Studies in Carpal Tunnel Syndrome and Cold Intolerance

Studies in Carpal Tunnel Syndrome and Cold Intolerance

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Thesis submitted to the University of Nottingham for the degree of Doctor in Medicine

September 2007

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Abbreviations

˚C	Degrees Celsius
2PDT	Two-Point Discrimination Test
ACH	Acetylcholine
ACIs	Angiotensin Converting Enzyme Inhibitors
ANOVA	Analysis of Variance
AOI	Areas Of Interest
AOR	Adjusted Odds Ratio
ARAs	Angiotensin Receptor Antagonists
BP	Blood Pressure
cGRP	Calcitonin Gene Related Peptide
CI	Confidence Interval
CISS	Blond McIndoe Cold Intolerance Symptom Severity Score
cm	Centimetre
CoV	Coefficient Of Variation
CPT	Cold Provocation Testing
CTR	Carpal Tunnel Release
CTS	Carpal Tunnel Syndrome
$CTS^{Affected}$	Affected hand in the CTS group
CTS^{C}	Unaffected hand in the CTS group
DM	Diabetes Mellitus
GSS	Global Symptoms Score
GTN	Glyceryl Trinitrate
HAVS	Hand Arm Vibration Syndrome
$HI^{Affected}$	Affected side in the hand injury group
HI^{C}	Control side of the HI
HISS	Hand Injury Severity Score
ICC	Interclass Correlation Coefficient
ICTP	Intra Carpal Tunnel Pressure
IV	Intravenous
Kg	Kilogram
LDF	Laser Doppler Flowmetry
LDI	Laser Doppler Perfusion Imaging
LDI^{0}	Mean Perfusion Prior To The Delivery Of The Iontophoresis Charge

LDI_{Max}	Maximum post-iontophoresis perfusion readings
LDI_{Mean}	Mean perfusion values of the first three images post-delivery of iontophoresis
LOA	Limits Of Agreement
m 2PDT	Moving Two-Point Discrimination Test
MC CTS	Medically Confirmed Carpal Tunnel Syndrome
mm	Millimetres
mmHg	Millimetres Mercury
MRI	Magnetic Resonance Imaging
ms	Millisecond
Mv	Microvolt
NC	Normal control group
NC^{Left}	Normal control group, Left hand
NC^{Right}	Normal control group, Right hand
NCS	Nerve Conduction Studies
NHS	National Health Service
Nm	Nanometer
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PL	Palmaris Longus
PPT	Purdue Pegboard Test
PRP	Primary Raynaud's Phenomenon
PTCI	Post Traumatic Cold Intolerance
r	Pearson Correlation Coefficient
RBC	Red Blood Cells
RP	Raynaud's Phenomenon
sec	Second
s 2PDT	Static Two Point Discrimination
SD	Standard Deviation
SN	Sensorineural
SNP	Sodium Nitroprusside
SPSS	Statistical Package For Social Sciences
SSc	Scleroderma

SSS	Symptom Severity Score
SWM	Semmes-Weinstein Monofilament Pressure Aethesiometer
SWS	Stockholm Workshop Scales
T30secs	Temperature Rise In The First 30 Seconds
T_{5oC}	Time Taken For The Hands To Re-Warm By 5°C
TA	Thermal Aesthesiometry
TICAS	Trauma Induced Cold Associated Symptoms
V	Vascular
VWF	Vibration White Finger
WBC	White Blood Cell

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Acknowledgements

At this point I would like to thank the many people who have supported my work and guided me along the way. I would like to start by thanking Mr L C Bainbridge, whose determination and strength of conviction paved the path for my research and led me into this journey. His ideas and comments lit the path on numerous occasions and helped me to overcome some of the hurdles during my research. Thank you.

I would like to thank Dr G Manning, whose organisation, patience and academic approach to research were enlightening and her dedication to research remains inspiring. Thank you.

I would like to thank all the members of the Division of Vascular Medicine: Professor R Donnelly, Mrs Jean Clarke and Sue Lane. My deepest gratitude has to go to Mrs Margaret Baker and Mrs Kelly Mitchell, both of whom were and will always be my family away from home and stood by me when I needed help the most. Thank you.

This piece of work was not only the product of the cooperation between the members of our research group but also the R&D Department staff at Derby Hospitals NHS Foundation Trust, especially Dr R Hilliam and Mr A Fakis. My sincere thanks to both.

Declaration

The author declares that:

1- All the work contained in this thesis is my own, unless stated.

2- My role in the modification of the cold provocation testing was to undertake a detailed analysis of the data from subjects that had been studied by the team prior to the start of my research post.

3- I recruited and studied the majority of the studies within Chapters 4 and 5 with technical support from Mrs M Baker.

4- The clinical audit studies were entirely my own work.

Research Presentations

Various parts of this thesis have been published in peer reviewed scientific journals and/or presented in abstract form in national and international meetings.

A list of these publications is shown below:

Published

1. **Salem KM**, Baker M, Manning G, Bainbridge LC, Donnelly R Analysis of Rewarming curves in patients with Raynaud's phenomenon of various aetiologies *Revesta Iberoamericana De Cirugia de la Mano* (2005) *33(66): 76* (**Abstract**)

Accepted

2. **Salem K,** Baker M, Hilliam RM, Davies S, Deighton C, Bainbridge LC, Manning G Analysis of rewarming curves in patients with Raynaud's phenomenon of various aetiologies (**Original Article**) The Journal of Hand Surgery [Br] (Manuscript number: JHSB-D-06-00228), Submission date: June 2006

Submitted

3. **Salem K**, Donnelly R, Manning G, Bainbridge LC Post traumatic cold intolerance, a review (**Review Article**) The Journal of Hand Surgery [Br] (Manuscript number: JHSB-D-06-00347), Submission Date: August 2006

Poster presentations

1. Does Cold Provocation Testing have a role in the assessment of people with suspected Hand Arm Vibration White Finger Syndrome (HAVS)? Society of Occupational Medicine Annual Scientific Meeting, Science in Practice, Manchester June 2005

International and National meeting oral Presentations

2. Analysis of re-warming curves in patients with Raynaud's phenomenon of various aetiologies XVII National Congress SECMA Surgery of the Hand, in association with the British Society for Surgery of the Hand. Valladolid- Spain, April 2005

3. A new objective re-warming test Advanced Course for Hand Surgery, Pulvertaft Hand Unit, Derbyshire Royal Infirmary, May 2005

ABSTRACT

Carpal tunnel syndrome (CTS) presentation is usually classic but cold-related Raynaud's phenomenon (RP)-like symptoms were described in CTS and more commonly in the injured hand (HI).

The work presented in this thesis is divided into two domains; the first aims to extend understanding of the response of the hand to cold in CTS and HI using two processes. [1] The modified cold provocation test (CPT) validated in a group of controls and both primary and secondary (vibration induced) RP subjects. Both hands were immersed in a 12°C water bath and the digital temperature recorded every 6 seconds using thermocouples until the digital temperature dropped to 15°C. The hands were then removed and allowed to passively re-warm. Baseline temperature (difference between the ambient temperature and the digital temperature), T_{30sec} (temperature gain in the first 30 seconds post-cooling) and $T_{5°C}$ (time required to gain 5°C) were assessed. [2] Laser Doppler Imaging (LDI), a well-established method for investigating skin microcirculation with an endothelial challenge (facilitated by iontophoresis delivery Sodium Nitroprusside and Acetylcholine). The second domain centred on the management of CTS and in particular outcome assessment of conservative versus surgical treatment in registrar and nurse practitioner CTS clinics in a community hospital.

Data on 86 controls, 31 primary RP and 59 secondary RP were collected. In the control group the baseline temperature was >6°C, which was higher than the primary and secondary RP groups (p-value <0.05, sensitivity 79%, 78%, specificity 43%, 45%, inter-class correlation 53%, 49%); T_{30sec} in secondary RP was >1.8°C, which was higher than controls and the primary RP groups (p-value <0.001, sensitivity 70%, 71%, specificity 76%, 79%, inter-class correlation 3%, 40%); and $T_{5°C}$ in primary RP was >300 seconds, which was longer than that of the controls and secondary RP groups (p-value <0.001,

sensitivity 64%, 61%, specificity 70%, 64%, inter-class correlation 70%, 70%); data given for left and right hands respectively.

CPT and LDI studies were undertaken on 60 controls and 60 CTS patients pre-operatively and repeated on 40 subjects 5-7 months post-decompression. Post-operatively, the baseline temperature increased by 1.5°C (p-value <0.05) in both hands and 2.5°C (p-value <0.001) in the median nerve supplied digits, T_{5oC} was reduced in the hands (pre- versus post-operative from 474 to 348 seconds) (p-value 0.06) and from 468 to 273 seconds in the median nerve supplied digits (p-value 0.01). Endothelial dependent and independent control at mean and maximum pre- and post-cooling perfusion was significantly depressed (p-value 0.05) post-cold exposure in the control group. LDI limited to the dorsum of the hand identified no significant difference pre- and post-operatively (p-value >0.05).

HI subject recruitment was challenging: the absence of a financial incentive and the possible income loss during working days for a young working cohort might have contributed to the poor recruitment. Of the 60 subject targets only 14 recruited and the injury severity varied widely between the recruits; the data gathered through CPT and LDI in this group did not show a significant difference from that collected in controls.

CTS management audits on 74 subjects in a nurse-led clinic and 173 subjects in a registrar-led clinic identified a high failure rate of the conservative management (60%) at 6 months follow up in both clinics with unclear success predictors suggesting an extra burden on clinics providing decompression surgery.

Conclusion

Firstly the modified CPT is a valid method in the differentiation between controls, primary and secondary (vibration induced) RP. Secondly, surgical release in patients with CTS results in a rise in the baseline temperature and a faster $T_{5°C}$ mainly in the median nerve supplied digits. Thirdly, the conservative management of CTS has a high failure rate and medical practitioners in a CTS clinic should be able to perform decompression surgery or have direct access to theatre lists which deliver such a service.

To my parents, without whom nothing would ever have been possible

CHAPTER 1: INTRODUCTION

1.1 CARPAL TUNNEL SYNDROME (CTS)

1.1.1 Definition and prevalence

CTS is used to describe a collection of clinical symptoms and physical signs secondary to a median nerve insult at the level of the transverse carpal ligament. It was first described by Paget in 1854 in two cases, both traumatic; the first was in a male who had a cord drawn tightly around his wrist and the other was following a distal radial fracture, both presenting with sensory, motor symptoms and ulceration. Paget alluded to the benefits of removing the pressure of the nerve in the treatment of the second case. The first case underwent an amputation (Lo *et al.* 2002).

CTS is the most common peripheral compressive neuropathy with a 10% lifetime risk of development (AAN 1993). Based on a socioeconomic study conducted in the United States of America, CTS is the most common condition seen by hand surgeons with costs in excess of 2 billion dollars/year (Palmer *et al.* 1995). Awareness of this condition and its possible link to occupation in the early 1980s dramatically increased the prevalence of CTS (Franzblau *et al.* 1999). Based on the response to a symptoms questionnaire from about 500 subjects in the Netherlands, minimum prevalence estimates for CTS in the general population were 0.6% for males and 5.8% for females (de Krom *et al.* 1992).

In a more recent study a mailed questionnaire identified 14% of the study population (2,466 subjects) as suffering from median nerve entrapment symptoms with one in five having CTS based on clinical examination and electrophysiological testing (Atroshi *et al.* 1999).

1.1.2 Pathophysiology of CTS

The pathophysiology of CTS is multifaceted, characterised by an increased intra-carpal tunnel pressure (ICTP) as a final common pathway (Szabo *et al.* 1987). Using the forearms of five cadavers, Cobb *et al*. perfused the flexor compartment with saline in an attempt to determine whether elevated pressure in this compartment is transmitted to the carpal tunnel. The author concluded that the carpal tunnel functions as a relatively closed compartment with respect to the transfer of pressure from the flexor compartment of the forearm (Cobb *et al.* 1995).

1.1.2.1 The carpal tunnel pressure

Using a wick catheter, measurements of the ICTP obtained from 12 normal subjects were lowest when the wrist was in neutral (mean 2.5 mmHg (0-7)), with pressure readings rising to 30 mmHg during flexion and extension (Gelberman *et al.* 1981b).

To investigate the pressure threshold for peripheral nerve dysfunction, a human model of acute nerve compression was used by applying a controlled external pressure on the carpal tunnel and measuring the ICTP using a wick catheter. External pressure challenges of 40, 50, 60 and 70 mmHg were applied with the wrist in neutral. Using nerve conduction studies (NCS) pre, 30 and 240 minutes into the compression phase and during the recovery phase, the authors concluded that at 40 mmHg some nerve function was lost but at 50 mmHg all nerve function was blocked. They hypothesised the presence of a critical pressure between 40 and 50 mmHg where nerve function is acutely endangered (Gelberman *et al.* 1983b).

The above study was repeated on the non-dominant wrist of nine hypertensive controls (diastolic blood pressure (BP) ≥90 mmHg). The critical pressure

threshold in the hypertensive group was greater than that previously reported for normotensive subjects (40-50 mmHg). Further analysis revealed that the critical ICTP threshold was consistently 30 mmHg below diastolic BP (approximately 45 mmHg below mean arterial BP) for both the normotensive and hypertensive population (Szabo *et al.* 1983). In support of this finding, CTS was reported in hypertensive patients following the successful treatment of their hypertension (Emara *et al.* 1988).

When the ICTP was measured in 15 patients with CTS the mean pressure was 32 mmHg in neutral increasing to 94 and 110 mmHg in flexion and extension respectively. Surgical release produced an immediate and sustained reduction in pressure (Gelberman *et al.* 1981b). This drop in the ICTP was statistically significant using both open and endoscopic release (Figure 1.1) (Brown *et al.* 1993).

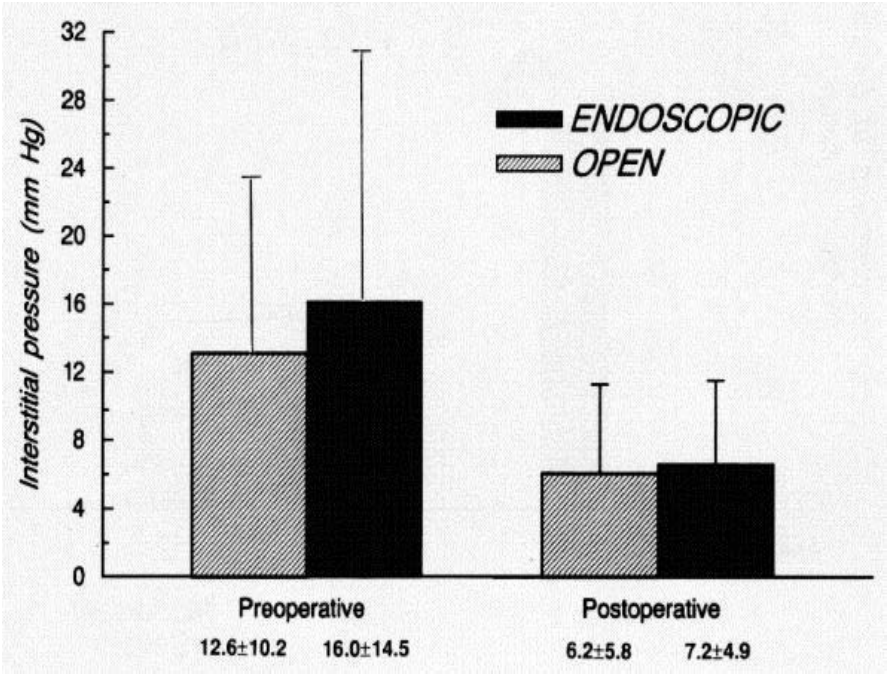


Figure 1.1 The pre- and post-op interstitial pressure in CTS (whiskers=SD) (n=15) (Brown *et al.* 1993)

It is suggested the ICTP is a product of two generators: the interstitial fluid pressure within the carpal tunnel and the direct contact pressure on the median nerve from the adjacent tissues (Werner *et al.* 2002).

1.1.2.1.1 The interstitial fluid pressure within the carpal tunnel

Build up of the interstitial pressure over time is thought to reflect a synovial thickening in a limited space (Werner *et al.* 1997). This thickening has been demonstrated in cadaveric studies to be most evident at the entrance and exit of the canal, probably as a result of the mechanical effect of the tendon sliding over a fulcrum of the flexor retinaculum (Armstrong *et al.* 1984; Werner *et al.* 2002).

1.1.2.1.2 Pressure from the surrounding structures

In addition to the U-shaped formation of the carpal bones with the overlying flexor retinaculum, there is an annular group of ligaments that extend dorsally to form the extensor retinaculum and volarly the volar carpal ligament. These annular rings are separated by longitudinal elastic elements which stretch and compress the underlying soft tissues in extension and buckle and wrinkle on flexion, the flexor retinaculum protecting the carpal contents from this pressure (Werner *et al.* 2002) (Figure 1.2).

