial and ulnar arteries was tested using the Allen's test. A negative result was verified using Laser-Doppler flowmetry.

Table 1b: Patient characteristics.

| Pat | Sexe | Nerve | Age | BMI | Imai | CISS | FU | Active |
|---|---|---|---|---|---|---|---|---|
| A | M | U | 25 | 30.9 | 4 | 62 | 4 | No |
| B | F | M | 21 | 26.9 | 5 | 50 | 5.5 | No |
| C | F | U | 42 | 23.3 | 5 | 51 | 9 | No |
| D | M | M | 24 | 23.8 | 3 | 29 | 24 | Yes |
| E | M | M | 42 | 23.3 | 5 | 55 | 29 | No |
| F | M | U | 62 | 30.5 | 3 | 12 | 37 | Yes |
| G | M | M | 26 | 24.9 | 3 | 4 | 40 | Yes |
| H | F | U | 42 | 25.0 | 3 | 39 | 43 | No |
| I | M | M | 15 | 18.8 | 3 | 66 | 52 | Yes |
| J | M | U | 16 | 23.8 | 3 | 44 | 62 | Yes |
| K | M | M | 15 | 22.8 | 2 | 4 | 63 | N.A. |
| L | M | U | 23 | 26.1 | 3 | 4 | 76 | Yes |
| Mean (SD) | | | 29 (14) | 25.0 (3.3) | 3.5 (1.0) | 35 (23.6) | 37 (24) | |

Patients are ordered based on the follow-up (FU) after injury. FU= follow-up in months. Nerve: U= ulnar nerve, M= median nerve. CISS= score of CISS questionnaire. Imai is Imai score (sensibility). Active indicates if active re-warming in the affected digits (for median nerve injuries digits 2 and 3 and for ulnar nerve injuries digit 5) is present. Patient K had an abnormal re-warming pattern in all ten digits. Therefore it was not possible to compare the affected digits to the unaffected digits.

Table 2: Distribution of Imai classification[63] for sensory recovery and the corresponding Semmes-Weinstein monofilament number.

| Quality of sensation (range 1-5) | Filament | Control subjects (n=13) | Patients, (n=12) |
|---|---|---|---|
| 1: Normal | 2.83 | 13 | 0 |
| 2: Diminished light touch | 3.61 | 0 | 1 |
| 3:Diminished protective sensation | 4.31 | 0 | 7 |
| 4: Loss of protective sensation | 4.56 | 0 | 1 |
| 5: Anaesthetic | 6.10 | 0 | 3 |

**Cold stress and re-warming**

This study was approved by the local Medical Ethical committee of the Erasmus MC (MEC-2005-037) and informed consent was obtained from the subjects. To calculate the reliability of our experimental set-up, the experiment was conducted twice in control subjects. The first measurement was performed in September or October 2006 and the experiment was then repeated in January or February 2007, resulting in a time period of 4-5 months between the two experiments. One volunteer was not able to return for the second test and was therefore excluded from this study. After acclimatization for 15 minutes at room temperature (22 -24 ºC), both hands were immersed up to the ulnar styloids for 5 minutes in a water bath with a constant temperature of 14.5°C (range 14.0-15.0). After removing the hands from the water, they were carefully and quickly dried using a cotton towel. Then, the subject was seated in a comfortable chair with both hands resting on a Plexiglas standard with the dorsal sides facing the camera. The delay between removal of the hands from the water bath and thermographic recording was less than 1 minute. Thereafter one image per second was obtained, using a FLIR ThermaCam SC2000 video camera with a resolution of 320x240 pixels and a distance of 68 cm. This results in a resolving capacity on the skin of 0.8 $mm^2$. Emissivity of the skin was set at $\varepsilon = 0.98$. The emissivity of a material is the ratio of energy radiation by the material to energy radiated by a black body at the same temperature. Temperature was measured until both hands had re-warmed to a stable temperature with a minimum of ten minutes and a maximum of thirty minutes.

**Data analysis**

Thermographs were analyzed using FLIR Thermacam Researcher Pro (2001 HS) software, temperature readings of the fingertips were exported to MS excel® 2003 and further analyzed with Matlab® software (version 7.1).

For each digit, temperature was measured dorsally in the middle of the distal phalanx as the average of a 3-5 mm diameter circle, representing approximately 9 to 24 individual temperature values [Figure 1]. Data were smoothed with a second-order low-pass Butterworth filter with a cut-off value off 0.015 Hz and were plotted in a time-temperature curve for further analysis of the re-warming pattern [Figures 2 and 3] The curves could be divided in a passive phase with slow, steady, and minimal re-warming, and an active phase with rapid, exponential re-warming to baseline temperatures. Using in-house software, the first derivative of the time-temperature curve was plotted. This allowed measurement of the maximum change in temperature with time (ºC/min). The second derivative was calculated to determine the rate of change of temperature gradient with time (ºC/min$^2$). The peak of this signal indicates the maximum increase in the rate of change of temperature, and this point defined the onset of active re-warming (lag time)[55].

To determine the total amount of heat added to the digits during re-warming, following Merla et al.[22], Q-values were calculated as the area under the curve from the start of the active phase over a time period of 600 seconds (10 minutes) (equation 1):

| | |
|---|---|
| $Q = \int_{t_0}^{t_{0+600}} T(t)\, d(t)$ | Equation 1 |

In this equation, t is time, $t_0$ is the time when active re-warming starts, $t_{0+600}$ is 600 seconds after the start of re-warming, T is the temperature of the digit. The offset is 15°C, representing the temperature of the water bath and therefore the minimum temperature of the hands. Active re-warming was defined as a maximum re-warming speed (slope) of more than 1ºC per minute and a Q-value of more than 300.

Statistical analysis was performed using SPSS version 10.1. To test repeatability of our experimental setup, test-retest reliability was analyzed using the intraclass correlation coefficient. Student’s t-test was used to compare Q values and maximum slopes between groups. In patients, affected digits were compared to unaffected digits. For median nerve injuries we regarded digits II and III of the injured side as affected, and for ulnar nerve injuries digit V. Digit IV was not included in the analysis due to its dual innervation. Unaffected digits and affected digits of patients were compared to the average values of the digits of the control group, as no significant difference between the digits was found. Differences between sensory recovery and CISS score in patients with active re-warming and without active re-warming were compared using the non-parametric Mann-Whitney U test. The correlation between sensory recovery and CISS-score was calculated using the non-parametric Spearman's rank correlation coefficient.

## RESULTS

At baseline, the hands showed a symmetrical temperature distribution (Figure 1) with a maximum temperature difference of 0.6°C between left and right hand. Figure 2 shows a typical example of videothermography curves starting at t=0 after 5 minutes of cooling. The figure shows that the temperature distribution after cooling was no longer symmetrical, and there were temperature differences between the digits of 2-5 °C. In the control subject (Figure 2a), several minutes of slow and steady re-warming (passive phase) was followed by a fast and exponential re-warming phase (active phase). In the latter phase, digits re-warmed within minutes to baseline temperatures, and temperature of the fingertips oscillated around a steady state. In the ulnar nerve injury patient (Figure 2b), however, the passive phase was often not followed by an active phase in the affected digit (nr V) while in digit IV the active phase was diminished.
Parameters that were derived from the re-warming curves to compare between subjects were the start and stop of the active re-warming phase, maximum slope and the definition of the Q value (grey area, Figure 3). Average values of the Q-value and maximum slope for the first and second experiment in each control are shown in Table 3. Repeated measurement of the Q values and the maximum slopes in the control subjects showed good reliability with ICC's of 0.64 (p=0.007) for the Q value and 0.79 (p=0.0004) for the maximum slope.
The results of the Q values and maximum slopes for both nerve injury patients and control subjects are presented in Table 4. In control subjects, generally, a passive phase (vasoconstriction) was followed by an active phase (vasodilatation), starting at the fingertips. In peripheral nerve injury patients, however, the passive phase is not always followed by an active phase of re-warming. The amount of heat necessary to re-warm the digits, estimated by the Q value and the maximum slope, were significantly lower in the affected digits than in the unaffected digits and control subjects. However, after long-term follow-up and satisfactory sensory recovery, normalization of the re-warming pattern as determined by Q values and maximum slope was observed.

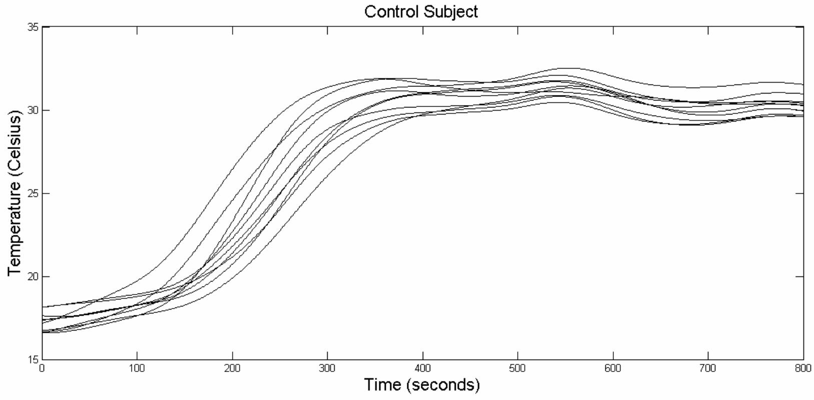
Nerve-injury patients could be divided in two groups: an active re-warming group, with Imai classification 2 or 3 and a minimum follow-up of 24 months, and a passive re-warming group, consisting of nerve injuries that were either recent injuries or did not have adequate sensory recovery. Imai scores in this second group were 3, 4 or 5. We found a significant inverse correlation between the presence of active re-warming and CI (rho -0.714, p=0.009). However, this pattern was not consistent over all patients; 2 patients with return of active re-warming had significant subjective symptoms of post-traumatic CI. There was no significant difference (p>0.05) between the Q values and maximum slopes of the control subjects, unaffected digits and affected digits that showed active re-warming. In the digit innervated by the ulnar nerve in figure 2b (digit V) both maximum slope and Q value were significantly diminished (p<0.05).

Better sensory recovery was found in patients with active re-warming (25-50-75 percentiles: 3.5-5.0-5.0) than without active re-warming (3.0-3.0-3.0, p=0.01). In addition, lower CISS-scores were found in patients with active re-warming (4-12-44) than without active re-warming (51-56-58, p=0.06). The patients' Imai scores in the affected digits were significantly correlated with their CISS-score (rho=0.642, p=0.024), indicating less severe post-traumatic CI with better sensory recovery.

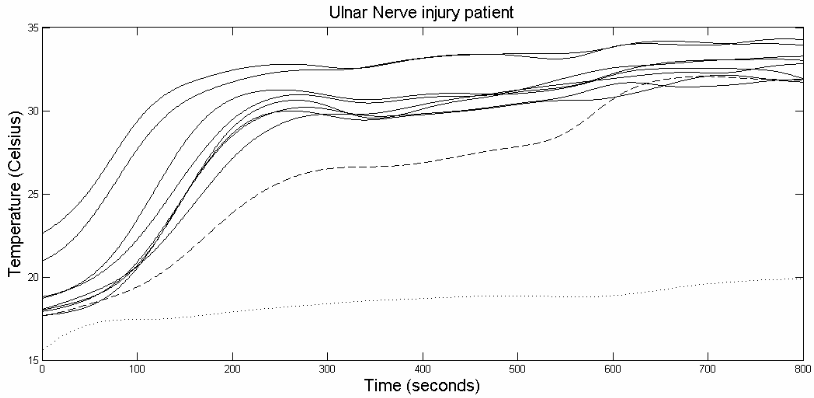
In three control subjects, re-warming in one or more digits remained passive up to 900 seconds (15 minutes) after removal of the hands from the water bath. One control subject failed to re-warm several digits for more than 1800 seconds (30 minutes). This may be related to an underlying pathology, such as RSI, Raynauds' disease or secondary scleroderma. This was also the case in one male nerve injury patient, who showed an absence of active re-warming in the majority of his digits.