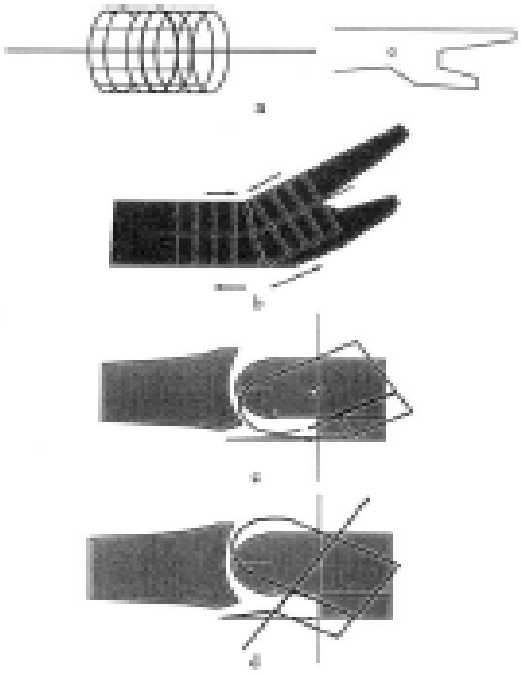


Figure 1.2 The annular elements around the wrist and their movement with flexion and extension (Werner *et al.* 2002)

The movement of the carpal bones during extension result in the proximal carpal margin gliding volarly against the flexor retinaculum, consequently squeezing the carpal contents between the bone and ligamentous components of the tunnel.

Digital and wrist extension draws the more proximal, thicker part of the tendons into the carpal tunnel leading to an increase in the content volume and an increased pressure on the nerve. It is hypothesised that this also occurs in volar, radial and ulnar deviation but to a lesser extent (Werner *et al.* 2002).

Histological studies of the tenosynovium in patients with CTS support ischemia-induced changes rather than inflammation. These findings include cloudy white hypertrophy of the tenosynovium with no inflammatory infiltrate. Fibrous hyperplasia was also noted with an increased disorganised collagen deposition (Fuchs *et al.* 1991; Kerr *et al.* 1992). In a retrospective review of synovial specimens from 625 carpal tunnel releases, the authors reported 96% (601) to have a synovial tissue histological diagnosis of benign fibrous tissue without

inflammation, 4% (23) showed chronic inflammation, and 0.2% (1) revealed evidence of acute inflammation (Kerr *et al.* 1992).

More recently, histological studies from the Mayo clinic, comparing the subsynovial connective tissue (SSCT) layer in patients with primary CTS to cadaveric controls, identified changes in the SSCT similar to those observed following injury including an increase in fibroblast density collagen fibre size, and vascular proliferation in the specimens from the CTS patients ($p < 0.001$) (Ettema *et al.* 2004; Jinrok *et al.* 2004; Oh *et al.* 2005; Oh *et al.* 2006).

1.1.3 Clinical picture

Intermittent pain and paresthesia in the region of the median nerve distribution in the hand (the thumb, index, middle and the radial half of the ring fingers) sparing the palmer cutaneous branch area of innervation is classical for CTS (Omer 1992). Variations to the classical sensory disturbance are described ranging from a single digit being affected to all the digits being reported by patients to be numb and tingling.

Regardless of the distribution, symptoms progress with time and patients report sleep disruption and nocturnal dysthesia relieved by shaking the hand (Michelsen *et al.* 2002). Nocturnal symptoms have been described as cardinal in CTS and the tendency to adopt a flexed wrist position during sleep was proposed as a cause. The normal increase in the tissue pressure in the carpal tunnel during sleep might also be a factor in the nocturnal complaints (Sunderland 1976; Michelsen *et al.* 2002).

Chronic CTS sufferers often report additional motor complaints; the thenar intrinsic muscle compartment is weakened, affecting dexterity and grip strength. Eventually thenar muscle atrophy becomes clinically evident. In some cases,

the sensory fascicles are spared and the compression damages the motor component of the nerve leading to a delayed presentation. The patient is often unaware of the problem until significant muscle atrophy develops (Michelsen *et al.* 2002; Burke *et al.* 2003).

In a literature review, CTS was classified into early, intermediate, advanced and acute stages based on an observed progression of symptoms, and clinical and electro-diagnostic findings. The early stage was less than one year with sensory but no motor component while the intermediate and late stages were associated with weakness for which operative treatment was advocated (Gelberman *et al.* 1988).

Based on a hypothesis suggesting that the sympathetic supply to the hand is mostly carried by the median nerve, Phalen suggested that the vasomotor control of the hand will be affected by compressive neuropathy to the median nerve (Phalen 1966). Despite the high prevalence of CTS and the large amount of published literature related to it, the autonomic disturbance associated with CTS is frequently missed clinically or unreported in the literature. First reported in 1957, RP-like symptoms in CTS have subsequently been addressed in a very limited number of studies (Garland *et al.* 1957; Linscheid *et al.* 1967; Pal *et al.* 1996).

More recently, a prospective review of 139 cases in 76 CTS patients identified 62% of the patients to have “dysautonomia”. Verghese *et al.* (2000) considered eight items related to the autonomic function and reported the incidence of those in the study cohort as follows: swelling of the digits (60%), dry skin (40%), RP (33%), blanching (32%). No patients presented with digital ulceration or nail dystrophy. Cold sensation in the fingertips was found to be non-specific in a pilot study and was excluded. Although this study subjectively demonstrates the high prevalence of the autonomic symptoms, several limitations can be

identified: unclear clinical definition swelling, dryness and RP, the exclusion of sweating, and the large number of females in the cohort resulting in a bias in prevalence calculations (higher in females).

The prevalence of the autonomic symptoms reported in other studies varied. A retrospective review of the notes of 2,800 patients in the Mayo Clinic in the 1960s reported 28 complaints of autonomic symptoms but a systematic analysis of the autonomic pattern was lacking and minor symptoms were not recorded (Linscheid *et al.* 1967). In a more recent study, the incidence of RP was higher (36%) in a CTS group (93 subjects) compared to a control group 12% (57 subjects) (Pal *et al.* 1996) . Reporting on 30 subjects, Chung *et al*. found 60% complaining of RP and then reported an improvement in 78% of the affected following surgical release in a subsequent publication (Chung *et al.* 1999; Chung *et al.* 2000).

A variety of provocation tests designed to reproduce or provoke the sensory component of the symptoms was suggested such as Phalen's test (Phalen 1972), Reverse Phalen's (Werner *et al.* 1994), Tinel's (Bowles *et al.* 1983; Tinel 2005) and Durkan's tests (Bowles *et al.* 1983). In a systematic review of literature to determine the accuracy of history taking and physical examination in the diagnosis of CTS, the authors concluded that elements in the history such as age and nocturnal symptoms and in the physical examination such as thenar atrophy, Tinel's sign and Phalen's sign, pressure provocation tests and sensory tests have limited or no value in distinguishing patients with CTS from controls (D'Arcy *et al.* 2000). In another study, the prevalence of Tinel's sign in a control group was reported to be as high as 45% (Seror 1987).

1.1.4 Diagnosis criteria

Although the presentation in the majority of CTS cases is classical, the diagnosis in some cases remains difficult. This is mainly due to the variations in the dysthesia distribution and the limited usefulness of provocation tests in cases where no other clinical signs are present (weakness and muscle wasting). In an effort to identify diagnostic and staging criteria for CTS, 14 experienced researchers could identify no gold standard for the diagnosis within the literature (Rempel *et al.* 1998). This reflects the problem junior doctors and nurse practitioners face in their clinical practice.

In his diagnosis, Phalen required CTS patients to have one or more of three signs: dysthesia limited to the area of the median nerve distribution, a positive Tinel's sign and a positive Phalen's sign (Phalen 1981). In an attempt to establish a consensus on case definitions for several common work-related upper limb pain syndromes, a core group of 29 United Kingdom experts representing various disciplines managing these conditions (including rheumatologists, surgeons, GPs and therapists) concluded that a diagnosis of CTS requires sensory symptoms limited to the median nerve distribution in addition to one or more of the following: nocturnal symptoms, median nerve motor signs, a positive Tinel's sign, a positive Phalen's sign or an abnormality of the nerve conduction studies (NCS) of the median nerve across the wrist (Harrington *et al.* 1998).

In a survey of the members of the American Society for Surgery of the Hand only 33% of the surgeons used NCS as an aid in the diagnosis of CTS (Duncan *et al.* 1987). This reflects the tentative views on the usefulness of NCS amongst surgeons. In correspondence, the "under utilisation" of the NCS in the management of CTS in the USA was reported despite guidance advocating its use (Mainous *et al.* 1996). This "under use" relates to the test's shortcomings:

the lack of standardisation even within the same department, the absence of population-based reference intervals, the limited sensitivity (70%) and specificity (76%), the absence of evidence for the test's ability to predict or improve the treatment outcome and the lack of correlation with the patient's symptoms (Atroshi *et al.* 1999; Kilmer *et al.* 2002; Smith 2002).

In an attempt to evaluate the agreement between the clinical examination, the sensory nerve conduction testing and symptom surveys including hand diagrams, only 23 out of 449 subjects with one or more symptoms suggestive of CTS met all three criteria (symptoms, examination and NCS) with a very poor agreement between the assessment parameters (kappa coefficient between 0.00 and 0.18) (Homan *et al.* 1999). In the same study, the majority of the subjects with NCS evidence of median neuropathy were asymptomatic and vice versa (Homan *et al.* 1999). In an 11-year longitudinal study following up 558 subjects with an abnormal NCS, the authors concluded that an abnormal NCS is not a predictor of future CTS (Nathan *et al.* 1998).

CTS severity assessment questionnaires have been proposed. Levine *et al*. developed a self-administered CTS symptoms and function assessment questionnaire. The authors concluded that the questionnaire is reproducible, internally consistent, and responsive to clinical change when studied on a sample of 76 patients diagnosed clinically and by NCS to have CTS. These conclusions were based on repeatability assessment using the Pearson correlation coefficient (r) = 0.91 and 0.93 for severity of symptoms and functional status respectively, a statistically significant drop in severity scores following surgical treatment (Levine *et al.* 1993). It is clear that this study had limitations; the authors used an inappropriate test (r) to assess repeatability, the study lacked a control group limiting its conclusions and, despite a significant improvement in the scores post-operatively, there is no evidence to suggest that it is responsive in the conservative management group. This may explain the

findings of a subsequent study which concluded that the Levine questionnaire has only limited value in establishing the diagnosis of CTS (You *et al.* 1999). More recently Bland described a questionnaire with an overall sensitivity of 79% and specificity of 55% for the diagnosis of CTS and an ability to predict the findings of nerve conduction studies based on a study of 8,223 suspected CTS subjects and compared with the neurophysiological findings (Bland 2000).

The use of tools such as ultrasound, CT and MRI scanning has been reported but their role in the diagnosis of CTS is not established (D'Arcy *et al.* 2000; Beekman *et al.* 2002).

1.1.5 Risk and prognostic factors

The cause in the majority of CTS cases is unknown (idiopathic) (Kerwin *et al.* 1996) but some of the risk factors have been identified. A case-control analysis of the data from 3,391 CTS cases from the UK General Practice Research Database identified a higher risk in patients suffering rheumatoid arthritis (OR=2.23), osteoarthritis of the wrist and carpus (OR=1.89), previous wrist fracture (OR=2.29), obesity and thyroxin. The authors also acknowledged Diabetes Mellitus (DM) (OR=2.06) and its treatment (Insulin, Sulphonylureas, Metformin) as risk factors, yet the reported risk with DM treatment may be biased by the higher risk of developing the syndrome in the diabetics to start with (Geoghegan *et al.* 2004).

Most studies report a prevalence three to fourfold higher in females compared to males (D'Arcy *et al.* 2000; Burke *et al.* 2003). The cause of this higher prevalence was explained by a narrower carpal tunnel outlet, therefore a pronounced decrease in the tunnel volume in females compared to males (Dekel *et al.* 1980).

The strongest factor associated with the development of CTS is vibration exposure (Mackinnon 2002). In a population assessed for compensation for Hand Arm Vibration Syndrome (HAVS) through the miner's compensation scheme in the UK, a prevalence of 15% was reported. This figure is likely to be higher than expected due to the potential financial gain for those diagnosed with both conditions within the scheme (Burke *et al.* 2005). In a small prospective review of eight patients (15 hands) diagnosed with both CTS and HAVS, a 6-month follow up from surgical decompression for CTS revealed an improvement in the CTS symptoms in all subjects and HAVS symptoms improvement in 50% of the participants suggesting a link between the two conditions (Savage *et al.* 1990).

In recent years, claims for compensation due to occupation-related disease have increased. This is true for work-related repetitive strain injuries of which only about 2% are CTS (Mackinnon *et al.* 1997). In a study based on the 1988 National Health Interview Survey in the United States, the data on approximately 30,000 workers were analysed to identify the prevalence of CTS and its risk factors. The authors reported 1.5% of the study population to have what they termed self-reported CTS (not medically confirmed) and 0.5% medically confirmed CTS cases (MC CTS). Within the MC CTS group the following risk factors were identified: exposure to bending and twisting at work, (Adjusted Odds Ratio (AOR) 5.5); exposure to vibration (AOR 1.9); white race (AOR 16.7); female gender (AOR 2.3); BMI >25 (AOR 2.0); history of cigarette smoking (AOR 1.6); age >40 (AOR 1.2); and education >12 years (AOR 1.2) (Tanaka *et al.* 1997). Findings supporting the association between repetitive movement of the hand and CTS have also been reported by others (Bernard 1997; Lo *et al.* 2002). Nonetheless, a direct relation between specific forms of work (including the use of a keyboard) and CTS is still lacking (Burke *et al.* 2003).

A strong family history due to a hereditary neuropathy was reported to result in a higher predisposition to pressure palsies (Lane *et al.* 2001).

The prediction of the response to treatment remains difficult. In a prospective study of 96 patients undergoing CTS surgery, the pre-operative health profile measured using the Nottingham Health Profile score was significantly worse in the 27 cases dissatisfied with their surgery (Rege *et al.* 2001). In their analysis, the authors included diabetic patients and grouped the patients with post-operative complications (14 cases) with those whose symptoms did not improve, rendering conclusions based on this group greatly biased by the iatrogenic side-effects of surgery and they did not identify the effect of diabetes (a known cause of mono-neuropathy) on poor outcome.

Another study suggested that complete restoration of clinical and electrophysiological nerve function was observed only in patients with mild CTS based on history, clinical examination and NCS (Aulisa *et al.* 1998) but these views are not accepted by all. Glowacki *et al*. presented 227 CTS cases treated surgically and showed no correlation between the NCS findings and the post-operative improvement (Glowacki *et al.* 1996).

Other factors reported to affect the prognosis are compensation claims which point to a poor post-operative course (De Smet *et al.* 1995) and favourable response to steroid injection constituting a good prognostic sign (Green 1984).

1.1.6 Treatment of CTS

1.1.6.1 Conservative treatment

The surgical risk, the increased number of patients seeking treatment for CTS, the reported success rate for conservative treatment ranging from 13-92% in some of the studies and the mild-to-moderate presentation picture in some cases keeps the conservative treatment options as a more appealing choice as

a first line of treatment (Osterman *et al.* 2002). Various modalities of non-operative treatment have been suggested. These include:

1- Lifestyle modification

Avoiding repetitive wrist and hand motion may reduce the intensity of symptoms (Viera 2003). This advice is based on the hypothesis that repetitive use of the hands provokes flexor tenosynovitis (von Schroeder *et al.* 1996). However, the results of a synovial tissue histological study on 625 patients diagnosed with idiopathic CTS uncovered only 4% (23) as having histological evidence of chronic inflammation and 0.2% (1) to have acute tenosynovitis. The authors concluded that tenosynovitis is not a part of the pathophysiological process in chronic idiopathic carpal tunnel syndrome (Kerr *et al.* 1992).

The same applies to using a wrist support and/or improved wrist positioning when using a computer (Viera 2003). Avoiding vibration exposure is believed to reduce the frequency and intensity of the symptoms (Stevens *et al.* 1992). Adjustment of work height or tools to optimise the position of the wrist in neutral and avoid extreme ranges has also been suggested (Burke *et al.* 2003).

2- Exercise

Tendon and nerve gliding exercises have been shown to reduce the need for surgical intervention in CTS; in a study of 240 CTS cases, patients were divided into two groups. Both groups received similar conservative treatment but an additional programme of nerve and tendon gliding exercises was added to one of the groups. Of those who did not perform the nerve and tendon gliding exercises, 71.2% underwent surgery compared with only 43% of patients who did perform them. Out of 47 patients presenting at a mean of 23 months, 70.2% reported good or excellent results (Rozmaryn *et al.* 1998). It is thought that nerve tethering and adhesions are minimised through nerve mobilisation, and

oedema and congestion are reduced by facilitating the venous return (Burke *et al.* 2003).

3- Wrist splints

The pressure in the carpal tunnel is lowest in the neutral position (0-7 mmHg): Gelberman *et al*. measured the intra-carpal pressures at neutral, 90° flexion and 90° extension in 15 idiopathic CTS cases and 12 controls; pressures in neutral were lowest in both groups but higher in the CTS group compared to the controls (32 mmHg in CTS compared to 2.5 mmHg in controls, means) (Gelberman *et al.* 1981b). The splint aims to hold the wrist in a neutral position and is reported to be helpful in mild-to-moderate cases and less effective in cases of continuous paresthesia or numbness (Osterman *et al.* 2002; Burke *et al.* 2003).

It is common practice to advise patients to use the splint at night and only occasionally during the day if an activity is expected to exacerbate the symptoms. However, the symptoms and functional deficits, measured by Levine's self-administered questionnaire and physiologic impairment measured by NCS assessed in a small randomised trial with short follow up (six weeks), were better in the group wearing the splint full-time compared to the group wearing the splint at night (Walker *et al.* 2000).

4- Oral medications

In a survey of American hand surgeons, diuretics, Vitamin B6 supplement (Pyridoxine), Non-steroidal anti-inflammatory drugs (NSAID) and oral steroid treatment were used in the treatment of CTS (Duncan *et al.* 1987). A recent prospective randomised double blind and placebo-controlled trial evaluated the effectiveness of commonly used oral medications in the treatment of mild-to-moderate CTS based on NCS findings. The authors reported no difference between the placebo, NSAID and diuretics in outcome based on a global

symptom score (GSS) (Herskovitz *et al.* 1995) at two and four weeks. The authors found a significant improvement in the symptom scores of patients on oral steroid (using prednisolone 20 mg/day for two weeks followed by two weeks on 10 mg/day, p = 0.00001) despite the small sample size (18 subjects) (Chang *et al.* 1998).

A more recent meta-analysis of the randomised controlled trials evaluating the efficacy of conservative treatment in CTS showed similar conclusions. Additionally, pyridoxine and laser acupuncture were reported as ineffective in providing short-term symptom relief (Gerritsen *et al.* 2002).

5- Local steroid injection

Local steroid infiltration has been shown to give superior results compared to an oral systemic steroid. In a prospective randomised double blind trial comparing the effectiveness of a local steroid (methylprednisolone) to a systemic oral steroid (prednisolone 25 mg/day for 10 days) using GSS, the authors reported a significantly better symptomatic relief in the infiltration group ($p < 0.05$) at two, eight and 12 weeks (Wong *et al.* 2001).

The patient's forearm is placed on the examination table with the palm facing up. Using a sterile technique, the needle is advanced from the point of entry at the distal wrist crease adjacent to the ulnar aspect of the Palmaris Longus (PL) tendon. The bevel of the needle should run parallel to the longitudinal nerve fibres to minimise trauma. The needle is advanced distally at 45° towards the carpal tunnel. If the patient reports paresthesia during the insertion, the needle should be withdrawn and repositioned (Girlanda *et al.* 1993; Armstrong *et al.* 2004). The injectable steroid is water soluble and can be combined with an anaesthetic to minimise the discomfort associated with the injection (Osterman *et al.* 2002).

Despite the care taken during the infiltration process, steroid injections are not hazard free and the most important complication is a direct needle injury to, or an intra-neural injection into, the median nerve (Burke *et al.* 2003). To avoid this potentially disastrous complication and, based on median nerve anatomical observations in 93 wrists undergoing endoscopic surgical release for CTS, it was found that the median nerve extends ulnar to the PL tendon in 82% of the cases by a mean of 4 mm and may extend radial to the PL over 6 mm. The authors suggested that the safest location to insert a needle in the carpal tunnel for a steroid injection is through the Flexor carpi radialis tendon (Racasan *et al.* 2005).

A randomised trial with one year follow-up compared steroid injection to limited incision CTS release in 123 cases (57 injected, 66 treated surgically). The authors reported a better subjective outcome in the injection group at the early stages following treatment. No significant difference in outcome was reported at one year apart from a perceived better functional outcome in the surgical group (Andreu *et al.* 2006). The study had several limitations; the researchers did not include patients with thenar atrophy, which represents the more severe stage of the disease. Nocturnal symptoms were used as a primary outcome measure for improvement, which is not a universal feature in all the patients (Michelsen *et al.* 2002). Subjective measurement was used to determine patient improvement and the follow-up period was short (one year) after which a significant body of evidence suggests a high failure rate ranging between 50% and 86% of the injected cases (Green 1984; Ozdogan *et al.* 1984; Weiss *et al.* 1994; Dammers *et al.* 1999b; D'Arcy *et al.* 2000; Kanaan *et al.* 2001; Burke *et al.* 2003; Hui *et al.* 2004).

There was no significant difference in the outcome measured by the GSS following the treatment with one versus two steroid injections in idiopathic CTS

at eight, 24 and 40 weeks according to a randomised controlled double blind trial on a group of 40 subjects (Wong *et al.* 2005).

A prospective study on 50 CTS cases aiming to define the role of steroid injection and splinting as a method of treatment of CTS concluded that patients with mild symptoms, a short history of less than one year, normal sensibility, normal thenar strength and mass, and one- to two-millisecond prolongations of either distal median motor or sensory latencies had the most satisfactory responses to injections and splinting (Gelberman *et al.* 1980).

1.1.6.2 Surgical treatment

Despite the good short-term response to local steroid infiltration, long-term failure rates are high. This makes the surgical option amongst hand surgeons treating CTS preferable (Duncan *et al.* 1987). The surgical management of CTS has advanced in the last three decades. Surgery through a limited palmer approach has been advocated with comparable results to the older wide incision decompression and more recently the endoscopic CTS release is being popularised.

The traditional open incision technique with a longitudinal incision crossing the wrist flexion crease was described as an effective approach of treatment with a low complication rate in major operative text books (Eversmann 1988; Gelberman 1991). In 1998, Lee *et al*. described a limited incision approach utilising a 1-1.5 cm palmer incision for the release of the transverse carpal ligament with the advantage of avoiding a long post-operative sensitive scar crossing the wrist crease and avoiding the incision of the facial convergence between the thenar and hypothenar compartments, a problem blamed for the slower post-operative recovery in the conventional release (Lee *et al.* 1998) (Figure 1.3).

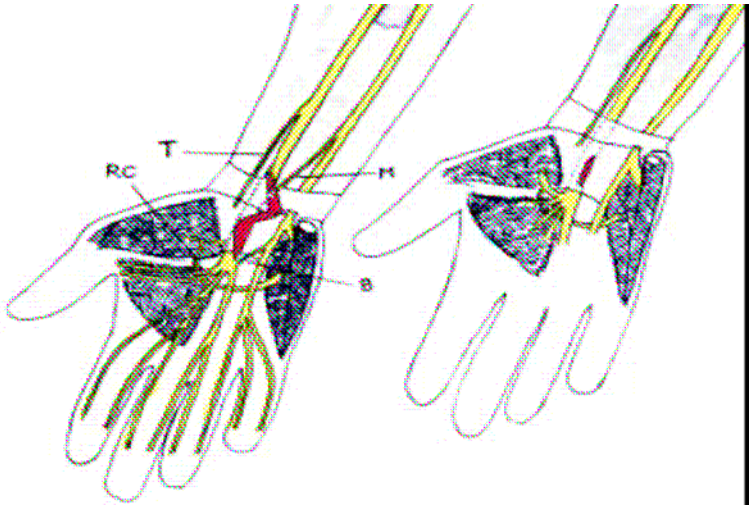


Figure 1.3 The difference in the skin incision between the conventional and limited incision carpal tunnel release (Jugovac *et al.* 2002)

A randomised trial investigating the outcome difference between the conventional and limited carpal tunnel release in 72 cases (36 in each limb of the study) with a three-month follow-up concluded that there is no difference in the symptomatic relief and the post-operative NCS parameters between the two approaches. However, the functional recovery of the hand measured by the return to daily activities and the return to work was significantly quicker in the limited approach group (return to daily activities: 5 days vs. 10 days, return to work 15 days vs. 30 days, $p = 0.001$ results are means for limited and conventional approaches respectively) (Jugovac *et al.* 2002).

Endoscopic procedures to treat CTS were introduced with the claimed advantage of decreased post-operative pain and faster recovery. The findings of a number of randomised trials designed to assess the differences between endoscopic and traditional surgical decompression were consistently in favour of the endoscopic release when post-operative scar pain was assessed, yet no difference in the recovery of strength, return to daily activities or work was noticed between the groups. The cost of the endoscopic technique was higher and more complications were reported in this group, too (Brown *et al.* 1993; Atroshi *et al.* 2006; van den Bekerom *et al.* 2006).

A literature review, the findings of 68 studies of 22,327 cases treated endoscopically and 5,669 treated with an open release (limited and conventional) were analysed to determine post-operative complications. Complications not due to a structural injury such as complex regional pain syndrome, scar hypersensitivity, grip weakness, incomplete symptom resolution, pain due to perineural adhesion to the local scar leading to gradually increasing disabling pain, tendon dislocation over the hook of the hamate, pillar pain and wound healing problems were excluded. The authors reported the prevalence of nerve injury (palmer cutaneous nerve of the palm, motor branch of the median nerve, median nerve, ulnar nerve and digital nerve), tendon injury (partial or complete) and arterial arch injury (Table 1.1). This indicates that the complication rate in open and endoscopic CTR is very low but the endoscopic approach carries a significantly higher risk ($p < 0.005$) due to limited visibility and inadequate experience (Braun *et al.* 2002).

Complication	Open CTR	Endoscopic CTR
Transient neurapraxia	0.25%	1.45%
Major nerve injury	0.1%	0.13%
Digital nerve injury	0.39%	0.03%
Tendon injury	0%	0.008%
Arterial arch injury	0%	0.02%
Overall complication rate	0.74%	1.63%

Table 1.1 Complications of CTR

Recurrence or failure rates varied from 1-25% and symptoms persisted following re-do surgery in 25-95% of the subjects (Braun *et al.* 2002; Steyers 2002).

Patients with CTS have an isolated insult to the median nerve within the carpal tunnel. As discussed before, this is associated with a group of autonomic symptoms that have also been described following hand injury. There is no evidence to suggest the symptoms relate to a specific injury. The following review presents the current views concerning post-traumatic cold intolerance and its pathophysiology.

1.2 POST-TRAUMATIC COLD INTOLERANCE (PTCI)

Cold intolerance is a common problem in the injured hand with significant consequences for a patient's work and leisure activities. Many patients consider it the most disabling outcome from their hand injury (Lithell *et al.* 1997). Attempts have been made to unveil the underlying pathophysiology and tailor treatment accordingly, but the cause of cold intolerance remains uncertain. In this paper we review the available literature.

1.2.1 Definition

The selection of a satisfactory working definition has been challenging; this has led to inconsistency in case reporting and follow-up. "An icy cold feeling that can progress to pain sometimes lasting for several hours following cold exposure" is an early attempt to define the condition (Engkvist *et al.* 1985). However, this definition did not extend to cover the varied spectrum of symptoms including stiffness and colour changes, which meant a proportion of sufferers were missed (Lithell *et al.* 1997). Other definitions were proposed such as "An exaggerated or abnormal reaction to cold exposure of the injured part causing discomfort or the avoidance of cold" (Kay 1985), "Symptoms triggered by exposure to cold and represent discomfort or problems that are perceived by the patient as a sequel to their hand injury" (Lithell *et al.* 1997), and a "collection

of acquired symptoms resulting in an abnormal aversion to cold" (Campbell *et al.* 1998).

Although the majority of the studies continue to refer to cold intolerance as such (Freedlander 1986), various alternative terms have been used; cold sensitivity (Nylander *et al.* 1987), cold hypersensitivity (Craigen *et al.* 1999), and finally "trauma induced cold associated Symptoms (TICAS)" (Campbell *et al.* 1998). In this review we opt to refer to this syndrome as Post-Traumatic Cold Intolerance (PTCI); this term reflects the causation (trauma), the trigger (cold) and generally describes the reaction to cold (intolerance).

1.2.2 Clinical presentation

In broad terms cold-related symptoms fall into four main groups: 1- Pain/ discomfort, 2- Altered sensation, 3- Stiffness, 4- Colour changes (Campbell *et al.* 1998). In a review of 128 subjects complaining of cold-related symptoms post-hand injury, pain was the most prevalent symptom, affecting 77%, followed by stiffness in 60% and colour changes and sensory symptoms in around 50% of the subjects (Campbell *et al.* 1998). In 398 patients, Irwin *et al*. reported numbness and stiffness as being most prevalent followed by weakness, pain and colour changes. Proximal radiation was noted as far as the wrist (but not more proximally) in 33% of cases (Irwin *et al.* 1997).

The effects of the syndrome are significant and far reaching, forcing changes in habits, hobbies and even work (Backman *et al.* 1993; Collins *et al.* 1996). Although the incidence of medico legal complaints due to PTCI is not well reported in the published literature, it is thought that those who complain run a more severe course (Koman *et al.* 1998).

1.2.3 Pathophysiology

The pathogenesis of PTCI remains unclear. Educated hypotheses based on vascular and neurological assessment of the effected suggest a multi-factorial origin.

The hypothesis of reduced digital perfusion following hand injury was first investigated by Porter *et al*. using Doppler digital flowmetery (Porter 1968). Using digital pulse pressure, Gelberman *et al*. demonstrated that values less than 75% in the injured digit, compared to the corresponding digit in the contra-lateral hand, are associated with more severe symptoms while the symptoms were milder with values >80% (Gelberman *et al.* 1978). A low digital baseline temperature (<2.2±1.9°C compared to the unaffected side) was also reported in patients suffering from PTCI (Engkvist *et al.* 1985).

Two-digital-artery re-anastomosis was reported to positively correlate with reduced symptoms in a review of 100 digital replantation or revascularisation cases but the development of cold intolerance was felt to be due to both arterial and neural impairment (Morrison *et al.* 1978). Using a cold challenge and pulp temperature measurement aided by thermocouples on 14 patients following digital revascularisation or replantation, Kay found no correlation between the digital re-warming time (an indirect indicator of perfusion) and symptom severity (using a questionnaire). In his study, Kay identified patients with better sensory recovery to be mildly affected and vice versa suggesting a defect in local blood flow neuro-regulation but his conclusions were based on a small sample size with varied injury severity (Kay 1985).

Based on a prolonged response (symptoms free >12 months) to an IV guanethidine block (a sympathetic blocking drug that reduces the release of catecholamines) in nine out of 24 patients with intolerance to cold after partial or

complete finger amputations, and based on a transient elevation in a temperature of 2.7±2.1°C above the corresponding area on the uninjured hand with a significant symptomatic improvement even after the return to baseline temperature 2-4 weeks in all participants, Engkvist *et al*. speculated that neurogenic rather than vascular dysfunction is mainly behind PTCI. The author suggested that cold-related symptoms are due to either a direct neuronal sensitivity to cold or indirectly through hypersensitivity to a normally increased noradrenalin following cold exposure. Earlier findings suggest neuronal sensitivity to mechanical stimuli and noradrenalin (Wall *et al.* 1974; Engkvist *et al.* 1985). Other studies have shown that two-point discrimination does not correlate with the severity of the symptoms in PTCI patients (Freedlander 1986; Nylander *et al.* 1987; Lenoble *et al.* 1990; Backman *et al.* 1991). The cause of this is unknown but a possible hypothesis would be an all or nothing effect of trauma on the damaged neural ends with resultant cold intolerance independent of the extent of the nerve damage sustained.

Multiple limitations in studies touching on the underlying mechanisms in PTCI are obvious: small sample size, retrospective, non-specific assessment technique or a combination of these factors. We still understand very little about PTCI pathogenesis. In recent years, the utility and reproducibility of laser Doppler techniques have improved considerably. Our own work has shown that laser Doppler fluximetry, combined with trans-cutaneous iontophoretic administration of endothelial-dependent and -independent vasodilators (acetylcholine and sodium nitroprusside, respectively), provides a reproducible, non-invasive method for exploring cutaneous microvascular dysfunction in diverse clinical conditions ranging from pre-eclampsia to diabetes and peripheral arterial disease (Davis *et al.* 2001; Klonizakis *et al.* 2003; Klonizakis *et al.* 2006). These techniques provide new opportunities to study the regulation of cutaneous microvessels in the hand following injury, and to assess the vascular effects of local or systemic interventions.

1.2.4 Incidence and natural history of PTCI

The lack of a specific definition led to a wide range for the prevalence reported (50-100%), although >70% is generally accepted (Table 1.2). There is agreement on the early onset of this condition (Backman *et al.* 1991; Backman *et al.* 1993; Lithell *et al.* 1997; Craigen *et al.* 1999). In a study of 65 patients, more than 50% of the patients developed cold intolerance immediately after injury, with a further 39% developing symptoms within six months of the injury (Nancarrow *et al.* 1996). A review of 331 patients with hand injuries reported a PTCI prevalence of 83% with 90% of those affected developing symptoms within the first six months of injury and 35% developing the symptoms immediately post-trauma (Irwin *et al.* 1997). Predictors of PTCI development are listed in Table 1.3.