When looking at the re-warming at different locations in the hand over time, we found that the process of active re-warming starts distally in the fingertips and moves in proximal direction., as shown in consecutive thermographs during the active re-warming phase of a control subject in Figure 4. This pattern of distal to proximal was not different between patients and controls.

Figures 2a and 2b: a typical example of the re-warming curve of a control subject and of a nerve injury patient.

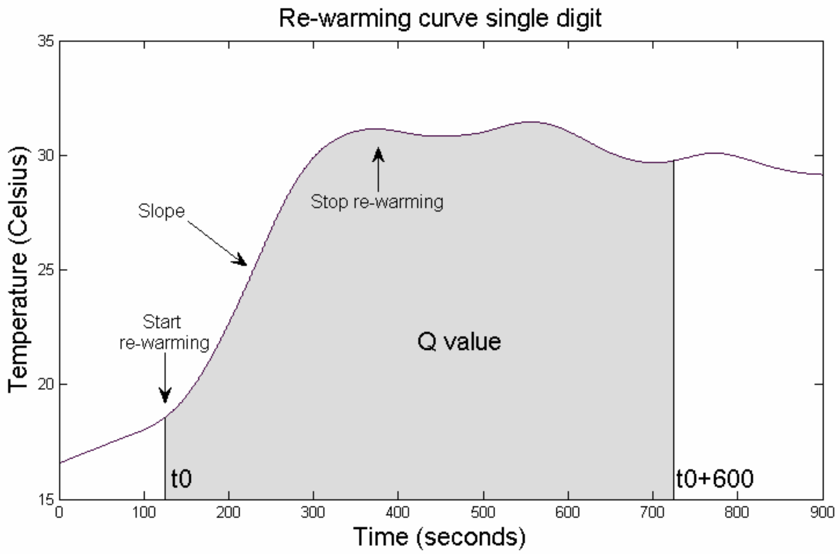



*All digits show active re-warming. Note that asymmetry between the digits is approximately 5ºC.*




*This patient was measured nine months after repair of a right-sided ulnar nerve injury. Digit 5 (r5) shows passive re-warming only. Digit 4 (r4), supplied both by the median and ulnar nerve, shows active re-warming comparable to the unaffected digits.*

Figure 3: typical example of a re-warming curve of a single digit in a control subject.




*After a passive phase, active re-warming starts at 110 seconds in this subject, this is defined as t0. The slope of the curve indicates the rate of re-warming (ºC/min). The Q value is defined as the area under the curve from t0 to t0+600 (shaded area) and indicates the total amount of heat added to the digit. In a digit without active re-warming, the Q value will be reduced.*

## DISCUSSION

In this study we described re-warming patterns of the digits after cold-stress testing, using the maximum slope of the time-temperature curve and calculated Q-values. In our control group we found that the test-retest reliability was good for both parameters. In our patient group, consisting of median and ulnar nerve injury patients, we found that the presence of active re-warming and cold intolerance were negatively correlated and the return of sensory recovery was correlated with the presence of cold intolerance and the return of active re-warming.

To our knowledge, this study is the first to apply this experimental design to nerve injury patients. A limitation our study is the relatively small number of nerve injuries. Despite of this small number of subjects, we were able to show significant differences between patients and controls and significant relations between re-warming patterns, CI and sensory recovery. A strength of this study is that we were able to continuously filming the re-warming patterns of the hand with 1 images per second and were therefore able to perform mathematical calculation of parameters derived from the re-warming curves. In future studies, reliability of the patient group should also be determined.

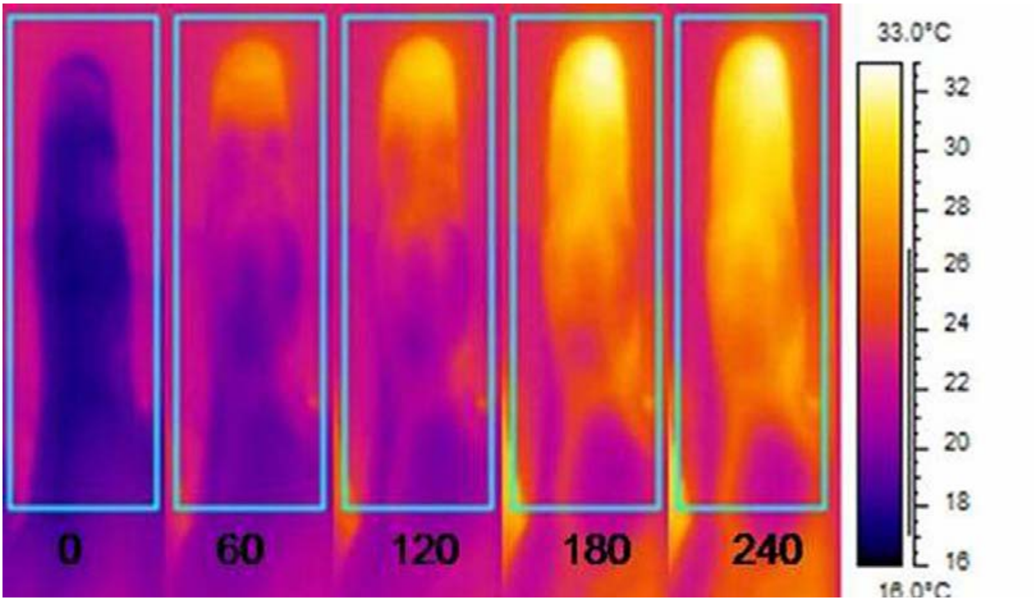
Previous studies in nerve injury patients showed vasodilatation in the acute phase up to 6 months after injury and vasoconstriction up to 19 months after nerve injury[40, 59]. Our results showed that after a longer follow-up, return of active re-warming is possible. In a number of studies in patients with replantation, revascularisation and raising of a radial fore-arm flap, low digital blood flow did not correlate with subjective symptoms of CI [27, 30, 31, 34, 36]. As described in previous literature [27, 28, 30, 31, 34, 39], we found a correlation between sensory recovery, active re-warming, and CI. This suggests that as the nerve progressively recovers active re-warming returns. However, it may be that for cessation of symptoms of CI, a higher level of sensory recovery would be needed, a level that may not be reached by all patients, even after a follow-up of more than 4 years.
In two control subjects, active re-warming was absent in 3 or more digits. One of these subjects was known with chronic RSI symptoms. In the nerve injury group, one patient had passive re-warming in the majority of digits, including the affected digits. It has been reported that up to 18% of control subjects (depending on method of measurement) have absence of an active re-warming response that could not be explained by their previous medical history[23, 52, 55].
Abnormal digital blood pressure has been reported during local cooling at 15ºC in 25% of control subjects and in 35% of control subjects with a history of cold fingers[25]. Cleophas et al[64] found better re-warming at a room temperature of 24ºC

then at 20ºC in control subjects, although 8% did not re-warm well in the higher room temperature group. In our study, we used a room temperature of 24ºC. Factors explaining an abnormal re-warming in control subjects might be a pre-consisting pathologic condition of the vessels resulting from aspects such as non-freezing cold injuries in the past, pharmacotherapy, generalized disease, exposure to vibratory trauma[52], RSI, Raynauds' disease or secondary scleroderma[22]. A longitudinal study might be able to elucidate this underlying pathology.

As cold intolerance is mentioned by patients to be the most disabling symptom following nerve repair[11, 13, 15, 18-21], limiting activities of daily life, using an outcome instrument in clinical practice is very important. With this study we have developed a safe, reliable and objective testing method and have found parameters that can be calculated accurately. This allows hand surgeons to evaluate the return of active re-warming and hence the protective abilities of the hands against cold. This information can influence the patient in deciding to return to their previous work and using protective clothing while being outdoors. Future studies could be aimed at following a larger group of nerve injury patients prospectively, performing multiple tests during long-term follow-up. Also the effects of different treatment options (medical, behavioral or training) could be evaluated using cold-stress testing.

In conclusion, re-warming patterns revealed using infrared video-thermography could be analyzed quantitatively using Q-values and maximum slopes of the re-warming curve. Test-retest reliability was good and it was possible to objectively record the return of active re-warming after sensory recovery. Sensory recovery was strongly related to the presence of active re-warming in the nerve injury patients, suggesting that sensory recovery is an important aspect of the pathophysiology of CI. Restoration of active re-warming was correlated with less subjective CI. However, our hypothesis that CI is related to the re-warming pattern could not be confirmed in all patients.

Figure 4: Typical consecutive re-warming thermographs.




*Consecutive thermographs of the right index finger of a control subject during active re-warming (time in seconds). At t=0, the finger has been cooled down, theTskin is around 18ºC. At 60 seconds, active re-warming has started at the fingertip. At 120 seconds, the warm area moves proximally. At 180 seconds, the superficial venous system is evident. At 240 seconds, most of the digit has re-warmed to baseline temperature..*

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# Chapter 8

## Cold Induced Vasodilatation after median and ulnar nerve injury

Aleid CJ Ruijs[1,3]
Sjoerd P Niehof[2]
Steven ER Hovius[1]
Ruud W Selles[1, 4]

Affiliations:

1 Department of Plastic and Reconstructive Surgery, Erasmus MC - University Medical Hospital Rotterdam, the Netherlands.
2 Department of Anesthesiology, Pain Treatment Centre, Erasmus MC - University Medical Hospital Rotterdam, the Netherlands.
3 Département de Chirurgie Orthopédique, UCL St LUC, Bruxelles, Belgium.
4 Department of Rehabilitation Medicine, Erasmus MC - University Medical Hospital Rotterdam, the Netherlands.

## SUMMARY

**Background** - peripheral nerve injury of the upper extremity frequently causes changes in the thermoregulatory system of the hands and fingers and complaints of cold intolerance. In this study, we aimed to measure the influence of median or ulnar nerve injury on cold induced vasodilatation (CIVD) during prolonged cooling at low temperatures.

**Methods** - Twelve patients with a median (n=6) or ulnar (n=6) injury were tested 4 to 76 months after nerve repair. The palmar sides of both hands were cooled continuously using a cold plate of 5°C. The skin temperature of the fingers was measured using videothermography and graphs were plotted of the temperature changes of the nail bed of the distal phalanx. The presence of a CIVD reaction was defined as a minimum increase in temperature of more then 2.5°C starting at the distal phalanx.

**Results** - A CIVD reaction was absent in the affected digits of 4 patients (follow-up 6-37 months) whereas the CIVD reaction in the non-injured hand was present. The CIVD was present in 6 patients after 50 months follow-up (24-76). Two patients did not have a CIVD reaction in both injured and uninjured hands. All patients with a CIVD response had at least diminished protective sensation. The absence or presence of the CIVD reaction was not correlated with CISS score.

**Conclusion** - After peripheral nerve injury it is possible to restore normal thermo-physiological responses of the fingers and this is most likely an indication of nerve recovery. However, subjective symptoms of post-traumatic cold intolerance can be present when thermo-physiological responses to cold are normal.

## INTRODUCTION

Cold Induced Vasodilatation (CIVD), also known as the Hunting reaction, is a cyclic regulation of blood flow during prolonged cooling of protruding body parts, such as the hands, feet, chin and nose[7, 17]. Lewis et al. first described it in 1930[18] and it is generally considered to be a protection mechanism against frostbite, as it warms the skin temperature of the fingertips considerably. The CIVD reaction is better when the body core temperature is high, and thus there has been some debate recently, as Flouris et al.[10] suggested that it is primarily a mechanism to lose excessive heat from the body.

In healthy subjects, the CIVD occurs after a minimum cooling time of 5 to 7 minutes in an environment of maximally 15°C, with cooling in water leading to a stronger reaction than cooling in air[32]. In general, lower environmental temperatures (less than 4°C) lead to more reliable CIVD reactions and a better synchronicity between the fingers. However, since these low temperatures are very painful, for experimental testing, higher temperatures are generally used.[5, 7, 24, 32]

The presence and nature of the CIVD reaction depends on a large number of variables. For example, a higher body core temperature as well as the intake of food lead to a stronger and faster CIVD reaction[7, 9, 31]. Also, the CIVD reaction differs between individuals. In fact, Mekjavic et al. have described 7 different patterns of the CIVD reaction[22] based on the shape of the CIVD wave. The most common was the typical wave, followed by the early plateau, late plateau, double wave and big wave. Although the CIVD is considered a functional reaction to a cold environment, previous studies did not find a change in CIVD after repeated immersion of the hands in cold water during 2 or 3 weeks[12, 22] or during a two-week stay in the arctic or other cold climate[20].