Study	Sample size	Study type	Injury reviewed	Reported PTCI Incidence	Mean follow-up period
(Gelberman *et al.* 1978)	29	Prospective	Digital replantation for a complete amputation	100%	Not given
(Morrison *et al.* 1978)	100	Retrospective	Digital replantation and revascularisation	100%	NA
(Poppen *et al.* 1983)	10	Prospective	Great toe to thumb transfer	100%	42 months
(Earley *et al.* 1984)	14	Prospective	Thumb replantation	71%	Not given
(Kay 1985)	14	Prospective	Digital replantation and revascularisation	73%	33 months
(Tark *et al.* 1989)	153	Retrospective	Digital replantation and revascularisation	100%	NA
(Lenoble *et al.* 1990)	82	Prospective	Ulnar and median nerve injury	75% post-ulnar injury 50% post-median injury	42 months
(Povlsen *et al.* 1995)	8	Prospective	Digital replantation	5 patients	12 years
(Nancarrow *et al.* 1996)	65	Prospective	Hand injury requiring surgical intervention	65%	5.8 years
(Lithell *et al.* 1997)	40	Retrospective	Digital trauma	100%	NA
(Irwin *et al.* 1997)	398	Retrospective	Upper limb peripheral nerve injury	83%	NA
(Campbell *et al.* 1998)	167	Prospective	Hand injury (non specific)	73%	24 months
(Koman *et al.* 1998)	261	Retrospective	Hand injury (non specific)	62%	NA
(Craigen *et al.* 1999)	123	Prospective	Hand injury (non specific)	85%	11 months, 3 years for severe cases

Table 1.2 The incidence of PTCI

Predictors of cold intolerance development	
Positive predictors	Factors related but with no predictive value
Crush injuries	Age
Sex (more in females) (Koman *et al.* 1998)	Sex (Irwin *et al.* 1997)
Smoking (current)	Site of the injury in the hand
More distal injuries	Number of nerves injured
Severe post-operative pain (Nancarrow *et al.* 1996)	Associated fracture in the hand
	Grade of the surgeon
	Type of repair

Table 1.3 Predictors of PTCI development.

1.2.5 Nature and severity of symptoms

Factors affecting the severity of PTCI can be classified into patient-related, injury-related and management-related.

Patient-related factors

1- Age: there is no uniformity on its effect. Age had no influence on the severity of the disease in some studies (Porter 1968; Irwin *et al.* 1997). Others observed more severe symptoms in those older than 35 years (Schlenker *et al.* 1980).

2- The psychological susceptibility. Nancarrow *et al*. hypothesised that, in susceptible patients and those who continue to experience post-operative pain, the vaso-constrictive reflex is severe and prolonged leading to chronic pain, which was described by the author as a continuous process of perception and response influenced by psychological factors (Nancarrow *et al.* 1996).

3- Current smoking increases the severity of the symptoms (Irwin *et al.* 1997). The symptoms intensify as the pre-existing pathological vasospasm is accentuated by further reduction in the peripheral blood

flow after smoking (Mosely *et al.* 1977; van Adrichem *et al.* 1992; Backman *et al.* 1993; Monfrecola *et al.* 1998).

4- An ongoing compensation claim (Koman *et al.* 1998).

Gender and hand dominance have no bearing on the severity of the symptoms.

Injury-related factors

Retrospective studies of upper limb peripheral nerve injuries have shown the following to be associated with worse symptoms: complete nerve division, presence of a vessel injury and an associated fracture (Irwin *et al.* 1997; Koman *et al.* 1998). The mechanism of injury (sharp or crush) has no bearing on the severity of the symptoms.

Management-related factors

Patients with both the digital arteries repaired in replantation cases are less affected by cold-related symptoms post-operatively compared to those with a single arterial repair (Morrison *et al.* 1978; Freedlander 1986; Tark *et al.* 1989). The number of injuries to any single nerve does not affect outcome, nor does the number of nerves injured, the type of surgical repair, the grade of the surgeon or the time of repair after the injury (Nystrom *et al.* 1991; Irwin *et al.* 1997).

1.2.6 Symptom scoring systems

Cold intolerance is difficult to score or measure objectively (Koman *et al.* 1998). However, there have been attempts to score this condition.

1 – Kay's numerical cold intolerance score (Kay 1985)

Based on a questionnaire with points awarded for the following:

A- the presence of any of the main four symptoms (pain, numbness, stiffness and loss of function)

B- the degree of avoidance of cold exposure

C- the degree to which the patient's activities and work are affected by the symptoms

D- the patient's own assessment of the severity of their symptoms.

Neither the text of the questionnaire nor evidence of validation was provided by the author. The maximum possible score was 22.

2 – Cold sensitivity scale (McCabe et al. 1991)

Designed to reflect the patient's subjective grading of the disability caused by cold exposure in given situations. To eliminate the variability of presentation between the patients, direct symptom-specific questions were avoided. Questions targeted cold-related scenarios, which were divided into two scales:

1- the cold sensitivity severity scale.

2- potential work exposure scale.

The items were selected from circumstances that patients commonly felt provoked cold-induced symptoms in their hands. The response to each item was obtained by marking a 100 mm line to reflect the severity of the symptom in a manner similar to a visual analogue scale. The sum of the scores in each subscale in millimetres gives the corresponding final score for that scale. The test/re-test correlation coefficient for the Cold Sensitivity Severity Scale was reported at 0.92 and for the potential work exposure scale at 0.94. The authors presented a statistically significant difference in the score between the nerve-injured patients and the control group with mean values of 171 and 80 respectively.

3 – Blond McIndoe Cold Intolerance Symptom Severity (CISS) Score (Irwin et al. 1997)

This is a modification on the cold sensitivity scale, designed to provide more information on a wide range of symptoms and stratify the frequency and persistence of symptoms and how they disturb daily activities.

The maximum score is 100 grouped into four ranges (0-25, 26-50, 51-75, 76-100) corresponding to mild, moderate, severe, and extreme severity respectively. A score/re-score correlation coefficient of CISS for 26 subjects completed six months apart was reported as 0.90 and a mean difference between scores of 0.48 (SD=11.4). No information on validation was provided but the severity score corresponded well to the patient's subjective assessment of the symptoms, particularly in the severe and extreme groups.

1.2.7 Resolution

The variability in the follow-up duration, subjectivity of severity assessment and variability in symptoms considered related to PTCI yielded variation in resolution observations. Short- to medium-term studies (up to five years follow-up) revealed only partial improvement (less pain) in less than one-fifth of the sufferers while the majority continued to have the same symptoms and 2% were getting worse (Gelberman *et al.* 1978; Freedlander 1986; Backman *et al.* 1993; Nancarrow *et al.* 1996). Long-term follow-up studies varied from no improvement at 12 years follow-up (Povlsen *et al.* 1995), partial improvement with time (Kleinert *et al.* 1980), and an up to 63% complete resolution at 10 years (Matsuda *et al.* 1999).

The most important predictors of improvement were reported as the Blond McIndoe Cold Intolerance Symptom Severity (CISS) Score and the smoking

status of the patient (i.e. the higher the score, the worse the prognosis and that smoking adversely affects the clinical course of the condition) (Irwin *et al.* 1997).

1.2.8 Treatment

Cold evasion appears to be the most practical way to manage PTCI, although this is not always possible. Conservative modalities and surgical techniques (sympathectomy) have been described with limited success. It is worth considering different approaches to potential medical therapy, and in particular how these treatments might be evaluated in placebo-controlled studies in PTCI.

1.2.8.1 Vasodilator therapies

Drugs which relax vascular smooth muscle in medium-large arteries and arterioles, especially the resistance vessels that are important determinants of systemic BP, have been tried with varying success in PTCI. For example, α-Blockers have been used to enhance the digital blood flow with limited or no effect (Nylander *et al.* 1987; Isogai *et al.* 2004). Similarly, the calcium channel blocker nifedipine has been shown to effectively reduce the frequency and severity of symptoms in Raynaud's phenomenon (Smith *et al.* 1982), but no studies have yet assessed calcium antagonists in PTCI. In a controlled double blind trial, nifedipine was shown not to affect the skin temperature recovery time (Rodeheffer *et al.* 1983). The role of other vasodilators is unknown: in particular blockade of the renin-angiotensin system using angiotensin converting enzyme inhibitors (ACIs) or angiotensin receptor antagonists (ARAs) is associated with non-BP-dependent vascular effects, including improved microvascular function (e.g. in the kidney & retina), which could be useful in patients with PTCI. Randomised trials are needed.

In future clinical studies, apart from evaluating symptoms, it would be useful to monitor the effects of vasodilators on large and small vessels in the hand using

newer non-invasive techniques such as laser Doppler fluximetry and pulse wave analysis. These techniques are now available, more reproducible and less operator-dependent, but few if any studies have applied the methodologies to study the hand.

1.2.8.2 Antiplatelet therapies

Platelet activation and aggregation in response to vascular injury plays an important role in microangiopathic complications, which prompts interesting hypotheses about whether aspirin or clopidogrel might improve microvascular cutaneous perfusion in PTCI.

1.2.8.3 Sympathetic nervous system blockade

In general, beta-adrenoceptor antagonists have an adverse effect on peripheral blood flow, but these drugs, in theory, may have beneficial effects in attenuating sympathetic nervous system pathways involved in arterio-venous shunting and cutaneous vasoconstriction. Newer beta blockers with vasodilator properties, e.g. carvedilol, offer a pharmacological profile which, theoretically, could improve some of the vascular mechanisms which are known to control skin blood flow and cutaneous responses to temperature change.

1.2.8.4 Prostacyclin analogues

Beraprost has been studied in 11 patients affected by cold intolerance at a dose of 60 μg three times daily for two weeks with a significant reduction in symptom severity in nine patients and no side effects. Beraprost elevated the skin temperature in eight of the cases (Isogai *et al.* 2004). The authors suggested that failure to respond to beraprost indicates that poor vascular flow is unlikely to be the cause of the symptoms in that particular case and that the mechanism might be related to a sympathetic dysfunction, psychological trauma due to the injury or the patient's personality. For resistant cases the authors suggested the use of nerve blocks, antidepressants or anxiolytics. They also expressed the

opinion that long-term therapy with beraprost may be useful in some patients with gradual dose reduction. No evidence to support the long-term usefulness of beraprost in such cases has been reported in the literature.

1.2.8.5 Regional neuronal block

Guanethidine intravenous regional blocks have been used to treat this condition; 20 mg of guanethidine are diluted in 40 ml of saline and injected over a minute through a vein on the dorsum of the hand after occlusion of the circulation with a tourniquet applied to the upper arm. Tourniquet pressure is maintained 50 mmHg above the systolic blood pressure and the tourniquet released after 20 minutes. Such blocks have been used with only limited short-term success (one-third of 20 patients showed symptomatic relief two to 12 weeks post-block). However some patients can be kept relatively symptom free during the cold season with repeated blocks (Engkvist *et al.* 1985).

1.2.8.6 Psychological interventions in symptom management

Success in using biofeedback, autogenic training and classical conditioning in the management of patients with Raynaud's phenomenon inspired the use of classical conditioning in the treatment of post-traumatic cold intolerance with encouraging results (Jobe *et al.* 1985; Jobe *et al.* 1986). In a small study of 10 patients, classical conditioning improved the symptoms in eight subjects and improved baseline temperature difference between the affected digits and the corresponding contralateral uninjured from 1.5°C to 0.1°C (Brown *et al.* 1986).

1.2.8.7 Surgical interventions

Surgical intervention to treat severe forms of Raynaud's phenomenon (RP) and scleroderma (SSc) has been described (Egloff *et al.* 1983; Ward *et al.* 1995). Although cervical sympathectomy was often unsuccessful due to the incomplete sympathetic denervation of the hand (Wilgis 1981), the selective digital approach is effective in preventing digital amputation due to severe ischemia in

this group of patients (RP, SSC) (McCall *et al.* 1999). There are no studies describing the use of digital sympathectomy in the treatment of PTCI. Hussel *et al*. described single digit treatment in four patients using a 12 cm thoracodorsal vascular bundle implanted microsurgically through an end-to-side proximal anastomosis with the radial artery in the radial fossa, passing the graft subcutaneously to reach the tip of the injured digit where its end is covered by a split skin graft. Details of the technique and the extent of improvement in the other digits after surgery was not described (Hussel *et al.* 1989). Repair of the two digital arteries and adequate post-operative pain management are associated with better PTCI symptom (Fagius *et al.* 1985; Tark *et al.* 1989; Isogai *et al.* 2004).

In conclusion, cold intolerance remains a significant problem after hand injury with its effects touching various aspects of the patient's life. The precise cause remains uncertain although a mixed neurovascular pathophysiology is thought likely. More vigorous studies are needed to help understand the exact nature of this problem. Adjustments to lifestyle can be very helpful in controlling symptoms. Biofeedback, conditioning and some pharmacological agents have been found to offer some additional benefits. Surgical intervention is unlikely to be helpful.

1.3 RAYNAUD'S PHENOMENON (RP)

Raynaud's Phenomenon (RP) describes a recurrent exacerbated vasospastic response to cold or emotional strain, mainly affecting the hands and feet while the nose, ears and even the nipples can be affected (Block *et al.* 2001; Wigley 2002). This response presents clinically as skin colour changes (white – ischemia, blue – deoxygenation, then red or crimson – reperfusion) associated with discomfort or pain in the affected part and numbness and tingling (Bowling *et al.* 2003) (Figure 1.4).

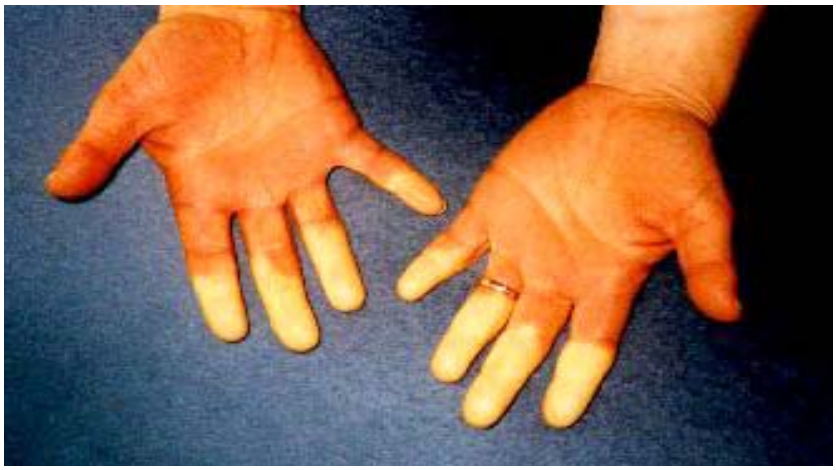


Figure 1.4 RP affecting both hands

1.3.1 Classification

The disease is classified into primary and secondary based on the presence of an underlying cause.

1.3.1.1 Primary RP (Disease, Idiopathic RP)

This form has an early age of onset (i.e. 2nd and 3rd decades), a milder course and a stronger female preponderance (Wigley 2002). The diagnosis is usually made on clinical grounds (mainly the history and very rarely through findings in examination). Diagnostic criteria include symmetrical attacks, absence of tissue ulceration, necrosis or gangrene, the absence of a secondary cause suggested by the patient's history and general physical examination, normal nail fold capillaries, normal erythrocyte sedimentation rate and negative serological findings, particularly a negative test for antinuclear antibodies (LeRoy *et al.* 1992). If a two-year patient follow-up showed no clinical or laboratory signs of a cause then secondary RP is highly unlikely (Wigley 2002).

A prospective study of a large cohort of patients (1,039 subjects) suffering from RP with a mean follow-up of 3.2 years (including 118 patients with >10 years

follow-up) identified the incidence of progression to develop connective tissue disease in RP based on Nielsen's test (Nielsen *et al.* 1977), plethysmography, digital arterial systolic blood pressure and serology (antinuclear antibodies and rheumatoid factor). The incidence was found to vary between four subgroups of patients: sero-negative spastic RP (2%, 6.3%), sero-positive spastic RP (16%, 33%), sero-negative obstructive RP (8.5%, 18%) and sero-positive obstructive RP (30%, 82%). The above figures are: over all incidence; incidence after 10 years (Landry *et al.* 1996).

1.3.1.2 Secondary RP

This is commonly the consequence of a systemic disease (occurring in 90% of SSc patients, 10-45% of Systemic Lupus Erythamotosis and 10-20% of Rheumatoid Arthritis) but a long list of predisposing factors has been outlined, e.g. mechanical injury, arterial disease, malignancy and infections (Block *et al.* 2001).

This form of RP runs a more aggressive course and those affected are usually over 40 years old. Secondary RP should be suspected if the patient is over 30 years old, suffering from intensely painful asymmetrical symptoms or associated with ischemic skin lesions. The presence of joint pain, stiffness, abnormal lung function tests, abnormal blood tests (inflammatory markers and serology) and evidence of microvascular disease on microscopy of the nail fold capillaries are also suggestive of an underlying cause (Kallenberg *et al.* 1988; Kallenberg 1990; Wigley 2002).

1.3.2 Prevalence

The incidence of RP in the general population is unknown. Prevalence rates range between 1-25% for men and 1.8-30% for women depending on the

population and the geographical regions studied (i.e. more prevalent in colder areas) (Maricq *et al.* 1993; Maricq *et al.* 1997; Fraenkel 2002; Wigley 2002).

Gender seems to be the most consistent risk factor in RP with a female:male ratio of approximately 4:1. A positive association between the family history and RP in women suggests a strong genetical expression of RP in females. Males did not show a similar association (Valter *et al.* 1998). Other observations such as a higher prevalence amongst women between menarche and menopause and a higher post-menopausal incidence in women using unopposed oestrogen replacement therapy suggests that oestrogen might be a significant reason for the skewed ratio towards females (Fraenkel *et al.* 1998; Fraenkel 2002).

A recent study of 720 children aged 12-15 reported an overall 15% prevalence; it also showed RP to be more common in girls (18%) than boys (12%) (Jones *et al.* 2003).

The effect of age, alcohol, smoking and marital status has also been investigated. In a cross-sectional study of 800 women and 725 men participating in the Framingham Offspring Study, the authors reported RP prevalence of 9.6% in women and 5.8% in men. In women, marital status and alcohol use were each associated with prevalent RP (for marital status adjusted odds ratio [AOR] 2.3, 95% confidence interval [95% CI] 1.4-3.9; for alcohol use AOR 2.2, 95% CI 1.0-5.2), whereas these factors were not associated with RP in men (marital status AOR 1.4, 95% CI 0.6-3.5; alcohol use AOR 1.0, 95% CI 0.2-4.4). In men, older age (AOR 2.3, 95% CI 1.0-5.2) and smoking (AOR 2.6, 95% CI 1.1-6.3) were associated with prevalent RP; these factors were not associated with RP in women (older age AOR 0.8, 95% CI 0.4-1.6; smoking AOR 0.7, 95% CI 0.4-1.1). DM, hypertension, and hypercholesterolemia were not associated with RP in either sex (Fraenkel *et al.* 1999).

Both current and ex-smokers were reported to have higher RP prevalence compared to people who never smoked (Fraenkel *et al.* 1999; Palmer *et al.* 2000). The link between smoking, alcohol and RP was not consistently found in the literature (Palesch *et al.* 1999; Voulgari *et al.* 2000). Other risk factors include β-Blockers, Carpal Tunnel Syndrome and Rheumatoid Arthritis (Brand *et al.* 1997).

1.3.3 Pathophysiology of RP

The pathophysiological pathway that leads to microvascular vasospasm in primary RP is unclear. Despite the wealth of research conducted on this process, only proposals for possible mechanisms have been suggested.

1.3.3.1 Central neurogenic factors

A dysfunction in the central sympathetic control of the microvasculature was first proposed by Maurice Raynaud (1862). Studies on the effect of stress (Freedman *et al.* 1983), sympathectomy and sympatholytic drugs (Olsen 1987; Olsen *et al.* 1991) all suggested that a sympathetic over-activity plays a role in the pathogenesis of RP. Whether this is a direct neurogenic effect or an abnormal neurovascular interaction (nerve-vessel wall dysfunction) is unclear (Fagius *et al.* 1985).

1.3.3.2 Local factors

"The Local Fault theory" was suggested as early as 1929 after an aberrant cold-induced vasospasm was noted in patients with RP post-sympathectomy (Lewis 1929). Neurogenic, humeral and endothelial faults have been reported. Nonetheless, the interaction between those factors makes it difficult to differentiate the cause from the effect in most cases (Turton *et al.* 1998).

A. Vascular α- Adrenoceptors

Both α-1 and α-2 receptors mediate the sympathetic response in the skin microcirculation despite a predominance in the effect of the α-2 subtype (Willette *et al.* 1991). An enhanced response to catecholamines is believed to play a role in the pathophysiology of RP through an exaggerated density and/or sensitivity of the α-2 receptors (Freedman *et al.* 1989).

Further work by Freedman *et al*. (1995) demonstrated that it is the activation of the α-2 receptors and not the α-1 adrenergic receptors that is necessary for the production of vasospastic attacks in idiopathic RP (Freedman *et al.* 1995).

B. Calcitonin gene-related peptide (CGRP)

This is a potent vasodilating neuropeptide found in nerve endings of the cutaneous unmylinated sensory neurons (Gibbins *et al.* 1987). Although the systemic levels in the RP patients are not different from the control group (Bunker *et al.* 1996), the favourable response to an IV infusion of CGRP on the hands of patients with RP suggests a local deficiency in those patients (Shawket *et al.* 1989).

C. Endothelin-1

This is a potent endothelial-derived vasoconstrictor (Turton *et al.* 1998). It has been shown that baseline and post-cold provocation measurements of endothelin-1 were elevated and continued to be elevated in patients with RP suggesting a role in the aetiology (Zamora *et al.* 1990; Biondi *et al.* 1991). Although the agreement on the role of endothelin-1 is not universally accepted (Bottomley *et al.* 1994), it is better considered as a marker of endothelial damage (Mangiafico *et al.* 1996).

D. Oestrogen

It is thought that oestrogen may sensitise the peripheral vascular bed to endogenous circulating vasoconstriction catecholamines – this may explain the 4:1 predominance of RP in females (Altura 1975).

E. Nitric Oxide (NO)

The vasodilatory ability is reduced in response to acetylcholine and nitroprusside in RP (Khan *et al.* 1997). The production of NO is also believed to be suboptimal in RP patients (Khan *et al.* 1994).

1.3.3.3 Blood cell-related factors

A. Neutrophils

In both primary and secondary RP, evidence exists suggesting an abnormal White Blood Cell (WBC) activation and a pathological release of free radicals (Lau *et al.* 1992a; Lau *et al.* 1992b). Cold exposure is thought to activate the neutrophils during the vasospastic attack in RP leading to increased neutrophilic-endothelial adhesion (Ciuffetti *et al.* 1995).

B. Platelets

An exaggerated expression of α-2 receptors on the platelets, mirroring a similar increase on the endothelium is thought to be the cause of the abnormal platelet aggregation and mediator release leading to vasoconstriction and increased permeability in patients with RP (Ikehata *et al.* 1980; Turton *et al.* 1998). This is magnified by the blunted responsiveness of the platelets to inhibiting factors such as prostacyclin and prostaglandin E1 (Hutton *et al.* 1984).

1.4 HAND ARM VIBRATION SYNDROME (HAVS)

The high incidence of RP in vibrating tool operators was first reported by Loriga (Loriga 1911). Seven years later, a direct link between RP and vibration as a

cause was suggested (Hamilton 1918). As the understanding of the multi-systemic nature of the condition grew, the term 'vibration white finger' (VWF) was replaced by a more representative name (Hand Arm Vibration Syndrome (HAVS)) in 1985. More importantly, and in the same year, HAVS became a prescribed disease for which sufferers can claim compensation (HMSO 1985; Taylor 1985).

1.4.1 Prevalence

According to a cross-sectional study published in 2000, it is estimated that vibration exposure is responsible for extensive blanching affecting at least eight digits or 15 phalanxes in about 222,000 cases in the UK (McGeoch *et al.* 2000), with approximately 100,000 of those claiming compensation (McGeoch *et al.* 2005).

The ratio between male and female is unclear but the causation (prolonged exposure to vibration mainly through work) tips the balance in favour of a male majority amongst the affected.

1.4.2 Patient assessment and diagnosis

Both subjective and objective methods of assessment and diagnosis have been described but confirming the diagnosis is difficult and very subjective (Lawson *et al.* 2003; McGeoch *et al.* 2005). A medical assessment process was created to aid in the diagnosis of HAVS and was implemented in all the assessment centres in the UK. The process included the following.

A- A questionnaire to ascertain the history of exposure to hand arm vibration followed by a questionnaire regarding any history of symptoms of HAVS (subjective tool).

B- A questionnaire to help with the differential diagnosis and the detection of any dual pathology (subjective tool).

C- Upper limb and neck examination to exclude other mimicking clinical condition.

D- Staging using the Stockholm Workshop Scales (SWS) (Brammer *et al.* 1987) (Table 1.4) (subjective tool).

E- Five standardised tests for both the sensorineural (SN) and vascular (V) disease components (objective tool).

- Sensorineural component assessment tests

    1- Vibrotactile perception threshold test (VPT)

    2- Thermal aesthesiometry (TA)

    3- Purdue pegboard test (PPT)

    4- Grip strength using a Jamar Dynamometer

- Vascular component assessment test

    5- Cold provocation testing (CPT)

The standardised tests outcome is scored (Table 1.4) and the scores are incorporated within the modified SWS.

Modification Of The Neurological Component Of The Stockholm Workshop Scales	
Stage	Criteria
0 SN	Vibration exposure but no symptoms
1 SN	Intermittent numbness and/or tingling with a sensorineural score of ≥3<6
2 SN (Early)	Intermittent or persistent numbness, and/or tingling, reduced sensory perception with a score of ≥6<9
2 SN (Late)	As 2 SN (Early) but with a score of ≥9<16
3 SN	Intermittent or persistent numbness, and/or tingling, reduced manual dexterity and an SN score of ≥19
Modification of the vascular component of the SWS	
Stage	Criteria
0V	No attacks
1V	Attacks only affecting the tips of the distal phalanges of one or more fingers – usually a blanching score of 1-4
2V	Occasional attacks of whiteness affecting the distal and middle (rarely also the proximal) phalanges of one or more fingers – usually a blanching score of 5-16
3V	Frequent attacks of whiteness affecting all the phalanges of most of the fingers – usually a blanching score of 18 or more
4V	As 3V and trophic changes

Table 1.4 The Modified Stockholm Workshop Scales (SWS) (McGeoch *et al.* 2005)

Scoring system used for the standardised tests				
VPT (index and little finger)	31.4 Hz	<0.3 ms² = 0	≥0.3 ms², <0.4 ms² = 1	≥0.4 ms² = 2
	125 Hz	<0.7 ms² = 0	≥0.7 ms², <1.0 ms² = 1	≥1.0 ms² = 2
TA 1ºC/s (index and Little finger)		<21ºC = 0	≥21ºC, <27ºC = 2	≥27ºC = 4
CPT (15ºC for 5 min, 10 min recovery)		*T*(+4º) ≤300 s = 0	>300 s, ≤600 s = 1	>600 s = 2

Table 1.5 Scoring system used for the standardised tests

In a cross-sectional study of 165 workers exposed to vibration for a mean of 23 years (range 3-47) investigating the correlation between the subjective assessment (i.e. SWS) and the objective tests, the authors reported a significant ($p < 0.001$) correlation between the SWS neurological stage and the findings of the neurological tests but could not demonstrate a correlation between the vascular stage and the CPT findings (McGeoch *et al.* 2000). In this study the overall prevalence of neurological findings of 62% was greater than the overall prevalence of vascular findings, which was 33%. Findings confirming the limited value of the CPT in the diagnosis of HAVS was also reported on review of approximately 20,000 CPT tests done through the Department of Trade and Industry scheme for the evaluation of miners (Proud *et al.* 2003b). Based on the above, the diagnosis of HAVS is largely subjective and unreliable due to the complicating expected financial gain.

Of note is the incorporation of the sensorineural score in the modified SWS within the neurological part while using a "blanching score" (Rigby *et al.* 1984) within the vascular part instead of the CPT score. This obviously creates an inbuilt bias within the score and may explain the significant correlation in the sensorineural examination and the SWS findings.

1.4.3 Pathology

Three major findings were noticed in finger biopsies from patients suffering from the condition (Takeuchi *et al.* 1986):

[I] intense thickening of the arterial muscular wall with individual cell hypertrophy;

[II] peripheral demyelination neuropathy with increased numbers of Schwann cells and fibroblasts;

[III] increased amounts of connective tissue causing perineural and perivascular fibrosis.

1.4.4 Pathophysiology

The causation remains unclear; generally speaking it can be divided into neural, vascular and cellular factors with some similarities to RP.

1.4.4.1 Neural factors

A- Autonomic dysfunction

It is thought that patients with HAVS have an increased sympathetic tone and/ or reduced parasympathetic function probably due to Pacinian corpuscle over stimulation (Bovenzi 1986).

It is interesting to note that long-lasting vibration exposure was found to provoke central sympathetic vasoconstrictor reflex mechanisms, which trigger primarily episodic arterial closure typical of HAVS (Olsen 1990).

B- Receptor and nerve ending dysfunction

Immunohistochemistry testing of skin biopsies obtained from patients exposed to vibration demonstrated that vibration exposure damages the local nerve endings, particularly the digital cutaneous perivascular nerves which contain neuropeptides with powerful vasodilator properties, i.e. CGRP (Goldsmith *et al.* 1994; Bunker *et al.* 1996).

Pyykko and Gemne (1987) described an aberrant vasoconstriction in response to cold in patients with HAVS secondary to excessive affinity of the efferent receptors to substances potentiated by cooling (Pyykko *et al.* 1987). Using iontophoresis and laser Doppler imaging, Ekenvall and Lindblad (1986) demonstrated an adrenoceptor imbalance in response to noradrenaline (stimulating both α-1 and α-2 receptors), phenylephrine (an α-1 stimulator) and B-HT 933 (an α-2 stimulator) with evidence suggesting α-1 adrenoceptor

dysfunction and predominance in the α-2 receptors in the digital arteries (Ekenvall *et al.* 1986). Similar findings were reported in RP (Section 1.3.3.2).

1.4.4.2 Vascular factors

A- Endothelial damage

The vascular response to methacholine (an endothelium-dependent vasodilator) was found to be reduced when measured by laser Doppler imaging (Taccola *et al.* 1998; Stoyneva *et al.* 2003). To support this, thrombomodulin plasma levels were found to be elevated in the symptomatic and asymptomatic vibration-exposed individuals (Kanazuka *et al.* 1996).

B- Endothelial dysregulation

The serum concentration of Endothelin-1 (a potent endothelial-derived vasoconstrictor) was found to be elevated in symptomatic HAVS patients (Toibana *et al.* 1995) compared to vibration-exposed asymptomatic individuals (Palmer *et al.* 1996). Nonetheless, an increase in the serum concentration of Endothelin-1 has been noted after cold challenge testing in the asymptomatic vibration-exposed individuals (Taccola *et al.* 1991; Stoyneva *et al.* 2003).

It seems likely that Endothelin-1 concentration is a reflection of symptom severity, being highest amongst the most symptomatic (Kohout *et al.* 1995). On the other hand it might merely be a marker of endothelial damage (Mangiafico *et al.* 1996).

It is thought that the increase in the Endothelin-1 concentration creates an imbalance with the CGRP resulting in the inhibition of the Nitric Oxide (NO) myo-relaxing effect on the smooth muscles (Stoyneva *et al.* 2003). This results in an accentuation of the Endothelin-1 vasospastic properties (Noel 2000).

1.4.4.3 Cellular activation

The endothelial damage consequent to the mechanical trauma and shear stress will result in leukocyte and platelet activation with consequences similar to those mentioned in the pathophysiology of primary RP (Bovenzi *et al.* 1983; Jen *et al.* 1984). Leukocytes are thought to play a role in the microvascular damage in patients with HAVS as it was found that the production of Leukotriene B4 – a pro-inflammatory product – and free radicals is increased (Lau *et al.* 1992b; Stoyneva *et al.* 2003).

1.5 LASER DOPPLER PERFUSION IMAGING (LDI)

The skin's microvascular blood supply is part of the thermoregulatory control system in the body and might play a role in the local cold-induced peripheral symptoms in patients with RP, HAVS and PTCI. The proposed vascular dysfunction was further non-invasively studied using laser Doppler techniques. The use of a laser emitting device to asses the skin microcirculation is by no means a novel idea (Stern 1975). Blood flow was measured under a single spot of skin defined by the incident and Doppler shifted reflected light – Laser Doppler Flowmetry (LDF); this represented an in situ sample of about 1 mm^3 (Holloway *et al.* 1977). Nevertheless, major site variation in blood flow recording with single spot devices was noticed and three or more measurements were often required to obtain an average estimate of the cutaneous blood flow (Bircher *et al.* 1994).

To evaluate the cutaneous perfusion, it is important to realise that not only a temporal variability exists but a spatial one as well; this is a reflection of the heterogeneity of the cutaneous microvascular network with arteriovenous anastomosis in some areas and capillaries in others (Nilsson 1997). The temporal changes can be assessed by continuous measurement using LDF but the spatial changes cannot be reliably assessed. This is due to the localised

nature of the test flow signal and the gross variability in the microvascular bed which effectively makes inter- and intra-individual comparison meaningless (Obeid *et al.* 1990).

LDI is a relatively new technology (Essex *et al.* 1991) described as "a non-contact system with a laser beam position controlled in the X and Y axes by a system of mirrors, in which a digital image composed of numerous single point recordings form a two dimensional flow map of the blood flow variability over an extended skin surface" (Fullerton *et al.* 2002). Its advantage is the ability to acquire a number of measurements to be taken at different sites almost in real time, a characteristic that takes the spatial changes in the microvascular flow variability into account (Svedman *et al.* 1998).

1.5.1 The technology

The concept rests on the idea that a laser beam scans the tissue step-wise by means of a computer-controlled mirror system around two perpendicular axes allowing the scanning of a square area. The system is housed in a camera-like scanner head positioned 10-30 cm above the tissue surface. The laser beam generated is a low power (1 mV) helium-neon red laser with a wavelength of 632.8 nm forming a light spot with a diameter of about 1 mm^2 (Fullerton *et al.* 2002).

The surface scanned can range from 1 mm^2 to a maximum of approximately 144 cm^2 scanned in about 5 minutes containing 4,069 measurement points in the processes. The laser beam generated penetrates the skin variably to a depth of 0.6mm (Anderson *et al.* 1981). The gradually decreasing sensitivity with depth reduces the sampling volume to be probed in a non-uniform manner with an average measurement depth of 0.3 mm (Jakobsson *et al.* 1993).

The back scattered light, partly Doppler shifted – by the moving red blood cells- along with the non-Doppler shifted light reflecting from the static tissue is gathered by a detector in the scanner head where both shifted and non-shifted light is transformed into a photocurrent.

The frequency of the photocurrent relates to the average speed of the moving red blood cells (RBCs), while the magnitude is determined by the number of moving blood cells within the scattering volume (Fullerton *et al.* 2002). This process is done on each scanned point before the beam is sequentially moved step by step to cover a predetermined area.