It is well known that the majority of patients following peripheral nerve injury suffer from painful, stiff, or discoloured hands after exposure to cold, also known as cold intolerance. In earlier experiments, we have shown that the re-warming of the fingers in median or ulnar nerve injury patients is altered following cold stress testing (that is, immersion of the hands during 5 minutes in a water bath of 15°C) and that active re-warming was absent in more acute nerve injuries while present in some of the more chronic nerve injury patients in which nerve function may have improved.

As in cold stress testing, evaluation of the CIVD reaction may be a tool to evaluate the quality of the thermoregulatory system in patients after a peripheral nerve injury. Until today, it is not clear if the CIVD reaction shows similar changes after peripheral nerve injuries as found with cold stress testing and whether the presence of absence of a CIVD reaction is related to the subjective experience of cold intolerance in nerve injury patients. Therefore, in this study, our objective was to study the presence and nature of CIVD reactions in the hand during prolonged cooling of more than 30 minutes at a low temperature of 8-10°C. To study this, infrared videothermography were used to record the skin temperature during prolonged cooling of both hands. Because skin temperature correlates highly with skin blood flow[15, 23], using this method, we can establish possible changes in central and peripheral mechanisms of blood flow regulation after peripheral nerve injury.

## PATIENTS AND METHODS

### Patients

Twelve peripheral nerve injury patients (nine men and three women) participated in our study (see Table 1). Six patients had a single ulnar nerve injury and six a single median nerve injury. All were sharp injuries between elbow and wrist level and were primary repaired using microsurgical techniques. Follow-up after injury was between 4 and 76 months. Five subjects smoked 2-20 cigarettes a day (average 11 cig/day), but refrained from smoking starting the day before testing. One ulnar nerve injury patient had agoraphobia, treated with a serotonin re-uptake inhibitor, and one was treated for hypercholesterolemia with statines. In addition, one median nerve injury patient had undergone surgery for an Arnold-Chiari malformation. In two ulnar nerve injury patients the ulnar artery was tied off during surgery and was therefore not patent. In all other patients both radial and ulnar arteries were patent, confirmed by the Allen’s test and echo-Doppler. Past medical histories showed burns and fractures of the upper extremity in eight patients and one had surgical removal of a dorsal wrist ganglion, without current complaints. All patients were able to participate in the experiment, although the cooling was reported to be painful and unpleasant. The study was approved by the local Medical Ethical committee of the Erasmus MC, Rotterdam, The Netherlands (MEC-2005-037) and informed consent was obtained from all subjects.

Table 1. Patient characteristics and CIVD reaction.

| Patient | Gender | Nerve | Age | BMI | Imai | CISS | FU | CIVD |
|---|---|---|---|---|---|---|---|---|
| 1 | M | U | 25 | 30.9 | 4 | 62 | 4 | III |
| 2 | F | M | 21 | 26.9 | 5 | 50 | 6 | II |
| 3 | F | U | 42 | 23.3 | 3 | 51 | 9 | II |
| 4 | M | M | 24 | 23.8 | 3 | 29 | 24 | I |
| 5 | M | M | 42 | 23.3 | 5 | 55 | 29 | II |
| 6 | M | U | 62 | 30.5 | 3 | 12 | 37 | II |
| 7 | M | M | 26 | 24.9 | 3 | 4 | 40 | I |
| 8 | F | U | 42 | 25.0 | 3 | 39 | 43 | I |
| 9 | M | M | 15 | 18.8 | 3 | 66 | 52 | I |
| 10 | M | U | 16 | 23.8 | 3 | 44 | 62 | I |
| 11 | M | M | 15 | 22.8 | 2 | 4 | 63 | III |
| 12 | M | U | 23 | 26.1 | 3 | 4 | 76 | I |
| **Mean (SD)** | | | **29 (14)** | **25.0 (3.3)** | **3.5 (1.0)** | **35 (23.6)** | **37 (24)** | |

*Patients are ordered based on the follow-up (FU) after injury. FU= follow-up after nerve repair in months. Nerve: U= ulnar nerve, M= median nerve. Age is age at injury. CISS= score of CISS questionnaire. Imai is Imai score (sensibility). CIVD: group I CIVD reaction in all 8 digits; group II CIVD reaction in unaffected digits, absent in affected digits or affected hand; group III CIVD reaction absent in all 8 digits.*

Table 2. Imai classification[63] for sensory recovery with corresponding Semmes-Weinstein monofilament.

| Quality of sensation (range 1-5) | Filament |
|---|---|
| 1: Normal | 2.83 |
| 2: Diminished light touch | 3.61 |
| 3:Diminished protective sensation | 4.31 |
| 4: Loss of protective sensation | 4.56 |
| 5: Anaesthetic | 6.10 |

**Methods**

To determine the level of the subjective experience of cold intolerance, all subjects completed the CISS questionnaire[14, 21, 26, 28], which has a minimum score of 4 and a maximum score of 100. A score of thirty or higher is considered abnormal CI (Table 1)[26]. Sensory testing was performed using Semmes Weinstein monofilaments (North Coast Medical Inc, Morgan Hill, CA) and outcome was classified according to Imai et al.[13] (Table 2).

For quantifying the CIVD reaction, after acclimatization for 15 minutes at room temperature (22 -24 ºC), both hands were immersed up to the ulnar styloids for 1-2 minutes in a water bath with a temperature of 10°C (range 9-11°C) to pre-cool the hands. After removing the hands from the water, they were carefully and quickly dried using a cotton towel. Then, the subject was seated in a comfortable chair with the palms of both hands resting on in-house fabricated aluminium cooling plate (30wx29bx3h cm). This aluminium plate contains a system of two water channels connected to a thermostatic bath (Ecoline, Lauda 104, Lauda-Königshofen, Germany) of 5°C. The flow rate was approximately 2 litres per minutes.

We used videothermography to measure skin temperature since it is able to capture the temperature of a whole extremity in a sequence of thermal (temperature) images without skin contact with a high accuracy and repeatability[30]. The delay between removal of the hands from the water bath and thermographic recording was less than 1 minute. Thereafter, one thermography image per second was obtained using a thermographic video camera (ThermaCam SC2000, FLIR, Danderyd, Sweden) with a resolution of 320x240 pixels and a distance of 68 cm. This results in a resolving capacity on the skin of 0.8 $mm^2$. The thermal sensitivity of the thermograph is 0.05°C at 30°C. Data were obtained using a data acquisition system coupled to a desktop PC (ThermaCAM Researcher 2001 HS).

**Data analysis**

Thermographs were analyzed using FLIR Thermacam Researcher Pro (2001 HS) software. From this software, temperature readings were exported and further analyzed with Matlab® software (version 7.1). For the index to the small finger of both hands, temperature was measured dorsally in the middle of the distal phalanx as the maximum of a 3-5 mm diameter circle, representing approximately 9 to 24 individual temperature values [Figure 1]. Data were smoothed with a second-order low-pass Butterworth filter with a cut-off value off 0.015 Hz and were plotted in a time-temperature curve for further analysis of the re-warming pattern.

**CIVD quantification**

Based on the temperature profiles for each of the digits two to five of each hand, the CIVD response was selected when present. The digits of the uninjured hand served as controls for the injured digits. A CIVD reaction was defined as an increase in skin temperature of more then 2.5°C. Also, it was verified that the temperature increase started in each finger at the distal phalanx, that is, at the beginning of the CIVD reaction, the temperature of the third phalanx must be higher than the second phalanx to be considered a true CIVD reaction (Figure 1). For each digit we noted if one or more CIVD cycles were present or absent.

## RESULTS

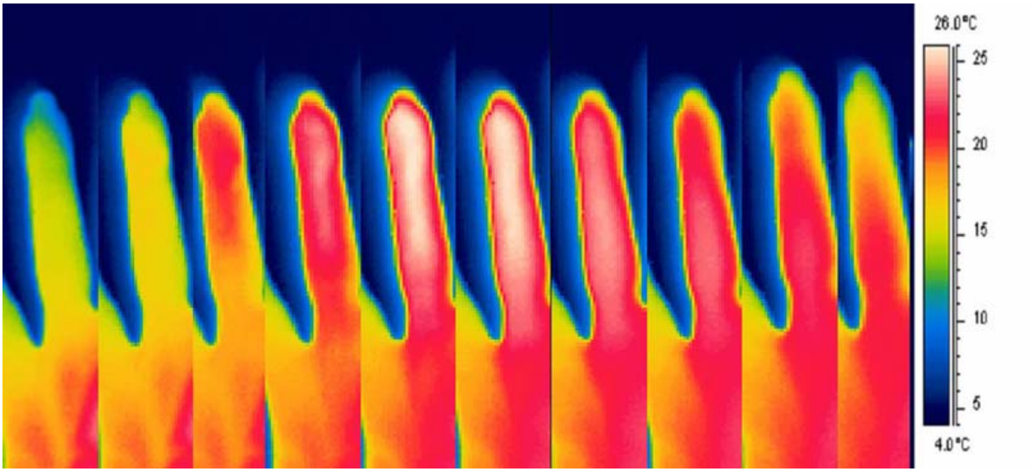
**CIVD reaction**

When classifying the CIVD reaction, we found a first group (Group I) of six patients showing a CIVD reaction in all digits of both hands (see Figure 2). A second group (Group II) consisted of four patients in whom the CIVD reaction was absent either in the injured digits (n=3) or in all digits of the injured hand (n=1) while the uninjured hand showed a CIVD reaction in all digits (see Figure 3). A third group (Group III) consisted of two patients without a CIVD reaction in any of their injured or uninjured fingers (Figure 4).

**Follow-up, age and CIVD**

When relating the CIVD reaction groups to follow-up time, we found that patients with absent CIVD responses in the affected digits (group II) had short follow-up times (six to 36 months) with the longest follow-up times belonging to two older patients (42 and 62 years old). The patients with CIVD responses in both injured and uninjured digits (group I) had longer follow-up times (average 50 months) than group II, except for one young (24 years old) patient with a follow-up time of 24 months. In group III, CIVD responses were absent in both hands (age 15 and 25, follow-up 4 and 63 months). However, since their uninjured hands also did not show a CIVD reaction, it is difficult to conclude on the relation between age, follow-up and CIVD reaction this group (Table 3).

Figure 1: Example of a normal CIVD reaction measured with thermography.




*Illustrated is the temperature of the fourth digit of the left hand with 1-minute time intervals. The temperature scale is presented at the right side of the figure. The CIVD reaction starts distally and has, in this example, an amplitude of 12°C. The cold plate in the background has a temperature of 4 to 5°C.*

**Sensory recovery**

When relating the CIVD reaction groups to sensory recovery, we found that all patients in group I had diminished protective sensation (Imai 3). In group II, two patients also had Imai 3 and two patients Imai 5 (loss of sensation). In group III, one patient had Imai 2 and one an Imai 4. However, since their uninjured hands also did not show a CIVD reaction, again it is difficult to conclude on the relation between sensory recovery and CIVD reaction in this group (table 3).