The data are then displayed as a colour-coded perfusion image of the spatial distribution of the microvascular blood flow accompanied by a black and white photo image. The total flow can then be calculated by using pixel values in a specified area of interest within the scanned area using the software provided with the device (Figure 1.5).

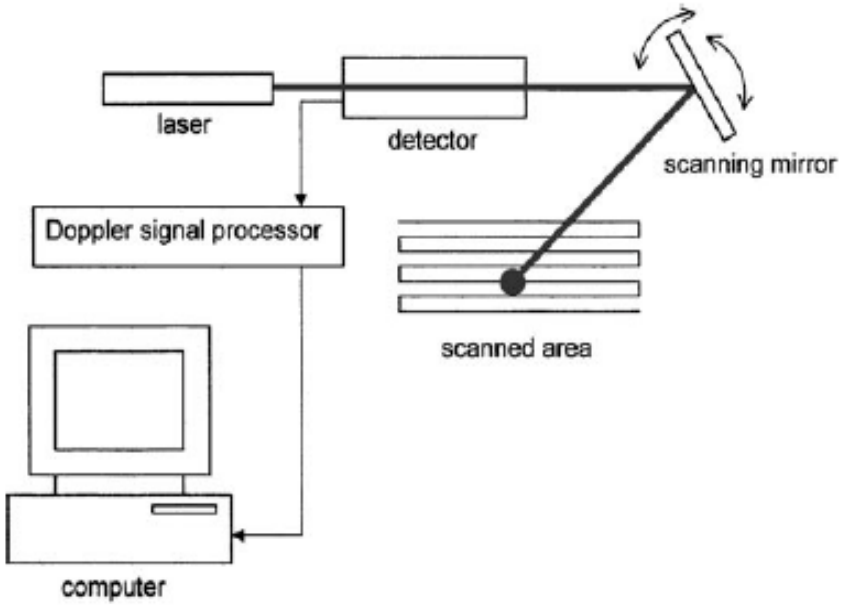


Figure 1.5 The LDI apparatus

1.5.2 Factors affecting measurement by LDI

Increasing the height of the scanner was shown to increase the LDI output both in vivo and in vitro. Although the manufacturer suggests a scanner head – tissue distance of 15 cm (Fullerton *et al.* 2002), no reason was given for this recommendation but at this level a good linear velocity response is maintained up to a rate of 3 mm/sec (Kernick *et al.* 2000).

A non-linear reduction in the LDI signal was observed with the increase in the skin thickness. This observation led to the conclusion that the technique is more sensitive to changes in the superficial blood flow as the sensitivity to changes in the flow will decrease exponentially as a function of the vascular depth.

It was found that increasing the RBC concentration increased the LDI output. This observation, however, demonstrated evidence of linearity between the LDI output and red cell velocity over a low heamatocrit of up to 1%. As the heamatocrit increased, the linearity was lost at lower velocities due to the multiple scattering that occurs at higher RBC concentrations (Kernick *et al.* 2000).

1.5.3 Advantages of LDI

The ability to measure the flow in up to 4,096 points in a single scan minimises the importance of point-to-point variability and gives greater confidence in comparing differences observed between one patient and the other (Fullerton *et al.* 2002). Another advantage is that the characteristics of the blood flow map are consistent from day to day and the relative difference between the spots generally persists (Nilsson 1997). Furthermore, the reproducibility of measurement at the same site on different days was significantly repeatable when tested in the forearm (Morris *et al.* 1996; Kubli *et al.* 2000) and gaiter area

(Klonizakis *et al.* 2003). The authors reported a small mean coefficient of variation values between the two visits as follows: (<10%, 10-20% (Kubli *et al.* 2000), 23%, 31% (Morris *et al.* 1996)) in the forearm and (10-20%, 10-20% (Kolonizakis 2004)) for the gaiter area, for ACH and SNP respectively.

1.5.4 Pitfalls in LDI

Although images can be recorded under different light conditions, the influence of the ambient light may alter the magnitude of the actual perfusion values to a degree dependent on the light source and its intensity. It is therefore advisable to record the image with the light on and off and then calculate the influence of the light of the perfusion values to judge on the feasibility of tolerating the ambient light in an actual test situation (Fullerton *et al.* 2002).

Factors affecting the cutaneous blood perfusion should be accounted for and standardised as much as possible. These include: temperature, anatomical site, physical and mental activity, food and drug intake, day-to-day and diurnal variations, posture, age, sex, menstrual cycle and race (Bircher *et al.* 1994; Fullerton *et al.* 2002).

In settings with possible altered skin transparency (i.e. skin ulceration with concomitant necrotic debris) there may be an influence on the laser Doppler results. Nevertheless, such effects appear to be less of a problem compared to other study techniques like capillary microscopy (Gschwandtner *et al.* 1999).

It is ambiguous to express the cutaneous blood flow in absolute terms due to the inter-sample and between the sample variability in the biological structure and function of the microvasculature. Therefore the experimental conditions, instruments' validation and setting, selection and pre-conditioning of study subjects, the measurement site selected, the environment and laboratory room

control and the experimental design should carefully be described to allow comparable results (Fullerton *et al.* 2002).

1.5.5 Applications of LDI

1.5.5.1 Inflammation

LDI was reported to be of benefit in the follow-up of patients with lateral epicondylitis through demonstrating a normalised pattern of skin perfusion compared to the contralateral side post-steroid injection treatment (Ferrell *et al.* 2000). Investigations into the role of histamine in the local dermal inflammatory response were also done using LDI (Clough *et al.* 1998). LDI was also used to further investigate the endothelial function in patients with vasospastic disorders (i.e. RP and SSc) through the analysis of the vascular response to iontophoresis of vasoactive substances which demonstrated impaired endothelium-dependent and endothelium-independent responses in the SSc group and a similar response to controls in the RP group (Anderson *et al.* 2004).

1.5.5.2 Healing processes

LDI combined with capillary microscopy has been utilised as an aid in identifying the healing capacity in various areas within an ischemic ulcer by assessing the laser Doppler area of flux (highest in healing granulation tissue) and capillary density (highest in normal skin followed by granulation tissue compared to very low density in areas without healing) (Gschwandtner *et al.* 1999) and investigating the blood flow patterns in patients at risk from pressure sores to aid in the early diagnosis in the condition (Nixon *et al.* 1999).

1.5.5.3 Burn assessment

LDI aids in obtaining accurate objective assessment of a burn's depth (clinical accuracy is 65-75%, boosted to 100%). The idea behind the use of this test in burns rests on the fact that burns with a high perfusion are superficial, needing

only dressing, while low perfusion burns require surgery (Kloppenberg *et al.* 2001; Pape *et al.* 2001).

1.5.5.4 Intra-operative measurement

Laser Doppler Flowmetry was used to demonstrate a significant reduction in the colonic perfusion particularly distal to the site of the mesenteric division in 10 subjects scanned after colon mobilisation during large bowel resection (Boyle *et al.* 2000). Similar perfusion drops were noted in the stomach and the jejunum following mobilisation during oesophageal resection (Boyle *et al.* 1998).

1.5.5.5 Dermatology

The uses of LDI in this field are numerous, including skin irritation measurements (Fullerton *et al.* 1995), patch tests (Bjarnason *et al.* 1999) and the diagnosis of malignant skin tumours including melanoma (Stucker *et al.* 1999).

1.6 ENDOTHELIAL ROLE IN VASOMOTION REGULATION

The vascular endothelium is a single layer of cells separating the blood from the vascular smooth muscles. The endothelium plays a pivotal role in the regulation of the vascular tone and growth, thrombosis, thrombolysis and platelets and leukocyte interaction in response to a stimulus (physical or chemical). Its function is mediated by the synthesis and secretion of substances such as nitric oxide (NO), prostacyclin, endothelins, interleukins and endothelial growth factors (Sader *et al.* 2002).

Following the publication of work by Furchgott and Zawadzki, which established that the aortic rings in the rabbit relaxed to acetylcholine (ACH) only in the presence of an intact endothelium through the secretion of a relaxing factor which they identified as NO (Furchgott *et al.* 1980), considerable interest

resulted in the synthesis and regulation of NO production and its effect on the smooth muscles (Griendling *et al.* 1996).

NO is synthesised from L-arginine mediated by the enzyme nitric oxide synthase (NOS). Secretion of NO is increased in response to increased blood flow due to the shear stress on the endothelium (Pohl *et al.* 1986) and by a variety of agents such as ACH and bradykinin acting on endothelial cell membrane receptors (Sader *et al.* 2002). NO functions through the reduction of the intracellular calcium levels resulting in vascular smooth muscle relaxation (Collins *et al.* 1986).

The endothelial function has been assessed predominantly using functional methods examining the NO-dependent vasomotion both in the coronary and the peripheral circulation. By assessing the vasomotion in response to a chemical or physiological stimulus, the tests examine the endothelial ability to release NO and cause vasodilatation. These tests take the form of invasive and non-invasive testing. Invasive testing is done using intravenous endothelium-dependent (e.g. ACH) and endothelium-independent (e.g. nitroprusside) substances and measuring the effects quantitatively using angiography or Doppler catheters (Drexler *et al.* 1991). Non-invasive vascular assessment in response to an endothelium-dependent stimulus (e.g. temporary occlusion with tourniquet distal to the target artery leading to proximal shear stress and flow mediated dilatation) and an endothelium-independent stimulus (e.g. sublingual GTN) and recording the response using LDI, LDF or a high resolution external vascular ultrasound (Celermajer *et al.* 1992; Joannides *et al.* 1995). More recently iontophoresis (Section 2.9) has been extensively used to non-invasively deliver the endothelial-dependent and -independent stimuli accurately and easily (Klonizakis *et al.* 2003; Klonizakis *et al.* 2006a).

A literature review revealed a gender difference in the effect of the sex hormones on the endothelial function and vascular reactivity. Oestrogen potentiated endothelial vasodilatation in both the coronary and systemic circulations in both genders, although this may require long-term administration in males (Gilligan *et al.* 1994; Sader *et al.* 2002). Using brachial artery ultrasound during the three phases of the menstrual cycle to assess the effect of oestrogen on the endothelial function, variation in vasodilatation between the different phases was noted with a maximal vasodilatation in the follicular and leuteal phases (Hashimoto *et al.* 1995).

Abnormalities in the endothelial vasoregulatory function is the hallmark of several vascular diseases including DM, hypertension and chronic hypercholesterolemia (Griendling *et al.* 1996). Several mechanisms underlying the endothelial dysfunction have been identified.

1- Substrate (Arginine) deficiency.
2- Poor NOS stimulation due to an alteration in the second messenger release resulting in a reduced calcium signal.
3- Receptor dysfunction due to an impaired agonist-receptor interaction or a reduced receptor expression.
4- Over-production of the constriction factors.
5- NO inactivation due to super-oxide anion (Figure 1.6).

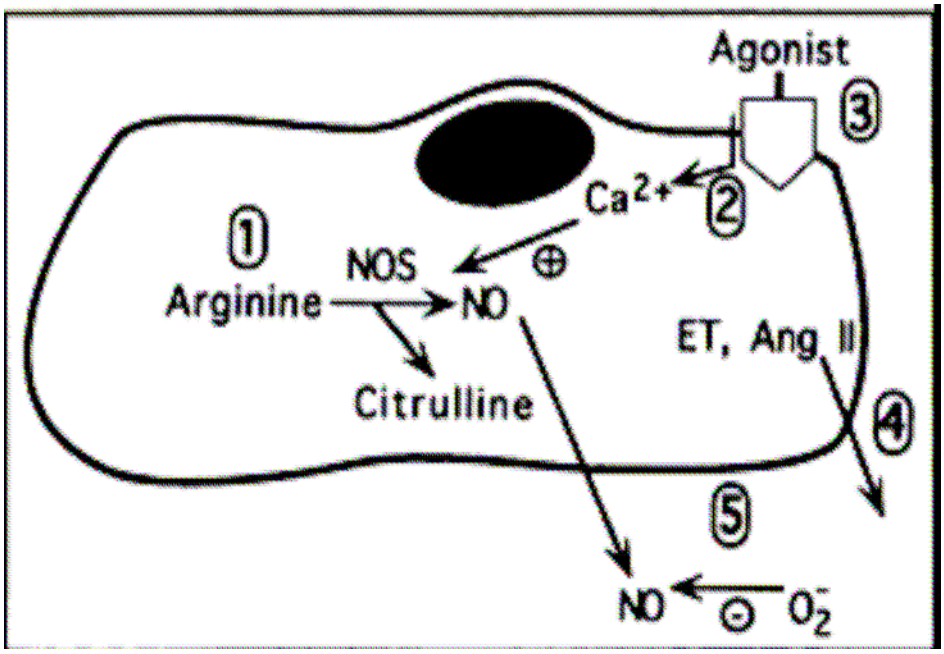


Figure 1.6 Potential mechanisms of impaired endothelial-dependent control of vasomotor tone by NO (Griendling *et al.* 1996)

1.7 AIMS

The overall aim of this work presentation is to investigate aspects within CTS through experimental microvascular research and reflect on applied practice-based audits to achieve the following aims.

1- Analyse cold provocation tests conducted on a series of subjects with HAVS, RP and normal controls to develop and standardise the data analysis methods for cold provocation testing.

2- Determine the methodology of techniques used in the methodology, namely CPT and LDI in the hand.

3- Determine the normal vascular response of the hand to a cold challenge using CPT and LDI.

4- Determine the effect of CTS and hand injury on the microcirculation of the hand.

5- Assess the effect of CTR and hand injury on the vascular response in the hand.

6- Determine the outcome of conservative management of CTS and its predictors, and compare the outcome of conservative to surgical treatment in a carpal tunnel clinic.

CHAPTER 2: GENERAL METHODS

2.1 INTRODUCTION

This chapter reviews the general background information on the research subjects and the methods I have used in each study. The review explains the function, limitations, protocol and rationale for the use of each technique.

2.2 ETHICAL APPROVAL

Research studies were commenced following approval by the Local Research Ethics Committee and the NHS Trust concerned (Southern Derbyshire Local Research Ethics Committee and Derby Hospitals NHS Foundation Trust). Audits performed at Ilkeston Community Hospital (Erewash Primary Care Trust) were formally reported to the local Clinical Governance body in the Primary Care Trust and written approval was obtained in accordance with the policy and the procedures of the Trust. No identifiable data was recorded during the implementation of the research protocol (psuedonomised: referred to with a code) or the data collection for the audit, in accordance with the Data Protection Act 1998 (Al-Shahi *et al.* 2000; Strobl *et al.* 2000).

2.3 CLINICAL SETTING

Patient studies involving Laser Doppler Imaging and Cold Provocation Testing were performed in the clinical investigation facilities within the Clinical Sciences Wing of the Graduate Entry Medical School of The University of Nottingham, based at Derby.

2.4 SUBJECT RECRUITMENT

Subjects were invited to participate by direct contact, mail or through study posters displayed in areas where potential study candidates might attend within

the premises of the Derby Hospitals NHS Foundation Trust and The Graduate Entry Medical School.

Subjects were recruited from:

The Orthopaedics and Hand Outpatient Clinics

Current and past patients attending orthopaedic and hand clinics at Derbyshire Royal Infirmary. CTS and RP patients were invited to participate through information leaflets provided in clinics or by mail.

The Pulvertaft Centre Hand Surgery Database (Delta Database)

The Pulvertaft Hand Centre keeps an up-to-date database of all the hand surgery patients reviewed in the unit since 1987 with details of their clinic appointments and last operative intervention date. This system was designed in-house as a clinical office management system and is updated on a daily basis by the secretaries as they process the clinical tapes. The database currently holds information on approximately 80,000 patients.

Normal (control) volunteers

Control subjects were recruited from a database in the Division of Vascular Medicine, via posters within the Graduate Entry Medical School and through invitation letters to suitable people registered in a medical practice in which one of the lead investigators works.

Advertising in miners welfare clubs

Advertising leaflets and information sheets were sent to the surrounding miners welfare clubs (nine clubs contacted).

The premises of the Derby Hospitals NHS Foundation Trust

Advertised within the premises in clinics (Vascular and Rheumatology).

The HAVS patients undergoing CPT for medical reports in the private practice of the chief investigator had their fully anonymised data included in the study.

Patients attending a Registrar-Led Carpal Tunnel Clinic in Ilkeston Community Hospital (Erewash Primary Care Trust).

2.5 PATIENT CONSENT

All study patients gave written informed consent at least 24 hours after reading the information sheet for patients/volunteers prior to participating in a research study. Copies of the consent form and patient information sheet were filed in the hospital notes.

2.6 DEMOGRAPHIC INFORMATION

Basic information on each study subject was obtained and recorded using a standardised data collection sheet (referenced for each study in relevant chapters). Relevant history including age, sex, exposure to vibration, history of RP, DM, drug history and hand dominance was obtained. Clinical data including height (cm), weight (Kg), blood pressure (Section 2.7), clinical peripheral or central cyanosis, timed Allan's test (Gelberman *et al.* 1981a) and hand examination for neurological signs were collected and documented as per protocol.

2.7 BLOOD PRESSURE (BP) MEASUREMENT

A validated, maintained and calibrated OMRON 703 CP device was used (Medical Devices Directive (MDD: 93/42/EEC)) to measure the sitting BP in study subjects using a cuff of appropriate size. Two BP readings were taken; if a marked difference (10-15 mmHg in systolic or diastolic BP) between the

readings was obtained, a third reading was taken (Williams *et al.* 2004). The mean BP for each subject was used in the final analysis.

2.8 DATA ANALYSIS

All data collected were stored on an Excel® spreadsheet and analysed using one of two statistical packages (SPSS V13.0: statistical package for social sciences and MedCalc®). Ten per cent of the data entries in each database were checked by Mrs M. Baker (senior research assistant) for errors prior to analysis. A further detailed data review was planned when/if errors were detected in the pilot review. The Derby Hospitals NHS Foundation Trust statisticians (Dr R. Hilliam and Mr A. Fakis) were consulted on the most appropriate statistical methods of analysis at each step of the process and specific reference to the appropriate tests on each data set is provided in the corresponding chapter.

The data was analysed based on its type and distribution. Categorical data were analysed using the X^2 test, continuous data were analysed based on their distribution. Data normality was assessed based on the sample size using the Kolmogorov-Smirnov test for samples larger than 50 and the Shapiro-Wilk test for samples of 50 or smaller; a non-significant p-value (>0.05) indicates normality in either test. Data histograms were also inspected. The statistical test choice was then made as demonstrated in Figures 2.1 and 2.2 (paired data=data from the same subject). The data are presented as mean (SD) unless stated otherwise.

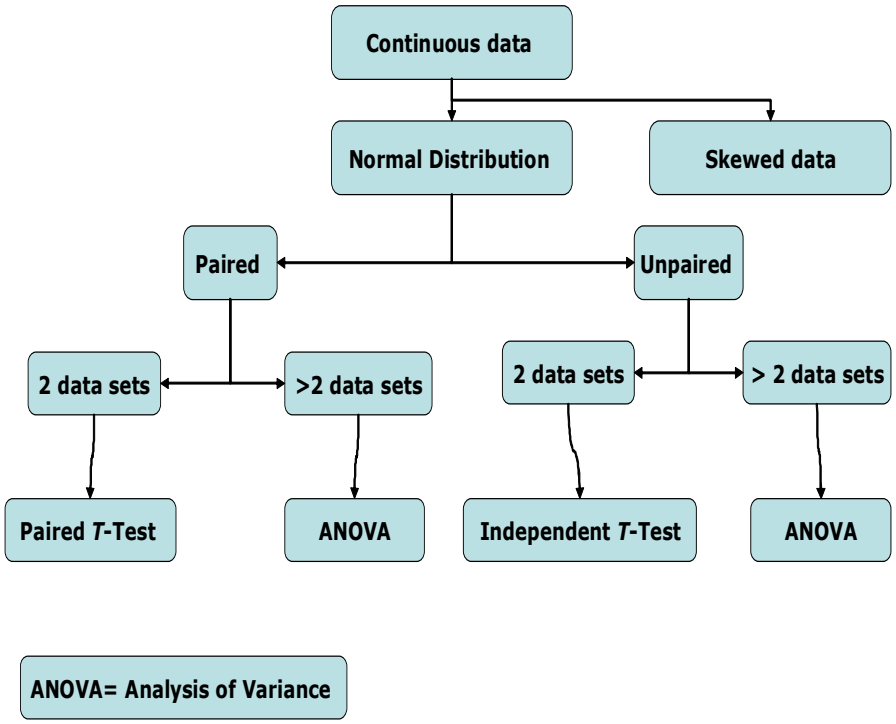


Figure 2.1 Guide flow chart for normal continuous data analysis

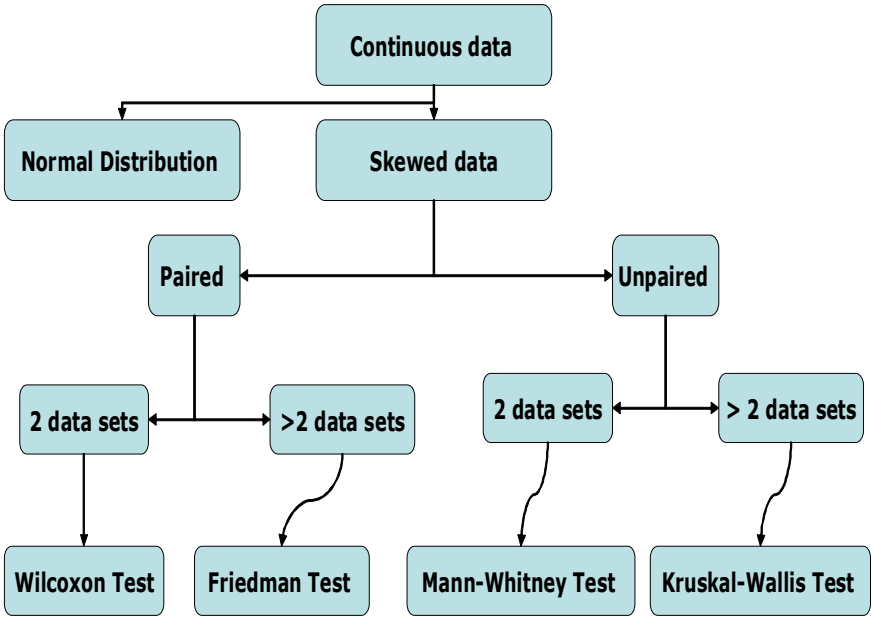


Figure 2.2 Guide flow chart for skewed continuous data analysis

The distribution of data was also used to guide the choice of a correlation coefficient test (*r*) when appropriate (Pearson *r* for normal distribution and Spearman *r* for skewed data). Additional statistical tests are explained when used in the corresponding chapter.

2.9 IONTOPHORESIS

2.9.1 Introduction

Iontophoresis is a method of drug delivery through facilitated movement of ions of soluble salts across a membrane under an externally-applied potential difference (Singh *et al.* 1994). It was only in the early twentieth century that the usefulness of this technique in drug delivery was established (Leduc 1900). More recently this method has attracted increasing attention by both experimental and clinical scientists from various specialties including clinicians, dentists, chemists and pharmacists, especially when used in conjunction with LDI.

The research group at the Division of Vascular Medicine, University of Nottingham is experienced in the use of iontophoresis to investigate the cutaneous microvascular function in the forearm and the gaiter areas (Davis *et al.* 2001b; Davis *et al.* 2001c; Dhindsa *et al.* 2003; Klonizakis *et al.* 2003; Klonizakis *et al.* 2006b).

2.9.2 Theory

Based on the concept that similar charges repel each other and opposite charges attract, iontophoresis delivers drugs through a membrane by increasing the rate of their penetration using an external energy source. Thus, to deliver a negatively-charged drug across an epithelial surface, the drug is placed under the negative drug delivery electrode where it is repelled and attracted to the

positive electrode placed elsewhere on the body. For anodal iontophoresis the electrode orientation is reversed (Singh *et al.* 1994). Cathodal and anodal iontophoresis can also be done simultaneously (Singh *et al.* 1994) (Figure 2.3).

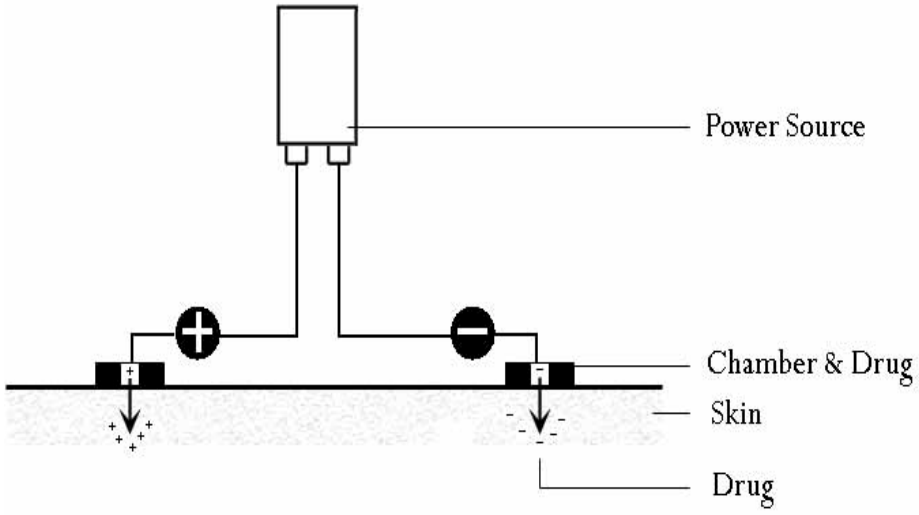


Figure 2.3 Simultaneous cathodal and anodal Iontophoresis

2.9.3 Equipment

A battery-operated Perilont-382 power supply (Perimed – Sweden) was used to provide a pulsed direct current (Figure 2.4). Attached to the power supply are two iontophoretic silver/silver coated electrodes (Moor Instruments Ltd, Axminster, UK).

Figure 2.4 Perilont-382 Power Supply (Perimed – Sweden)

2.9.4 Investigational drugs

Acetylcholine (ACH) (Sigma Chemicals, UK) and sodium nitorprusside (SNP) (Nipride, Roche Pharmaceuticals Ltd) were prepared as 1% solutions using deionised HPLC-Grade water. Higher drug concentrations had previously been shown not to result in a faster response and were associated with a risk of non-specific vasodilatation (Droog *et al.* 2003; Droog *et al.* 2004). The drugs were prepared in a quantity sufficient to cover a period of four weeks. The vials were covered with aluminium paper and the preparations were stored in a freezer to prevent the denaturation of the drugs due to high temperature or light exposure. To minimise errors, two persons were present during the preparation according to a standard operating procedure.

The choice of the drugs was based on previous work undertaken in the department (Davis *et al.* 2001c; Klonizakis *et al.* 2003; Klonizakis *et al.* 2006b). ACH is a non-specific vasodilator with effects on the C-fibres, vascular endothelium and smooth muscles; SNP acts on the vascular smooth muscles only (Green *et al.* 1996; Fujimoto *et al.* 1997; Berghoff *et al.* 2002).

2.9.5 Precautions and considerations

Factors known to affect the delivery of drugs using iontophoresis were controlled. The use of the same drugs with identical concentrations, delivered through an identical protocol, eliminated variations due to drug physiochemical properties (molecular size, charge and concentration), drug formulation (type of vehicle, buffer, pH, viscosity and the presence of other ions) and equipment factors (current used, the type of electrodes and the duration of the iontophoresis) (Singh *et al.* 1994).

Biological variation such as age and sex were balanced as far as possible during recruitment. All studies were conducted in a controlled environment with the air temperature maintained between 20-25°C. Subjects were allowed to acclimatise to the ambient temperature for 25-30 minutes before each study. The electrodes were applied on the dorsum of the chosen hand/hands as per study protocol.

2.9.6 Iontophoresis protocol

After a period of acclimatisation, the dorsal skin of the hand was carefully cleaned with an alcohol swab and dried thoroughly to minimise the risk of local spots of high current density (which might result in C-fibre activation, non-drug-related vasodilatation and local micro burns) (Gazelius 2005). Two chambers (electrodes) were used simultaneously on the dorsum of the hand and positioned 1-3 cm apart avoiding major dorsal veins. One of the chambers was connected to the anodal lead of the iontophoresis controller (PeriIont-382 Power Supply (Perimed – Sweden)) and filled with 0.5 ml of the positively-charged ACH, the other was connected to the cathodal lead and filled with 0.5 ml of the negatively-charged SNP (Figure 2.5).

The iontophoresis protocol used was the following:

Time	Current	Charge
20 seconds	120μamp	2400μCb

The same protocol was used in all study subjects.

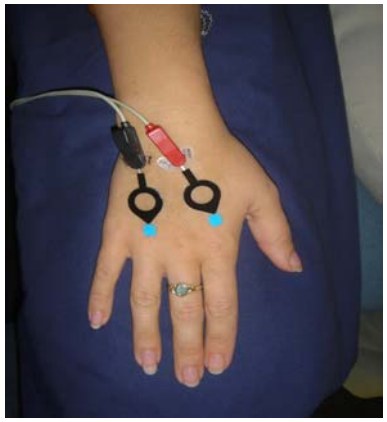


Figure 2.5
Two Iontophoretic Silver/Silver coated electrodes (Moor Instruments Ltd, Axminster, UK) attached to the back of the hand

2.10 LASER DOPPLER IMAGING (LDI)

2.10.1 Introduction

A comprehensive overview of the LDI was given earlier (Section 1.5).

2.10.2 Equipment

Periscan PIM II Laser Doppler Perfusion Imager (Perimed – Sweden) was connected to a computer (Compaq, Intel PIII), equipped with PeriScan Software – LDIwin 2.6 (Perimed – Sweden) (Figure 2.6).

Figure 2.6 Periscan PIM II Laser Doppler Perfusion Imager (Perimed – Sweden)

2.10.3 Precautions and considerations

A number of variables were controlled to achieve consistency in measurements. Temperature, anatomical site, physical activity, food and drug intake were accounted for (Bircher *et al.* 1994; Fullerton *et al.* 2002).

Changes in the ambient temperature variation are associated with changes in cutaneous flux readings. A light intensity of 6-8 microvolts was maintained in the test room during the imaging to minimise the effect of the ambient light (Nilsson 1997).

Temperatures >30°C markedly increase the skin microcirculation (Winsor *et al.* 1989); hence, all subjects were allowed to acclimatise in a temperature-controlled room (20-25°C for 30 minutes) to allow the skin temperature to stabilise.

The distance of the scanner head from the point of interest affects the sensor unit in the LDI; distances <10 cm saturate the detector unit while >30cm create an impaired signal-noise ratio (Fullerton *et al.* 2002). The scanner head was positioned 20 cm from the area of interest.

Food intake, age, sex, race, blood and serum parameters did not affect mean values of skin flux (Bircher *et al.* 1994). No blood samples were taken from study subjects.

Smoking has a negative correlation with the flux (Waeber *et al.* 1984). Smokers were instructed to refrain from smoking 6 hours prior to the test and were prioritised to be tested early in the morning session. Alcohol increases the cutaneous circulation (Wilkin 1986; Bircher *et al.* 1994) and subjects were instructed to abstain from alcohol for 6 hours prior to the test.

Patients on vasoactive medication were not recruited to eliminate variations in the vascular response to the iontophoresis challenge due to the vasodilatory action of these medications. Vasomotor reflexes such as deep inspiration and hyperventilation have a transient influence on the flux; if encountered, the study was stopped accordingly. Studies were conducted away from powerful audiovisual stimuli (Bircher *et al.* 1994).

2.10.4 Procedure/protocol

Following a standardised period of acclimatisation, the subjects were asked to relax and maintain their hand position. The LDI was adjusted to scan the area covered by the two iontophoresis chambers. The number of scans was determined by the study protocol. Following scanning completion, areas of interest were marked (Figure 2.7). The Periscan software was used to produce descriptive tables of statistical data representing the points of interest. Data included the minimum, maximum, mean and standard deviation, and percentage change in perfusion. This was stored on an Excel spreadsheet and used in the analysis.

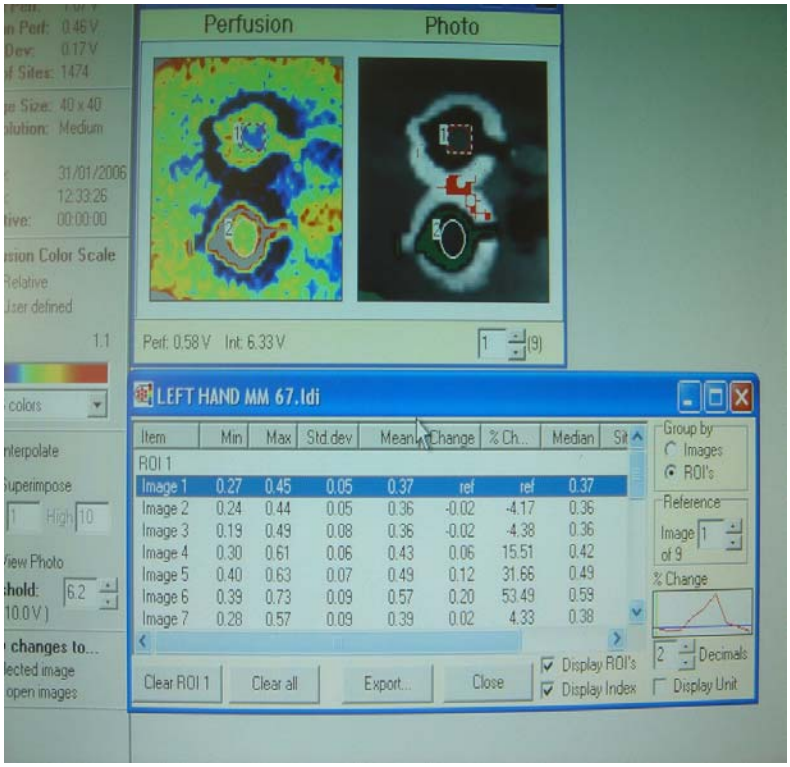


Figure 2.7 Data output after completing the imaging

2.11 COLD PROVOCATION TESTING (CPT)

2.11.1 Introduction

A comprehensive overview of the LDI is given in Sections 1.4.2 and 3.2.

2.11.2 Equipment

A laboratory water bath with a continuously-stirred temperature-controlled cooling and heating element was used, the water temperature being controlled to within 0.1°C (Clifton NE4-D, Digital Thermostatic Control, Nickel Electro. Ltd-UK). Thermocouples used were standard type-K thermocouples (T. M. Electronics (UK) Ltd) connected through Pico Technology TC-08 thermocouple adapters (8 channel thermocouple data logger).