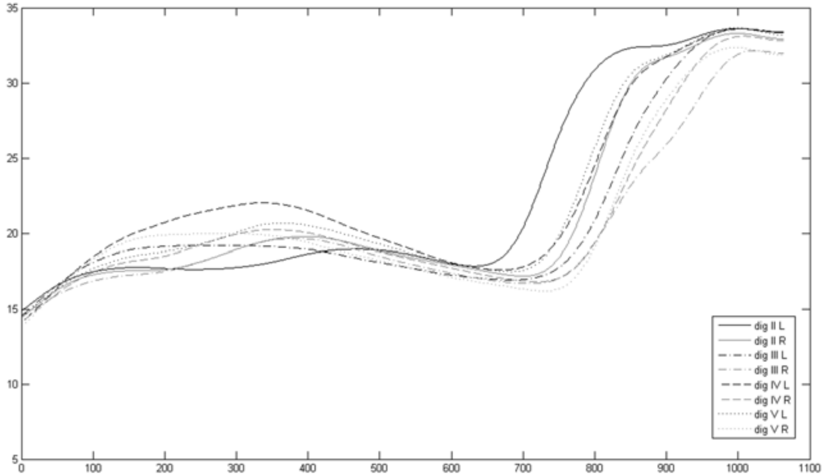
**Subjective experience of cold intolerance**

When evaluating the relation between the CIVD reaction groups and the subjectively experienced cold intolerance, we found abnormal cold intolerance (CISS score > 30) in three of six patients (50%) in group I (CIVD responses in all digits), in three of the four patients (75%) in group II (absent CIVD responses in the affected digits), and in 1 of the 2 patients (50%) in group III (absent CIVD in both hands). Although the subgroups are too small for statistical analysis, in this small population, the above-mentioned data do not indicate that there is a clear relation between the presence of a CIVD reaction and the subjectively reported cold intolerance (Table 3).

Table 3: Results, distribution of the CIVD reaction in patients. Values indicate the mean scores and the ranges.

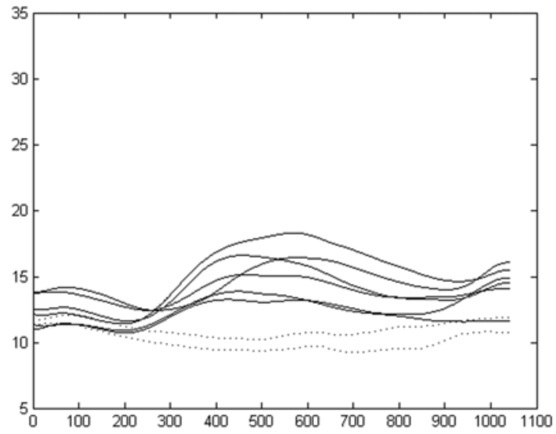
| **Group:** | **Number** | **Follow-up (months)** | **Age (year)** | **Imai (1-5)** | **CI present** |
|---|---|---|---|---|---|
| I: All digits show CIVD reaction | 6 | 50 (24-76) | 24 (15-42) | 3 | 3 (50%) |
| II: No CIVD in injured digits | 4 | 20 (6-37) | 42 (21-62) | 4 (3-5) | 3 (75%) |
| III: CIVD absent in all digits of both hands | 2 | 34 (4-63) | 20 (15-25) | 3 (2-4) | 1 (50%) |

Figure 2: Example of Group I with CIVD reaction in all fingers.



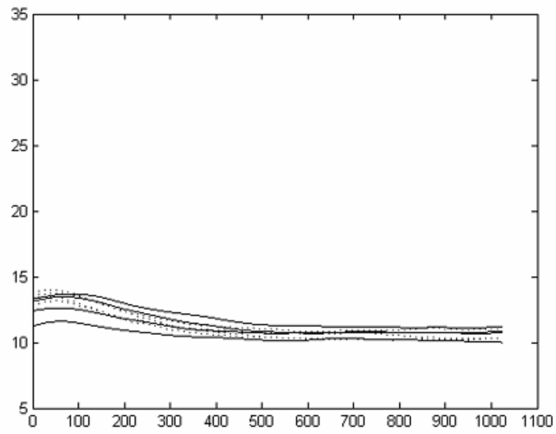

*Temperature (°C) of the distal phalanx of digits II to V of each hand plotted against time (s).*

Figure 3: Example of Group II with absent CIVD reaction in the injured digits (median nerve injury left side).




*Temperature (°C) of the distal phalanx of digits II to V of each hand plotted against time (s). The uninjured digits are plotted in black (solid line), the injured digits II and III of the left hand in grey (dotted line).*

Figure 4: Example of Group III, absent CIVD reactions in all digits of both hands.




*Temperature (°C) of the distal phalanx of digits II to V of each hand plotted against time (s). The left hand is plotted in black, the right hand is dotted.*

## DISCUSSION

Median or ulnar nerve injury was found to influence thermophysiological responses of the hands and fingers as measured by evaluating the CIVD response. While CIVD responses are not always reliable and can be absent also in the control/ uninjured hand (two patients), we found good bilateral CIVD responses in six patients who were a minimum 24 months after nerve repair. All of these patients had diminished protective sensation. In four patients (follow-up 6-37 months), however, a CIVD reaction was present in the uninjured digits but absent in the injured digits. These patients had either diminished protective sensation or no sensation in their injured digits. Two subjects had no CIVD response in of the digits of both hands, either injured or uninjured.

The absence of a CIVD reaction, as observed in 4 of our 10 nerve-injured patients, excluding the two patients with absence of CIVD reaction in both hands, indicates that the nervous system could be involved in the CIVD reaction. An asymmetrical CIVD reaction has also been reported in patients with Raynaud's disease and in patients with spinal muscular atrophy[1, 16], also suggesting neural involvement in the CIVD reaction.

In six patients a CIVD reaction was present in all digits of both hands. These patients had a longer follow-up time and a better Imai score, suggesting partial sensory recovery. Two patients did not show a CIVD reaction in both injured and uninjured hands. It is known that there is a great variety of CIVD reactions between individuals and that even in a normal population a CIVD reaction can be absent [22, 24]. This could be caused by external factors (temperature of cooling, ambient temperature, clothing) or internal factors (body core temperature, thermal balance, food intake). Therefore, in these two patients, we cannot draw conclusions on whether the absence of the CIVD reaction is related to the nerve injury.

Although the sample size of this study is small, the presence or absence of abnormal subjective symptoms of cold intolerance as measured by the CISS questionnaire does not seem to be correlated to the quality of the thermophysiological response to a cold stimulus; Even with a normal CIVD reaction in both injured and uninjured digits, patients still might suffer from symptoms of cold intolerance. This was also found in earlier studies where re-warming patterns after median and ulnar nerve injuries were measured and that reported that a normal thermophysiological response did not exclude the presence of a subjective experience of cold intolerance [25, 27].

Some limitations to the method used in the present study need to be addressed. Firstly, we were unable to provoke a CIVD response in all our subjects; this was also reported earlier by Chen et al[3, 4]. Also, the CIVD reaction was not homogenous between the fingers and hands, and there was a relatively large variation of amplitude of the CIVD reactions of the uninjured fingers. This could have been caused by insufficient cooling of the cold-plate, as the dorsal face of the digits cooled down to 10 to 20 °C, and the palmar side to approximately 6-8 °C. This is in line with the results of other studies in which temperatures of 8 to 15°C have been used[5, 6, 16]. Several studies have shown that cooling to temperatures lower then 8°C gives a better reliability and reproducibility[2, 7, 8, 11, 19, 20, 22, 24, 29, 31, 32], and temperatures below 4°C gives homogenous results (similar CIVD reactions in all digits at the same time)[2, 19, 20, 24, 31].

In conclusion, after median and ulnar nerve injury, several abnormalities can be found: subjective symptoms of cold intolerance [28], absence of active re-warming [25, 27] and CIVD reaction, and diminished sensibility [25, 27, 28]. This indicates that after peripheral nerve injury of the upper extremity, regulation of skin temperature of the hands and fingers is disturbed, and restoration of normal thermo-physiological responses could be indicative of nerve recovery. However, the restoration of normal thermo-physiological responses such as the CIVD reaction does not prevent the presence of subjective symptoms of post-traumatic cold intolerance and therefore do not seem causative for cold intolerance.

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# Chapter 9

## Discussion, Conclusion and future perspectives

## 9.1 Introduction

The aim of this thesis was to improve our understanding of post-traumatic cold intolerance by investigating both the patient's perspective using questionnaires and changes in thermo-physiologic responses in patients with median or ulnar nerve injury.
While frequently used and validated outcome scales exist for motor and sensory outcome, such as the BMRC (British Medical Research Committee)[25] scales, this is not the case for cold intolerance. While cold intolerance is frequently mentioned in studies examining outcome after peripheral nerve repair [21, 50, 61, 66, 97], there is no well-established standard for testing. During the meta-analysis on outcome after median and ulnar nerve injuries, we found that interest in symptoms of cold intolerance or cold sensitivity after peripheral nerve injury has increased over the years. Cold intolerance is now generally recognized as one of the major complications following upper extremity trauma. In this thesis, we have been able to answer several of our questions that we postulated in the Introduction of this thesis, and in this Discussion we will compare our results with those from earlier studies.

## 9.2 Outcome after median and ulnar nerve repair.

Studying recovery after peripheral nerve injury is complex because of the large number of factors influencing nerve regeneration. In addition, evaluation of outcome is complex, since peripheral nerve injury affects motor and sensory function and may be accompanied by cold intolerance, muscle contractures, neuropathic pain, Complex Regional Pain Syndrome (CRPS) and neuroma formation. The peripheral nerves providing motor and sensory function of the hands are the median and ulnar nerve. Because of their course superficial in the upper extremity, they are easily injured by sharp objects. To study outcome after peripheral nerve injuries, results of median and ulnar nerve repair were evaluated in a meta-analysis. The prognostic factors influencing outcome that were found differed for motor and sensory recovery. For motor recovery, age, delay, site, and type of injured nerve were found to predict functional outcome; for sensory recovery, age and delay were significant prognostic factors (**Chapter 2**).

Younger patients were more likely to have satisfactory motor and sensory outcome. This is also in accordance with research studies that could not be included in our meta-analysis. Where adults are unlikely to reach a normal recovery (sensory S4 and motor M5 on the BMRC scale), children under the age of 16 frequently obtain normal recovery. The effect of age on recovery may be explained by factors like a shorter regeneration distance in children as compared to adults and by a greater regeneration potential [1, 6, 7, 41, 53, 55, 76, 92, 99, 103, 104, 108]. In addition, recent research in primates indicates that children might have a higher potential for brain plasticity compared to adults.[72, 73] Some authors mentioned that especially sensory recovery benefits from a younger age, which is in accordance with our findings[95].

Delay between nerve injury and repair (direct repair within 1 week after injury, between 1 week and 1 month, within 3 months, within 6 months, between 6 months and one year and more than one year) was associated with outcome and the longer the delay between injury and repair, the smaller the chance of a favourable outcome. This confirms the results of earlier studies that found an unfavourable prognosis after more than 6 or 12 months' delay [1, 6, 7, 32, 55, 57, 75, 76, 99, 104, 111]. To know when the endpoint of recovery has been reached can provide the patient with a realistic prognosis, especially regarding the return to work[13]. The results of **Chapter 2** indicate that there is still a significant improvement for a follow-up period of at least 3 years, and significant improvements for up to 5 years after nerve repair have been described[95]. While thoroughly analysing the available literature on median and ulnar nerve injury, it was found that post-traumatic cold intolerance is frequently encountered, but is not evaluated in a standardized way. This challenged us to explore the subject of post-traumatic cold intolerance further in this thesis, by testing subjective symptoms of cold intolerance and objective changes in thermoregulation of the hands.

## 9.3 Testing of subjective symptoms of cold intolerance and incidence.

Symptoms and behavioural changes due to post-traumatic cold intolerance have been evaluated in multiple ways, such as a VAS scale, single questions[31, 91, 109], multiple questions [5, 70, 71] or validated questionnaires [15, 21, 26, 50, 77]. The estimated incidence of cold intolerance largely depends on the method of measuring and defining cold intolerance[4, 50, 68, 80, 94, 98 58]. For research and clinical purposes, a reliable, consistent and validated test is of great importance. Therefore, the Cold Intolerance Symptom Severity (CISS) questionnaire, which has been validated in English and Swedish[15, 50], was tested in a normative study population (**Chapter 3**, n=108). Subjects without a previous history of peripheral nerve injury or other upper extremity injury scored on average 12.9 points on the CISS questionnaire, which has a minimum score of 4 and a maximum score of 100. Based on the distribution of scores in this normative population, in Chapter 3, we suggest use of the upper limit of the 95% confidence interval (CISS score = 29.3) as the threshold for pathological cold intolerance. A score above this cut-off point (CISS - score 30 or higher) would indicate pathological cold intolerance.

When the cut-off score of 30 was applied to the results of the median or ulnar nerve injury patients, we found an incidence of 57% post-traumatic cold intolerance in these patients (**Chapter 4**, n=107), which is comparable to other studies on nerve injury patients, in which the incidences range from 50 to 83%[2, 4, 21, 26, 50, 66, 80, 84, 90, 94]. In our neuroma patients (**Chapter 5**, n=18), all patients showed abnormal cold intolerance (100%), with CISS scores around 90. This could be caused by their general high level of pain, but no comparative literature exists at the moment. To explain differences in severity of subjective symptoms of cold intolerance, a search for prognostic factors was made and the results will be discussed in the next chapter.

## 9.4 Prognostic factors for the presence of post-traumatic cold intolerance.

Cold intolerance is a severe problem following peripheral nerve injury, and has a significant influence on the patient's life and activities[21, 26, 50, 77, 83, 91]. For example, in **Chapter 4** we found that nerve injury patients with post-traumatic cold intolerance needed a longer time to return to work. In our study, 57% of patients had post-traumatic cold intolerance, and predictors for the presence or absence of post-traumatic cold intolerance were unsatisfactory sensory recovery, female gender and combined median and ulnar nerve injuries. The factors age, associated arterial injuries, affected hand, site of injury, and type of injury were not found to be predictors for cold intolerance. In neuroma patients, abnormal post-traumatic cold intolerance was present in all patients, with significantly higher CISS scores in patients with an avulsion injury of the peripheral nerve, increasing age, extreme spontaneous pain, sleep disturbances (SCL-90), and a higher disability score (DASH).

A significant finding was the correlation between CISS-score and return of sensory recovery. Patients with no return of sensation had higher CISS-scores than patients with normal sensory recovery. This is in agreement with the findings of other studies[62, 66, 100]. However, not all previous studies have identified this relationship[21, 37]. Although men and women were found to have a similar level of sensory recovery, women scored significantly higher on the CISS-scale than men, with an average difference of 15 points. This was also shown by Koman et al. [64] In the normative population however, we did not find a significant difference between men and women (n = 108; 59 men and 49 women)[98].
We found that patients with more severe cold intolerance needed a longer time to return to work. In earlier studies it was found that satisfactory motor and sensory recovery are predictors for return to work, in addition to other factors such as level of education, type of job and compliance to hand therapy (Bruyns et al., 2003; Jaquet et al., 2001). As sensory recovery and cold intolerance were highly correlated in our study, it is not clear if Cold Intolerance and return to work are correlated independently of sensory recovery. However, patients with outside jobs and severe cold intolerance may need an adjustment of their work environment, protection against cold or a change of their job[112].

The incidence of cold intolerance was significantly higher in the combined median and ulnar nerve injury group, possibly because of the more extensive tissue damage and the larger number of injured structures in combined nerve injuries. This finding is in contrast with other studies [50, 100]. While previous studies reported significantly increased cold intolerance after vessel injury [44, 50], our study did not show arterial injury as a predictor for cold intolerance. This is an important finding, as it may direct the pathophysiology of cold intolerance to a neurological disturbance instead of a vascular disturbance[3]. No significant relationship between the incidence of cold intolerance and age was found[21, 50].

In both patient groups (nerve injury and neuroma patients) we found no relation between the presence of cold intolerance and time after injury, in line with many other studies that showing that symptoms of cold intolerance do not decrease over time[2, 4, 21, 33, 37, 69, 83, 90, 113]. Only Gelberman et al.[43] postulated that the symptoms of cold intolerance are temporary following upper extremity injury and disappear over time.

In contrast to median and ulnar nerve injury patients, neuroma patients showed a significantly higher CISS score in patients with an avulsion injury. This finding is consistent with the finding of Irwin et al.[50] that sharp injuries are less likely associated with cold intolerance. Sharp injuries lead to better revascularization and a higher success rate of replantation of amputated digits than do crush or avulsion injuries[2, 44, 45, 50]. An explanation for the higher CISS score in patients with an avulsion type injury may be that adequate coaptation of the nerve ends is nearly impossible. This may cause several “micro-neuromas” at different levels. Another cause for the increased CISS score in avulsion injuries is the greater extent of the nerve injury.

After subjective testing of cold intolerance, an effort was made to objectivate the symptoms. It was hypothesized that a change in thermoregulation of the hands after nerve injury could explain the subjective symptoms of post-traumatic cold intolerance, and therefore we continued with experiments exposing the hands to cold.

### 9.5 Changes in thermoregulation.

To test the hypothesis that clinical symptoms of post-traumatic cold intolerance and thermophysiological changes of hands and fingers are related, we launched a pilot study on rewarming patterns of the hand after short-term cold stress testing **(Chapter 6)**, followed by a second, larger study **(Chapter7)**. To test the protection of the fingers against continuous cold exposure, the hands of nerve injury patients were also cooled during prolonged periods to investigate the absence or presence of Cold Induced Vasodilation (CIVD), also referred to as the Hunting reaction (**Chapter 8**).

### 9.6 Infrared thermography.

In the clinical experiments, thermoregulatory responses were filmed using an infrared videocamera. In **Chapter 6,** we found that rewarming patterns were visible both on the palmar side of the hands and on the dorsal side. This might confirm the results of an anatomical study by Campero et al.[14] showing that the ulnar nerve supplies vasomotor fibres to its cutaneous sensory territory and the median nerve provides supplementary vasomotor innervation to the skin of the radial aspect of the dorsum of the hand. Campero et al. also describe that the radial nerve does not contribute vasomotor sympathetic fibres to the skin of the hand, and therefore that the thermoregulation of the hands is solely mediated by the median and ulnar nerves. Following the results of **Chapter 6**, in **Chapters 7 & 8** rewarming patterns were measured on the dorsal side of the hands.
In previous studies thermocouples attached to the skin have been used to measure temperature regulation after upper extremity nerve injury[5, 51, 63, 91, 97, 107]. In this thesis we have shown that infrared thermography is an excellent tool to measure re-warming patterns after cold stress testing and to measure the CIVD reaction. Infrared thermography measures radiant temperature, wich can be translated to surface temperature by the emmissivity coefficent, which is constant in human skin independent of skin colour. It provides more data than

thermocouples, as it is able to measure the whole surface of the hand instead of a limited number of points. Downside to the use of the infrared camera are its costs, and difficulties of transportation for experiments in the field (for example at high altitudes).

## 9.7 Toleration of the experiments and reliability.

The cold water immersion (15°C) during five minutes (cold stress testing) was generally well tolerated by both patients and volunteers. Surprisingly, during the cooling phase, if there was pain or discomfort, it were usually not the affected nerve injury digits that were painfull, but the unaffected digits. The patients generally described that the affected digits felt numb. For the experiments where we measured the CIVD reaction, hands were cooled during one to two minutes by cold water immersion (10°C) and then immediately placed with palmar sides facing down onto a cold plate of 5°C. The prolonged cooling in the CIVD experiment was generally considered uncomfortable to painfull at the start, but this was getting better as the CIVD reaction started. Although uncomfortable to painfull, none of our subjects had to stop the experiments prematurely. Test-retest reliability was good for the rewarming experiment in the control group. In Chapter 8 we did not perform test-retest reliability. The non-injured hand served as a control. From previous literature it is known that the CIVD reaction has a high variability in between subjects, but a reasonable reliability [86].

## 9.8 Rewarming following cold stress testing.

In **Chapters 6 & 7** rewarming patterns of the hands and fingers after cold-stress testing were analyzed. In our patient group, consisting of median and ulnar nerve injury patients, we found that the presence of active re-warming and cold intolerance were negatively correlated and the return of sensory recovery was correlated with the presence of cold intolerance and the return of active re-warming.

Our results showed that after a longer follow-up, return of active re-warming is possible. As described in previous literature, we found a correlation between sensory recovery, active re-warming, and CI[37, 44, 51, 58, 62, 100].

In two control subjects, active re-warming was absent in 3 or more digits. One of these subjects was known with chronic RSI symptoms. In the nerve injury group, one patient had passive re-warming in the majority of digits, including the affected digits. It has been reported that up to 18% of control subjects (depending on method of measurement) have absence of an active re-warming response that could not be explained by their previous medical history[47, 52, 85]. Abnormal digital blood pressure has been reported during local cooling at 15ºC in 25% of control subjects and in 35% of control subjects with a history of cold fingers[74]. Cleophas et al.[20] found better re-warming at a room temperature of 24ºC then at 20ºC in control subjects, although still 8% did not re-warm well in the higher room temperature group, this was confirmed by Laskar et al.[65]. In our study, we used a room temperature of 24ºC. Factors explaining an abnormal re-warming in control subjects might be a pre-consisting pathologic condition of the vessels resulting from aspects such as non-freezing cold injuries in the past, pharmacotherapy, generalized disease, exposure to vibratory trauma[11, 19, 23, 24, 42, 85, 89, 96, 105, 106], RSI[22], CRPS[46, 49, 115-117], Raynauds' disease[8, 52, 54, 79, 81] or secondary scleroderma[79].

### 9.9 CIVD reaction after median and ulnar nerve injury.

In **Chapter 8** median or ulnar nerve injury was found to influence thermophysiological responses of the hands and fingers. While CIVD responses are not always reliable and can be absent also in the control/ uninjured hand (two patients), we found good bilateral CIVD responses in six patients minimum 24 months after nerve repair. All of these patients had diminished protective sensation. In four patients however (follow-up 6-37 months) a CIVD reaction was present in the control/ uninjured digits but absent in the injured digits. These patients had either diminished protective sensation or no sensation in their injured digits.

The absence of a CIVD reaction, as observed in 4 of our 10 nerve-injured patients, indicates that the nervous system could be involved in the CIVD reaction. In six patients a CIVD reaction was present in all digits of both hands, but this was after a longer follow-up time and a better Imai score, suggesting partial sensory recovery. Two patients did not show a CIVD reaction in both injured and uninjured hands. It is known that there is a great variety of CIVD reaction between individuals and that even in a normal population a CIVD reaction can be absent [78, 86]. This could be caused by external factors (temperature of cooling, ambient temperature, clothing) or internal factors (body core temperature, thermal balance, food intake).

The presence or absence of abnormal subjective symptoms of cold intolerance as measured by the CISS questionnaire seems not to be correlated with normal or abnormal thermo-physiological responses. Even with presence of a normal CIVD reaction in both injured and uninjured digits, patients might suffer from symptoms of cold intolerance.

### 9.10 Relation between rewarming, CIVD and Cold Intolerance.

In a number of studies in patients with replantation, revascularisation and raising of a radial fore-arm flap, low digital blood flow did not correlate with subjective symptoms of CI[37, 44, 51, 58, 107]. Also objective cold stress testing in healthy subjects was not correlated to self-reported cold intolerance[110]. This is consistent with the results of this thesis. While less subjective symptoms of cold intolerance were correlated with return of active re-warming, two patients had completely normal re-warming patterns whilst having high CISS scores (**chapter 7**). The same was found in **Chapter 8**, where 3 out of 6 patients with normal CIVD reaction in the injured hand had complaints of cold intolerance, and 1 out of 4 patients with absent CIVD responses in the injured hand did not have symptoms of cold intolerance.

To summarize, several abnormalities can be found following median and ulnar nerve injury: subjective symptoms of cold intolerance, absence of active re-warming and CIVD, and diminished sensibility. This indicates that after peripheral nerve injury of the upper extremity, regulation of skin temperature of the hands and fingers is disturbed, and restoration of normal thermo-physiological responses could be indicative of nerve recovery.

However, the restoration of normal thermo-physiological responses such as the CIVD reaction does not prevent the presence of subjective symptoms of post-traumatic cold intolerance and therefore do not seem causative for cold intolerance. Therefore, the mechanisms of cold intolerance remain uncertain and can not be only explained by a disturbance of thermoregulation[56].

**9.11 How does nerve injury cause a disruption in thermal regulation of the hands? Current hypotheses.**

To understand a complex matter such as cold intolerance, we need to first understand the basics of Thermal Physiology of the hands and fingers. Since there are no muscles in the fingers, except for the tendinous insertions of the lumbrical and palmar and dorsal interossei muscles to the proximal part of the proximal phalanx, temperature is regulated by the incoming blood flow through the arteries. Blood supply to the hand is provided by the radial artery and the ulnar artery, which join in the palm of the hand in a superficial and deep arc. Each finger has two digital arteries, which run sideways to the flexor tendons, but dorsally in relation to the digital nerves. From the arteries, the blood flows towards the capillaries, and the blood is drained by a network of veins mostly lying at the dorsal side and more proximally drain on the cephalic and basilica veins of the arm. However, in several parts of the body, such as the fingertips, nose and lips, arterio-venous anastomoses exist, which provide a direct transfer of blood of the arteries to the veins, bypassing the capillaries[10, 40, 67].

Arteries and veins have a vascular tone depending on both the outside temperature and the body core temperature (Tcore). Under short-term physiological conditions there is a dynamic balance between sympathic nerve-mediated vasoconstrictor tone and endothelial-mediated vasodilator tone. There is no parasympathic innervation of the skin of the hands. A continuous basal release of Nitric Oxide (NO) from particularly the arteries contributes to resting vascular tone[9]. The ulnar nerve supplies vasomotor nerve fibers to its cutaneous sensory territory. Vasomotor sympathic nerve fibers join the sensory nerve fibers to the skin of the hand. The median nerve however, supplies also vasomotor nerve fibers to the skin of the radial aspect and the dorsum of the hand in addition to its cutaneous sensory territory. The radial nerve does not normally contribute vasomotor sympathic fibers to the skin of the hand and this area is taken over by the median nerve.[14, 101]

In the acute phase after traumatic peripheral nerve injury, there is disruption of the sympathic signal and the balance shifts towards vasodilation. Ruch et al.[93, 97] showed that up to six months after nerve transection injury, the injured side is warmer than the control side. After a minimum interval of five to six months (depending on the level of nerve injury), vascular tone returns due to feedback mechanisms and there is continuous vasoconstriction[93]. Active vasodilation as in the re-warming patterns or in the Hunting reaction only returns after restoration of sensory function.

During prolonged periods of cooling of the hands, the sympathic system provides distal vasoconstriction to minimize heat loss. To protect the fingers from cold injuries, after 5 to 10 minutes, cold induced vasodilation (CIVD), also known as Hunting reaction, occurs[27, 28, 67, 86, 87] and augments the temperature of the hands and digits by opening the distal arterio-venous anastomoses (AVA's) in a cyclical pattern. Although recently it has been postulated that the purpose of the CIVD reaction is to remove excess heat from the body during for example exercise with the purpose of preserving thermal balance[35, 36]. Probably the CIVD reaction and protection of soft issue is optimal when the core temperature (Tc) is high, and suboptimal when the Tc is low to avoid further hypothermia.

In earlier research, it was thought that cold intolerance was caused by a vascular disturbance rather than a change in neural regulation. Several studies have addressed this question, for example Kay, who found no correlation between cold intolerance and vascular inflow to replanted digits in a study of 14 patients investigated by venous occlusion plethysmography [59]. This supports the case for a neural, instead of an arterial, origin of post-traumatic cold intolerance [16, 34]. However, it is still a debate how a disruption in neural regulation causes active vasodilation and active re-warming during and following cold exposure and at the moment there are several hypotheses on how this CIVD reaction is controlled:

1. One hypothesis is that cold induced vasodilation is controlled by an antidromic signal from the distal root ganglion (DRG) towards the vessels in the hands through a sensory branch of the peripheral nerve (median or ulnar nerve) [9, 114]. This antidromic signal triggers the release of potent vasodilators such as nitric oxide (NO)[60] and calcitonin gene-related peptide (CGRP)[12]. Because the absence or presence of vasodilation and the magnitude of the CIVD reaction depends largely on the body core temperature (Tc)[30, 102, 118], feedback from the hypothalamus on this system is likely[30, 39]. Our result that sensory recovery is linked to the presence or absence of an active re-warming mechanism supports this theory.

2. The axon reflex theory states that the cold stimulus excites the receptive unmyelinated nerve endings, probably via A-delta nerves. These impulses are transmitted centrally and via the axon branches. The sensory nerve endings then release vasoactive substances resulting in vasodilation[48]. This theory however has been dismissed by a study by Daanen et al.[29].

3. Decreased release of norepinephrine following cold exposure. The sensitivity of norepinephrine receptors increase in cold conditions and this will induce a reduced blood flow as a result of vasoconstriction. The further decrease in tissue temperature may result in reduction of adrenergic neurotransmission, such as norepinephrine due to cold (numbing of the nerve ending). As a consequence of this reduced adrenergic output an increase in blood flow will occur as a result of decreased vasoconstriction[38].

4. Flouris et al. developed recently a theory that CIVD is a centrally originating phenomenon caused by sympathic vasoconstrictor withdrawal. This was based on their observation that CIVD occurred only when both hands and core were cooled instead of cooling of the hands with immersion in warm water (42°C) of the body. They also found a shift of autonomic interaction towards parasympathethic dominance during the CIVD reaction based on heart rate variability data.

## 9.12 Shortcomings and limitations of our studies

A retrospective set-up was used in **Chapters 2 to 5**. This has as limitations that not all patients are measured at the same follow-up time and clinical information has to be extracted from the patient's status. A prospective study which measures the same patient at specific time-points during their follow-up time would give better insight in the natural history of post-traumatic cold intolerance.

A limitation of the experimental studies in **Chapters 6 to 8**, is the relatively small number of nerve injuries. However, this is a common limitation in nerve injury studies, as complete transection injuries of the peripheral nerves are not very frequent, and the nature of the patient population makes regular follow-up often difficult. Despite this small number of subjects, we were able to show significant differences between patients and controls and significant relations between re-warming patterns, CI and sensory recovery. According to our knowledge, this study is the first that continuously filmed the re-warming patterns of the hand and CIVD reactions with 1 image per second. In our experimental setup, not all healthy volunteers exhibit a normal re-warming curve or demonstrate a CIVD reaction in all digits, confirmed by previous literature [17, 18]. This makes it more difficult to assess an abnormal pattern in a nerve injury patient. If the pattern is normal, we know that thermoregulation has been restored. However, when active re-warming or CIVD is absent, this might have been pre-existent. Therefore, the presence or absence of the CIVD reaction in nerve injury patients, does not seem the test of choice in a clinical setting, whereas the cold stress testing with subsequent measuring of the re-warming pattern could be used to test the evaluation after nerve injury or measure the effects of treatment.

**9.13 Conclusions.**
Following our case in the introduction, several questions were raised regarding nerve injury and post-traumatic cold intolerance. In the chapters of this thesis, we have sought to answer these questions to enlarge our understanding of post-traumatic cold intolerance for the future aid of our patients.

*What is the incidence and severity of post-traumatic cold intolerance after different types of injuries to the upper extremity (nerve injury, digital re-plantation, fractures, soft tissue injury)? [Introduction, Chapters 2, 3, 4 & 5]*
Using the cut-off score of 30, 57% of median or ulnar nerve injury patients had abnormal cold intolerance, and this was their most important problem following their injury.

*What is its incidence and severity according to patient characteristics (age, gender, comorbidity, compliance to hand therapy). [Introduction, Chapters 3 & 4]*
Prognostic factors for post-traumatic cold intolerance in our study were unsatisfactory sensory recovery, female gender and combined median and ulnar nerve injuries. In patients with post-traumatic cold intolerance, the time to return to work was longer.

*How can the severity of subjective symptoms of cold intolerance be measured in a patient and followed over time? [Introduction, Chapters 3, 4 & 5]*
The Cold Intolerance Severity Scale (CISS) by Irwin et al., was found to be a reliable instrument to measure abnormal cold intolerance, when a cut-off score of 30 is applied.

*Do patients who develop a post-traumatic neuroma have more or less complaints of cold intolerance than other nerve injury patients?*
All neuroma patients showed abnormal post-traumatic cold intoleranc and very high scores on the CISS questionnaire. Prognostic factors for a higher score where an avulsion injury of the peripheral nerve, increasing age, extreme spontaneous pain, sleep disturbances (SCL-90), and a higher disability score (DASH).

*Can the symptoms of cold intolerance be measured objectively? [Chapters 6, 7 & 8]*
Thermo-physiological responses of hands and fingers can be measured objectively both following a short cold exposure (cold stress testing) and during prolonged cooling (CIVD reaction). However, the absence or presence of normal thermo-physiological responses did not correlate with the presence of subjective symptoms of cold intolerance.

*What changes in thermo-physiological responses to short cold exposure are found in nerve injury patients? [Chapters 6 & 7]*
Re-warming patterns revealed using infrared video-thermography could be analyzed quantitatively using Q-values (area under the curve from the start of re-warming for a period of 10 minutes) and maximum slopes of the re-warming curve. Test-retest reliability was good and it was possible to objectively record the return of active re-warming after sensory recovery.

*Are the changes in thermoregulation of the hands after nerve injury responsible for the subjective symptoms of cold intolerance? [Chapters 6 to 8]*
After nerve injury, an absence of an active re-warming pattern following cold stress testing and CIVD reaction upon prolonged cooling was found. However, when nerve regeneration continuous and sensory function returns, active re-warming and CIVD can be restored to normal. The presence or absence of active re-warming and CIVD is however not responsible for the subjective symptoms of cold intolerance. Restoration of active re-warming was correlated with less subjective CI. However, a number of patients with normal thermophysiological responses still had complaints of cold intolerance. Our hypothesis that CI is related to the re-warming pattern could therefore not be confirmed.

*Can the changes in thermoregulation of the hands after nerve-injury normalize over time? Is there a correlation with the degree of sensory recovery? [Chapters 6 & 7]*
Yes, in patients several years after their injury with a satisfactory sensory recovery, normal active re-warming patterns could be found. Sensory recovery was strongly related to the presence of active re-warming in the nerve injury patients, suggesting that sensory recovery is an important aspect of the pathophysiology of CI.

*Is cold induced vasodilation (CIVD, Hunting reaction) upon prolonged cold exposure altered in peripheral nerve injury patients? [Chapter 8]*
We found a disturbance of the CIVD reaction after median and ulnar nerve injury. In the early phase following nerve injury, the CIVD reaction was found to be absent. However, after a 2 to 3 year follow-up time, restoration of the CIVD reaction and therefore normal thermo-physiological responses are possible.

*How is the protection against frostbite altered after peripheral nerve injury? Should additional protective measurements against frostbite be undertaken when exposed to cold environments? [Chapter 8]*
CIVD is generally considered to be a protection mechanism against frostbite, as it augments digital skin temperature Tsk. It is therefore likely that as long as the CIVD reaction is absent after nerve injury, the internal protection mechanism against frostbite is also diminished. It is therefore necessary that the patient uses additional external protection when exposed to temperatures below freezing, for example in winter, during winter sports or at high altitude.

### 9.14 Future research.

Although outside the scope of this thesis, great progress could be found in biochemical studies showing the neurological/neurochemical pathways leading to post-traumatic pain and cold intolerance. At the moment there is great interest in cold sensitive transient receptor potential (TRP) ion channels, that may contribute to cold hyperalgesia after nerve injury[82, 88, 119].

Because it is not possible to influence the factors regarding the injury, except sometimes for delay, effort should be made to intervene with the postoperative parameters such as optimized peri- and postoperative pain control, hand therapy and psychological intervention. It would be advisable to follow a large cohort of patients prospectively with detailed measuring of possible predictors. Also, the use of a more extended test battery besides motor and sensory testing, including cold intolerance, activities of daily life (ADL), quality of life, and psychosocial factors, could give better insight into the outcome of peripheral nerve repair and regeneration and augment the chance of successful functional outcome after median or ulnar nerve injury.

Additional research focusing on the treatment of post-traumatic cold intolerance is necessary. Especially sensory re-education, mirror therapy and behavioural treatment seem promising.

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# Chapter 10

## 10.1 Summary

In Chapter 1, a case is presented to describe the clinical setting in which the research in this thesis is performed. Furthermore a general introduction is provided addressing signs and symptoms of posttraumatic cold intolerance, the incidence of upper extremity nerve injuries, the impact on society, the subjective and objective testing of cold intolerance. In addition, it explains infrared thermography and the therapy and treatment options for cold intolerance.

Chapter 2 presents a meta-analysis in which variables that influence outcome after median and ulnar nerve transection injuries are quantified. The meta-analysis is based on individual patient data about motor and sensory recovery after microsurgical nerve repair. Twenty-three articles were included, presenting individual data from 623 median or ulnar nerve injuries. For motor and sensory recovery, complete data were available for 281 and 380 nerve injuries, respectively. Motor and sensory recovery were found to be significantly associated and multivariate logistic regression analysis showed that age, injury site and delay were significant predictors of successful motor recovery. In ulnar nerve injuries, the chance of motor recovery was 71% lower than in median nerve injuries. For sensory recovery, age, and delay were found to be significant predictors.

Chapter 3 investigated self-reported symptoms of cold intolerance in a normative study population, while validating the Cold Intolerance Symptom Severity (CISS) questionnaire and defining the threshold for abnormal cold intolerance. One hundred and eight volunteers participated in this study. In addition to the CISS score, information about age, gender and previous surgery or trauma to the upper extremity was obtained. Volunteers with previous peripheral nerve injury or with a history of Raynaud's disease, upper extremity injury or surgery were excluded (n=40). The CISS scores of the normative population (n=68) averaged 12.9 (SD 8.2). Age and gender were not correlated with CISS score. The upper 95% confidence interval of the CISS scores for healthy subjects was about 30. We suggested this value as a threshold for pathological cold intolerance and used it as a cut-off point for abnormal cold intolerance in Chapter 4.

Chapter 4 describes the predictors for cold intolerance and the relationship with sensory recovery after median and ulnar nerve injuries. The study population consisted of 107 patients who were between two to ten years after median, ulnar or combined median-ulnar nerve injuries. Patients filled out the Cold Intolerance Severity Score (CISS) questionnaire and sensory recovery was measured using Semmes-Weinstein monofilaments. Fifty-six percent of the patients with a single nerve injury and seventy percent with a combined nerve injury suffered from abnormal cold intolerance. Patients without return of sensation had dramatically higher CISS-scores than patients with normal sensory recovery. Females had higher CISS scores post-injury than males. Cold intolerance did not diminish over the years and patients with higher CISS scores needed more time to return to their work. Age, additional arterial injury, site or type of the injury and dominance of the hand did not found have a significant influence on self-reported symptoms of cold intolerance.

In Chapter 5 the CISS questionnaire was used to measure cold intolerance in traumatic neuroma patients. Twenty consecutive patients with surgically treated neuromas of the upper extremities were invited to participate in our study. 18 patients returned a questionnaire composed of both general questions concerning epidemiologic determinants and more disease-specific and validated questionnaires. An incidence of cold intolerance of 100% was found, with a mean CISS score high above the cut-off point for abnormal cold intolerance. CISS scores were higher in patients with an avulsion injury of the peripheral nerve, with extreme spontaneous pain, and with sleep disturbances. A higher disability score as well as increasing age had a trend towards a significant correlation with the CISS score. It was concluded that cold intolerance is a difficult problem with a high incidence in patients with a painful traumatic neuroma. There was found to be a relation between severity of cold intolerance and spontaneous pain, sleep disturbances, depression, age, and upper extremity function and it is unlikely that cold intolerance disappears over time.

In Chapters 6, 7 and 8 we performed thermophysiological testing after either short term cooling (5 minutes) and continuous coling (>20 minutes) to objectivate thermophysiological disturbances after median and ulnar nerve injury.

The aim of the pilot study described in Chapter 6 was to investigate the use of infrared thermography for the analysis of thermoregulation after peripheral nerve injury. Four ulnar nerve injury patients and four median nerve injury patients (4-12 years after injury, six with symptoms of cold intolerance) immersed their hands in 15°C water for 5 minutes, after which infrared pictures were taken at 2 to 4-minute time-intervals. The regions supplied by the injured nerve could easily be identified in the patients with symptoms of cold intolerance. While at baseline there was a symmetrical temperature distribution of the hand, after cold stress testing the rewarming of the injured side was significantly slower. We concluded that the infrared temperature profile of the hand after immersion into cold water might be a helpful tool to assess thermoregulation after peripheral nerve injury.

In Chapter 7 we used the same experimental set-up to analyze a larger group of nerve injury patients while continuously recording the re-warming process. Additionally, a control group was added. Twelve median or ulnar nerve injury patients with a follow-up of 4 to 76 months after nerve repair and thirteen control subjects underwent isolated cold stress testing of the hands. Temperature curves were analyzed by calculating the Q value as an indicator of heat transfer (temperature added during the first 10 minutes after start active re-warming) and the maximum slope. Test-retest reliability was found to be 0.64 and 0.79 for the Q value and maximum slope, respectively. High Q-values and maximum slopes were interpreted as the indicating the presence of active re-warming in contrast to passive re-warming. Patients with return of active re-warming had better sensory recovery ($p=0.01$) and lower CISS-scores ($p=0.06$). Better sensory recovery was correlated with lower CISS-scores ($rho=0.642$, $p=0.024$).

The last experiment described in Chapter 8 aimed at measuring the influence of median or ulnar nerve injury on cold induced vasodilatation (CIVD) during prolonged cooling at low temperatures. Twelve patients with a median nerve (n=6) or ulnar nerve (n=6) injury were tested 4 to 76 months after nerve repair. The palmar sides of both hands were cooled continuously using a cold plate of 5°C. The skin temperature of the fingers was measured using videothermography and graphs were plotted of the temperature changes of nail bed of the distal phalanx. The presence of a CIVD reaction was defined as a minimum increase in temperature of more then 2.5°C starting at the distal phalanx. A CIVD reaction was absent in the affected digits of 4 patients (follow-up range 6-37 months) whereas the CIVD reaction in the non-injured hand was normal. The CIVD was normal in 6 patients that were 50 months after injury (range 24-76). Two patients did not show a CIVD reaction in both injured and uninjured hands. The patients with a CIVD response all had a diminished protective sensation. The absence or presence of the CIVD reaction was not correlated with CISS score. We concluded based on these results that subjective symptoms of post-traumatic cold intolerance can be present when thermo-physiological responses to cold are normal.

Finally, Chapter 9 discusses the results from the previous Chapters and compares it to the literature. We answered the questions that have been raised in the Introduction and describe directions for future research.

## 10.2 Samenvatting

Hoofdstuk 1 begint met een klinische casus die de setting van dit proefschrift weergeeft. Naar aanleiding van deze casus worden een aantal vragen gesteld, die we in het verloop van dit proefschrift proberen te beantwoorden. De introductie bespreekt verder de symptomen en klachten van patiënten met posttraumatische koude intolerantie, de incidentie van zenuwletsel van de bovenste extremiteit en de kosten voor de samenleving. Ook wordt een literatuur overzicht gegeven van subjectieve en objectieve methoden om koude intolerantie te meten. De werking van infrarood videothermografie wordt uitgelegd en de behandeling van koude intolerantie wordt besproken.

Het tweede hoofdstuk is een meta-analyse over de algemene resultaten van letsel van de n. medianus en n. ulnaris en van de factoren die van invloed zijn op de uitkomst van de behandeling. De meta-analyse is gebaseerd op data uit de literatuur van individuele patiënten waarvan de zenuw microchirurgisch gehecht is. In totaal zijn drieëntwintig artikelen geincludeerd met in totaal 623 zenuwletsels. Het functionele resultaat na zenuwletsel kan worden onderverdeeld in sensibel en motorisch herstel. Voor deze twee groepen waren van respectievelijk 380 en 281 zenuwletsels de individuele patiënten data aanwezig. Statistische analyse liet zien dat sensibel en motorisch herstel sterk aan elkaar gerelateerd zijn. Multivariabele logistische regressie analyse liet verder zien dat leeftijd, hoogte van het letsel en tijdsduur tussen het trauma en de operatie significant van invloed zijn op het motorisch herstel. Voor letsels van de n. ulnaris was de kans op een goed motorisch herstel 71 procent lager dan voor letsels van de n. medianus. Factoren van invloed op het sensibel herstel zijn de leeftijd van de patiënt en de tijdsduur tussen letsel en operatie.

Hoofdstuk 3 beschrijft de mate van subjectieve klachten van koude intolerantie in een normale populatie. De Cold Intolerance Severity Score (CISS) vragenlijst werd gevalideerd en normaalwaarden werden berekend. Honderd en acht gezonde vrijwilligers namen deel aan deze studie. Naast de score van de CISS vragenlijst werd informatie verkregen over leeftijd, geslacht en voorgeschiedenis. Er waren geen vrijwilligers met zenuwletsel in de voorgeschiedenis, en proefpersonen met de ziekte van Raynaud of met een historie van letsel van de bovenste extremiteit in de voorgeschiedenis werden geexcludeerd (n=40). De gemiddelde CISS score van de geïncludeerde proefpersonen (n=68) bedroeg 12.9 met een standaarddeviatie van 8.2. Leeftijd en geslacht waren niet gecorreleerd met de CISS score. Aangezien de bovenste limiet van het 95% betrouwbaarheidsinterval 30 bedroeg, werd deze waarde voorgesteld als ondergrens voor de aanwezigheid van abnormale klachten van koude intolerantie.

Hoofdstuk 4 beschrijft de ernst en incidentie van klachten van koude intolerantie bij patiënten met zenuwletsel van de n. medianus of n. ulnaris. De studiepopulatie bedroeg 107 patiënten, variërend van twee tot tien jaar na perifeer zenuwletsel van de bovenste extremiteit. De patiënten werden gevraagd om de CISS vragenlijst in te vullen en het sensibel herstel werd gemeten met behulp van Semmes-Weinstein monofilamenten. Er werd gevonden dat 56% van de patiënten met letsel van de n. medianus of de n. ulnaris abnormale koude intolerantie hadden Bij de patiënten waarbij beide zenuwen tegelijkertijd waren aangedaan was het percentage koude intolerantie zelfs 70%. Patiënten bij wie het sensibel herstel matig was hadden hogere scores op de CISS vragenlijst dan patiënten bij wie het sensibel herstel beter was. Vrouwen hadden na hun letsel meer last van koude intolerantie dan mannen. De klachten van koude intolerantie namen niet af over de tijd en patiënten met koude intolerantie hadden meer tijd nodig om terug te keren naar hun werk. De factoren leeftijd, arterieel letsel, hoogte van het letsel, letseltype en dominantie hadden geen significante invloed op de aanwezigheid van koude intolerantie.

In hoofdstuk 5 werd de CISS vragenlijst gebruikt om koude intolerantie te meten in patiënten met een posttraumatisch neuroom van de bovenste extremiteit. Twintig opeenvolgende patiënten die op de wachtlijst stonden voor een operatieve behandeling van hun neuroompijn werden gevraagd om mee te doen met onze studie. Achttien van de twintig patiënten deden mee en hebben een uitgebreide set van vragenlijst ingevuld met naast een aantal algemene vragen de CISS, de VAS pijn schaal, de SF-36 en de DASH vragenlijst. Het bleek dat 100% van de patiënten last had van klachten van koude intolerantie. Er werd een hogere CISS score gevonden in patiënten met een avulsieletsel, hevige spontane pijn en een verstoord slaappatroon. Een hogere invaliditeitscore en een hogere leeftijd waren ook gecorreleerd aan de CISS score. De conclusie was dat koude intolerantie een lastig probleem is met een hoge incidentie bij patiënten met een neuroom. Er is een relatie gevonden tussen koude intolerantie en spontane pijn, slaapproblemen, depressie, leeftijd en invaliditeit en het is onwaarschijnlijk dat de klachten verdwijnen met tijd.

In hoofdstukken 6, 7 en 8 hebben we twee verschillende thermofysiologische testen uitgevoerd bij patiënten met letsel van de n. medianus of n. ulnaris. De eerste test (hoofdstuk 6 en 7) is een afkoelingstest van korte duur (minder dan 5 minuten) waarna de opwarming wordt gemeten, terwijl de tweede test de thermphysiologische reacties tijdens langdurig afkoelen (langer dan 20 minuten) analyseert.

Het doel van de pilotstudy in hoofdstuk 6 was om uit te zoeken of infrarood videothermografie gebruikt kan worden in de analyse van thermoregulatie na perifeer zenuwletsel. Acht patiënten, waarvan 4 met letsel van de n. medianus en 4 met letsel van de n. ulnaris (4 tot 12 jaar na het letsel, en 6 van de 8 met klachten van koude intolerantie) ondergingen cold stress testing. Beide handen werden gedurende 5 minuten tot aan de pols ondergedompeld in een waterbad van 15°C, waarna iedere 2 tot 4 minuten foto’s werden genomen met de infrarood camera. Hierop was duidelijk een onderscheid te zien tussen het gebied van de hand dat door de n.medianus geinnerveerd wordt en het gebied door de n.ulnaris geinnerveerd wordt. De infrarood opname voor start van de het koelen liet een goede symmetrie zien tussen en binnen de handen. Na de cold stress testing bleek echter dat de regio van de hand geinnerveerd door de beschadigde zenuw kouder was en significant minder snel opwarmde dan de regio van de niet-aangedane zenuw. We concludeerden dat infrarood thermographie een goed bruikbare methode is om verstoringen in de thermoregulatie na perifeer zenuwletsel weer te geven en te bestuderen.

Vervolgens werd in Hoofdstuk 7 dezelfde experimentele opzet gebruikt, maar nu met meer patiënten en met continue meting van de opwarming. Ook werd er een controle groep van gezonde vrijwilligers toegevoegd. Twaalf patiënten met letsel van de n. medianus of de n. ulnaris ondergingen werden 4 tot 76 maanden na trauma gemeten. Vervolgens werden de temperatuur tijdens de opwarming (tijd versus temperatuur) geanalyseerd en werd de Q waarden gemeten, waarbij de Q waarde gedefinieerd is als de oppervlakte onder de curve gedurende 10 minuten na het begin van de actieve opwarming. Deze Q waarde is een maat voor warmteoverdracht. Ook werd de richtingscoëfficiënt van de opwarming gemeten, een maat voor de snelheid van opwarming. Test-hertest relativiteit bleek 0.64 en 0.79 voor de Q-waarde en de richtingscoëfficiënt. Een hoge Q-waarde met een steile richtingscoëfficiënt werd geïnterpreteerd als de aanwezigheid van een actieve opwarming, tegenover passieve opwarming waarbij de temperatuur van de vingers nauwelijks toeneemt. De patiënten waarbij er actieve opwarming was in de regio van de aangedane vingers hadden een betere sensibiliteit ($p=0.001$) en lagere scores op de CISS vragenlijst ($p=0.06$). Een betere sensibiliteit was ook gecorreleerd aan een lagere CISS-score ($rho=0.642$, $p=0.024$).

Het laatste experiment in Hoofdstuk 8 onderzocht de invloed van letsel aan de n. medianus en n. ulnaris op Cold Induced Vasodilation (CIVD) tijdens langdurige afkoeling van de handen bij een lage temperatuur. Twaalf patiënten met een letsel van de n. medianus of de n. ulnaris werden 4 tot 76 maanden na het zenuwletsel gemeten. De palmaire zijde van de handen en vingers werd continue afgekoeld door middel van een koude plaat met een temperatuur van 5°C. De huidtemperatuur van de vingertoppen werd continue gemeten met behulp van infrarood thermographie. Vervolgens werden de resultaten uitgezet in een grafiek (tijd versus temperatuur van de distale phalanx). De aanwezigheid van een CIVD reactie werd gedefinieerd als een minimale toename in huidtemperatuur van 2.5°C waarbij de opwarming distaal begint. Bij 4 patienten met een follow-up van 6 tot 37 maanden trad geen CIVD reactie op in de aangedane vingers, terwijl een CIVD reactie aanwezig was in de overige vingers zonder zenuwletsel. Bij 6 patienten was er een CIVD reactie aanwezig in zowel de aangedane als de niet-aangedane vingers gemeten gemiddeld 50 maanden (24 tot 76 maanden) na letsel. Twee patienten hadden geen CIVD reactie in zowel de aangedane als niet-aangedane vingers. De patiënten waarbij een CIVD reactie aanwezig was hadden een redelijk herstel van sensibiliteit. De aanwezigheid of afwezigheid van een CIVD reactie was niet gecorreleerd aan de CISS-score. We concludeerden dat subjectieve klachten van koude intolerantie aanwezig kunnen zijn terwijl de thermophysiologische reactie op koude normaal is.

Hoofdstuk 9 geeft bediscussieert de resultaten van dit proefschrift en vergelijkt deze met wat er bekend is in de literatuur. Voor zover mogelijk worden de vragen beantwoord die in de Inleiding (Hoofdstuk 1) naar voren kwamen naar aanleiding van de casus. Ook worden mogelijke richtingen voor toekomstig onderzoek besproken en eventuele vervolgstudies benoemd.

# Chapter 11

## Curriculum Vitae, bibliography and portfolio

## Curriculum Vitae

The author was born in Leiden (The Netherlands) on 17 July 1976. After secondary school at the Stedelijk Gymnasium, Leiden, The Netherlands, she studied chemistry at Leiden University for one year. In 1995 she started medical school at Leiden University Medical Centre (LUMC). Her interest in hand surgery was sparked during an early internship of 3 month’s, working on a research project on the SLAC-wrist supervised by Dr Van Drunen. During her last two clinical years of Medical School (2000-2002), she started a research project with Jean-Bart Jaquet for the ZeRo (zenuwgroep Rotterdam; Rotterdam Nerve Group), supervised by Prof. Steven Hovius, at the Erasmus Medical Centre, Rotterdam. In 2002, she completed a clinical rotation in hand surgery at the Radcliffe Infirmary and Nuffield Orthopaedic Centre at Oxford University, UK (Dr Henk Giele). After graduating in 2002, she worked as a house officer in Neurosurgery at the VU medical centre, Amsterdam under supervision of Prof. Vandertop. In 2003, she passed the American medical exams USMLE step 1, step 2 and step 2 clinical skills. From August 2004 to September 2005 she was a Netherlands-America Foundation - Fulbright fellow at the department of Plastic Surgery and the Orthopaedic Hand Services of the Massachusetts General Hospital, Harvard University, Boston, MA. After returning to the Netherlands in October 2006, she worked as a house officer and PhD student at the department of Plastic, Reconstructive and Hand surgery, Erasmus MC, Rotterdam, supervised by Prof. Steven Hovius. In June 2007 her orthopaedic residency training was started at the Université Catholique de Louvain, Bruxelles under supervision of Prof. Christian Delloye, with 2 years of basic surgical training at UCL Mont-Godinne, Belgium under supervision of Prof. Yves Louagie (2007-2009).

## Courses

| | |
|---|---|
| AO comprehensive course on operative fracture managment, Ovifat, Belgium | October 2009 |
| AO pelvic course, Leuven, Belgium | January 2009 |
| Medical wilderness training & Mountain Medicine, Chamonix, France | June 2007 |
| Course in Microsurgery, Skills Lab, Erasmus MC, Rotterdam, the Netherlands | October 2005 |
| Statistics for clinical research, MGH, Boston, MA, USA | Spring 2005 |
| Biomedical Research Modules of the web-based Basic course, 'Collaborative IRB Training Initiative (CITI)', Miami, Florida | January 2005 |
| Fulbright Seminar: "Achieving gender equity in education and the workplace." New Orleans, US | March 2005 |

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**Portfolio: Summary of PhD training and teaching activities**

| | |
|---|---|
| Name PhD student: ACJ Ruijs<br>Erasmus MC Department: Plastic Surgery<br>Research School: | PhD period: 2005-2009<br>Promotor(s): Prof. SER Hovius<br>Supervisor: RW Selles |

| **1. PhD training** | **Year** | **Workload** |
|---|---|---|
| **General academic skills** | | |
| - Laboratory animal science | 2005 | 20 h |
| **Research skills** | | |
| - Statistics, 2 courses | 2005 | 2 ECTS |
| - Methodology, 1 course | 2005 | 1 ECTS |
| **In-depth courses (e.g. Research school, Medical Training)** | | |
| - Basic Surgical Training, 2 years | 2007-2009 | |
| - Orthopaedic Basic Science, entrance exam third year | 2009 | 4 ECTS |
| - Internship Hand Surgery | 2009 | 4 ECTS |
| **Presentations** | | |
| - Poster | 2000 | 1 |
| - Presentation | 2002 | 1 |
| - Presentation | 2005 | 1 |
| - Presentation | 2006 | 1 |
| - Presentation + workshop | 2008 | 2 |
| **International conferences** | | |
| - FESSH | 2002 | 1 ECTS |
| - ASRM/ ASSH/ FESSH | 2006 | 2 ECTS |
| - FESSH | 2008 | 1 ECTS |
| - BHG/ SORBCOT | 2009 | 1 ECTS |
| **Seminars and workshops** | | |
| - Microsurgery | 2005 | 1 ECTS |
| - Mountain Medicine | 2007 | 2 ECTS |
| - AO pelvic course | 2009 | 1 ECTS |
| **Didactic skills** | | |
| - Fulbright Seminar | 2005 | 1 ECTS |
| - Fulbright Panel | 2006 | 4 hours |
| **2. Teaching activities** | | |
| | **Year** | **Workload (Hours/ECTS)** |
| - Supervision medical student Erasmus MC | 2007-2009 | 50 |
| - Supervision student, Massachusetts General hospital | 2004-2005 | 75 |

STELLINGEN:

1. Koude-intolerantie is een ernstig en veel voorkomend probleem bij letsels van de nervus medianus en/of nervus ulnaris. (Dit proefschrift).

2. Subjectieve symptomen van post-traumatische koude intolerantie zijn betrouwbaar te meten door middel van de gevalideerde Cold Intolerance Severity Scale (CISS) vragenlijst. (Dit proefschrift).

3. De hoge scores op de CISS vragenlijst bij patiënten met een *chronisch neuroom* kan duiden op een verstoring van de verwerking van pijnsignalen. (Dit proefschrift)

4. Infrarood thermografie is een goede meetmethode om veranderingen in de thermofysiologie van de handen te bestuderen. (Dit proefschrift).

5. Subjectieve symptomen van koude intolerantie gaan niet altijd samen met objectieve thermofysiologische veranderingen. (Dit proefschrift).

6. Met de huidige snelheid van global warming zal koude intolerantie spoedig een self-limiting disease zijn.

7. Vanwege het wegzakken van klinische kennis tijdens het doen van wetenschappelijk onderzoek, zou, in plaats van een jaar korting op de specialisten opleiding, een extra klinisch jaar beter zijn.

8. De anatomie van de onderarm houdt door zijn dubbele vascularisatie en anastomoses al rekening met frequente letsels van de onderarm.

9. Het voluit schrijven van cijfers onder de tien is duidelijk bedacht door alpha's zonder rekening te houden met beta's.

10. Het is wonderlijk dat huishoudelijke taken die in de privésfeer tot het domein van de vrouw behoren (koken, naaien), in de professionele sfeer voornamelijk door mannen worden verricht (chefkok, chirurg).

11. Geen etter zonder lagere organismen. Proefschrift JA Ruijs, arts, 1885.