Test descriptive data were generated and stored using a software package based on Microsoft Excel (1998).

2.11.3 Precautions and considerations

The study protocol was modified to provide an adequate cold challenge without a cold-induced reactive hyperaemia in the HAVS group (Hack *et al.* 1986; Coughlin 2004). A water temperature of 12°C with a mean digital cooling target temperature of 15°C delivered an adequate challenge and avoided prolonged immersion (Harada 2002).

Relevant precautions detailed in Section 2.10.3, including food, blood and serum parameters, alcohol, smoking and vasoactive medication, applied. The hand temperature was stabilised prior to the test by allowing subjects to acclimatise in a temperature-controlled room (20-25°C for 30 minutes) (Winsor *et al.* 1989; Harada *et al.* 1998; Harada 2002).

2.11.4 Procedure/protocol

After a period of acclimatisation, calibrated type K-thermocouples were attached to the volar surface of the fingertips on both hands by surgical tape (Figure 2.8). Subjects were seated with the forearms rested on pillows. Baseline temperature was recorded for 3 minutes (baseline phase). Cooling commenced after baseline temperature readings stabilised. The hands were covered with plastic bags and then immersed in the cold water bath (cooling phase). The cooling phase was discontinued when the temperature curves for the four ulnar digits reached a mean of 15°C. The hands were removed from the water bath and allowed to rest on pillows to passively re-warm (re-warming phase). Data on digital, water and room temperatures were collected every 6 seconds during the test until the digital temperature returned to body temperature or after 25 minutes of re-warming.

For descriptive purposes, the re-warming curve was divided into three phases: a baseline, a cooling and a re-warming phase (Figure 2.9).

Figure 2.8 The cooling water bath with thermocouples attached to the terminal pulp of the digits in both hands

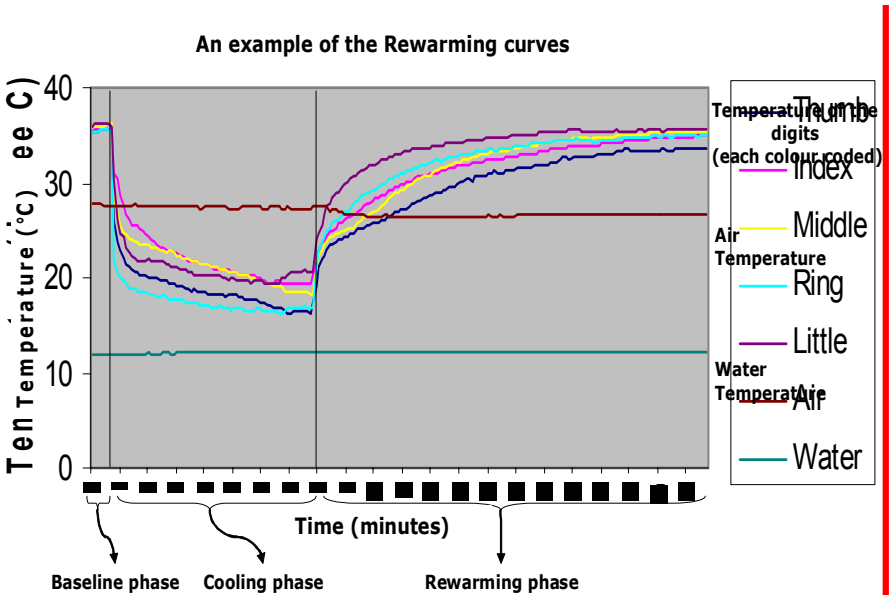


Figure 2.9 The phases of the re-warming curve

2.12 CLINICAL AUDIT

2.12.1 Introduction

A shift towards quality in health care culminated in the introduction of clinical governance to the NHS. Clinical audit, as part of clinical governance, is a quality assurance process aimed at improving patient care through a systematic review

of practice against explicit criteria and recommendations for change (NICE 2002). It was first integrated and encouraged in 1997 and then made mandatory in 2000 (NICE 2002). GMC Guidance described regular clinical participation in this exercise as a must (GMC 2001).

2.12.2 The audit process

To ensure patient care follows best clinical guidance, an audit cycle is vital. Current practice is measured against a standard, recommendations are made and practice re-checked to monitor change (Figure 2.10) (NICE 2002; Johnson 2005; Brown 2006). Audit findings should be publicised for the benefit of the team or institution.

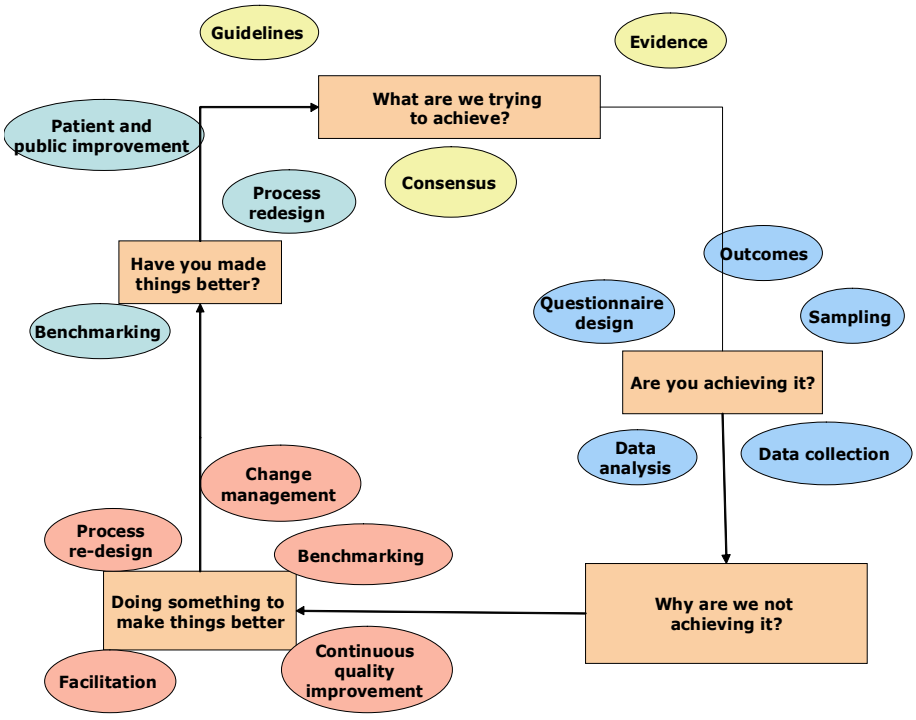


Figure 2.10 The Audit Cycle (NICE 2002)

The process can be subdivided into five stages (Figure 2.11):

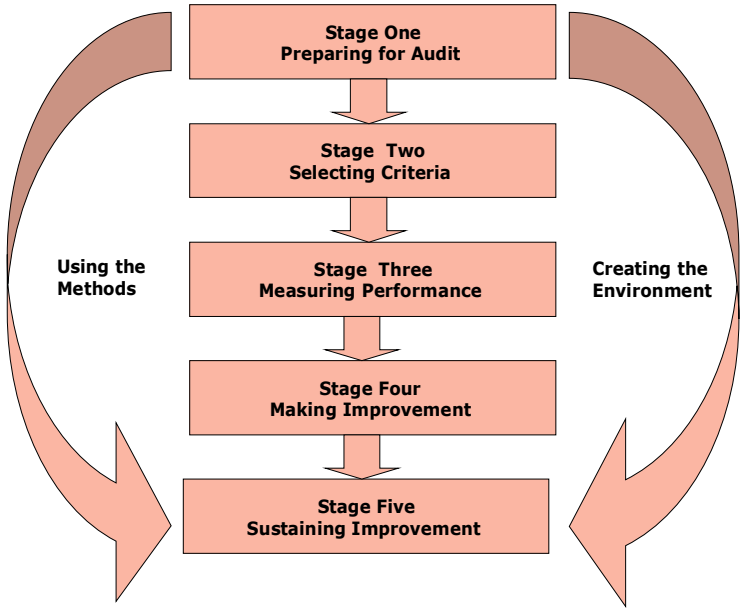


Figure 2.11 Audit stages (NICE 2002)

To help define audit aims the following verbs were suggested: to improve, to enhance, to ensure and to change (Buttrey 1998). Based on the aims, criteria are set to evaluate the process or the outcome of care.

Ideally, data collection should be done routinely. This improves accuracy and facilitates repeated monitoring with ease (NICE 2002).

2.12.3 Research or audit

There are similarities between research and audit. Both begin with a question, require data collection and the outcomes are dependent on using an appropriate design to reach a sound conclusion. Because audit outcomes reflect quickly on practice, the methodology quality in audits should be at least as robust as that of research (Wade 2005).

More recently, a national audit on diabetic retinopathy was presented to 28 ethics committees and 25 trusts for approval. Only six bodies considered the project an audit and not research (Wilson *et al.* 1999). Evident is the lack of uniformity in the decision as seen above, particularly when a substantial amount of data is collected (Wade 2005). It was argued that minimal changes in clinical practice such as collecting extra data amounting to a minor burden on the patient (5-10 minute questionnaire, taking measurements such as blood pressure and pulse rate) would rarely require ethical consideration (Kinn 1997; Wade 2005). Others are of the view that an audit should never involve disturbances of patients over and above normal clinical management requirements with no extra data collection and no extra clinical assessment (RDSU).

Although clinical governance guidance is available, it is primarily the responsibility of the investigator to seek the appropriate approval.

While conducting the CTS audit, the patient management was not influenced by the data collection. The data collection is part of a continuous process to monitor the standard of practice in the clinic. Measurements of sensation and power are common practice in the Pulvertaft Hand Centre and the questionnaires given to the patients take <5 minutes to complete.

2.12.4 Audit procedures

Two audit projects were designed and approved by the local clinical governance office: a retrospective audit of the outcome of patients managed by a nurse practitioner in a CTS clinic and a prospective audit on the clinic following the appointment of a hand fellow (myself).

2.12.5 CTS assessment tools

Validated, repeatable assessment tools were used to monitor the progress of patients.

1- The Two-Point Discrimination Test (2PDT)

The 2PDT was defined by Weber (1835) as "the distance between compass points necessary to feel two contacts" (Dellon 1981).

The 2PDT measures the innervation density of the afferent fibres (Johansson *et al.* 1979). The original 2PDT was a stationary test evaluating the slow adapting afferent fibres accounting for 10% of the large myelinated touch fibres (Johansson *et al.* 1979). Its main limitations included difficulty in standardising the applied pressure and discrepancy in contact timing of the two blunted pins with the skin which can introduce a critical error, subjects easily discriminating between two non-synchronous pressure applications (Lundborg *et al.* 2004).

A moving 2PDT (m2PDT) capable of evaluating the quickly adapting sensory fibres was described (Dellon 1978a). The m2PDT permits the assessment of a large percentage of the total touch fibres which recover early (Dellon *et al.* 1972; Dellon 1978a; Louis *et al.* 1984).

The 2PDT is influenced by age (decrease with age especially after the fifth decade), sex (females discriminate at smaller distances), nerve (less in ulnar nerve assessment than the median nerve), technique and operator (Louis *et al.* 1984). The subject's hand dominance had no influence (Louis *et al.* 1984).

The m2PDT was performed using a set of two plastic disks, each containing a series of metal rods spaced by varying intervals from 1 to 25 mm (The DISK-CRIMINATOR®) (Figure 2.12). The examined digit was supported on the

examination table. Using the 5-8 mm interval rods moving from proximal to distal and proceeding in stages down to 2 mm spaced rods (Dellon 1978a). The index finger was used as the sensory denominator for the median nerve and is tested in both hands (Moore *et al.* 2005). Values of less than 6 mm were considered normal (Gellis *et al.* 1977; Dellon 1981). A 2PDT >15 mm represented a useless digit and measurements between 6 and 15 mm suggested "some tactile gnosis" is preserved (Moberg 1964; Lundborg *et al.* 2004).

Figure 2.12 The DISK-CRIMINATOR®

2- The Semmes-Weinstein pressure aethesiometer (SWM)

A sensory threshold test, this measures the function of slow adapting afferent fibres (Levin *et al.* 1978; Dellon 1980). The SWM correlates accurately with symptoms of nerve compression and electro diagnostic tests (Gelberman *et al.* 1983a). It is used in the assessment of peripheral neuropathy in diabetes mellitus (Lee *et al.* 2003), and compressive and traumatic neuropathy (Dellon 1978a; Gelberman *et al.* 1983a).

The SWM was conducted using a Touch-Test® Sensory Evaluator (North Coast Medical, Inc. Morgan Hill, CA) (Figure 2.13), which consists of six individually-calibrated monofilament pencils (Table 2.1).

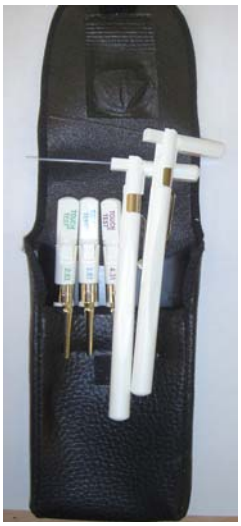


Figure 2.13
Touch Test® Sensory Evaluator (North Coast Medical, Inc. Morgan Hill, CA)

Evaluator size	Target force to bow evaluator (grams)	Sensory hand threshold
2.83	0.07	Normal
3.61	0.4	Diminished light touch
4.31	2	Diminished protective sensation
4.56	4	Loss of protective sensation
5.07	10	
6.65	300	Deep pressure sensation only

Table 2.1 Description of the SWM monofilament evaluators

After explaining the test, subjects were asked to rest the extremity on a stable surface and look away from the test site. The evaluator was pressed at 90° to the surface of the skin avoiding callosities until it bowed, pressure was maintained for 1-2 seconds and then removed. The test started with a 2.83 evaluator and was repeated using a larger monofilament if a response was lacking. The size of the evaluator dictated the number of applications (2.83 & 3.61 applied 1-3 times, 4.31-6.65 applied only once). The pulp of the index

finger was used as a denominator for median nerve sensory innervations (Moore *et al.* 2005).

3- Self-administered questionnaires

A. Levine-Katz symptoms and functional questionnaire

The questionnaire consists of two main parts. [a] Symptom severity scale assessing the six critical domains in CTS evaluation (pain, paresthesia, numbness, weakness, night symptoms and the overall functional status of the patient). Eleven questions with multiple choice responses scored from 1: (mildest) to 5: (most severe) and an overall symptom severity score calculated as the mean of the 11 scores. [b] Functional score assessing eight activities commonly performed. The answers were rated from 1: (no difficulty in performing the activity) to 5: (cannot perform the activity at all). The overall functional status was calculated as the mean of all eight scores (Levine *et al.* 1993) (Appendix 1.1).

The questionnaire was reported as repeatable (Pearson correlation coefficient =0.91 and 0.93 for severity and functional status scales respectively) and sensitive (defined as the response to clinical change) (Spearman coefficient was 0.5 for the symptom severity score and 0.54 for the functional score in a prospective cohort ($p<0.01$) (Duncan *et al.* 1987; Levine *et al.* 1993) (Section 1.1.3).

B. Quick Dash (disability of the arm, shoulder and hand) outcome measurement

A standardised questionnaire evaluating impairment and activity limitations through 30 questions with multiple choice responses ranging from 1 to 5 (1: no difficulty to 5: unable) (Hudak *et al.* 1996; Jester *et al.* 2005). A shorter version was devised containing 11 questions while maintaining an acceptable internal consistency, the Quick Dash (Appendix 1.2) (Beaton *et al.* 2005). The

questionnaire is repeatable (Interclass Correlation Coefficient =0.94) and validated (r≥0.64 with single item indices of pain and function) (Beaton *et al.* 2005).

In the CTS clinic, the Quick Dash was used. The total score was calculated if at least 10 of the 11 questions were answered. The assigned value for all completed responses was summed and averaged producing a score out of five. This value was transformed to a score out of 100 by subtracting one and multiplying by 25. This is done to facilitate comparing the outcome with other measures scaled 0-100. The higher the score the greater the disability (Beaton *et al.* 2005).

4- Dynamometers

Calibrated grip and pinch strength dynamometers were used (TEC, Clifton, New Jersey). The best out of three readings (kg) was recorded for both hands (Figure 2.14).

Figure 2.14
Grip and pinch strength dynamometers

This chapter has provided an overview of the methods used. The following chapters describe the projects undertaken to meet the stated aims of my work.

CHAPTER 3: DEVELOPMENT OF METHODS

1- **CPT modification**

2- **Repeatability of Methods**

   i. **Modified Cold Provocation Test**

   ii. **Laser Doppler Imaging in the hand**

3.1 INTRODUCTION

3.1.1 CPT modification

The large number of claimants on the miners' compensation scheme carried out by the Department of Trade and Industry (DTI) identified the need for an objective test for the diagnosis of HAVS. In 1998, a standardised CPT was adopted to assess the vascular component of HAVS (Griffin *et al.* 1998). The weak correlation between this test's findings and the vascular stage based on the Stockholm Workshop Scale generated debate on the validity of the test (McGeoch *et al.* 2000). Some authors suggested the standardised CPT to have "no" or "limited" value in evaluating the presence or severity of HAVS (Mason *et al.* 2003; Proud *et al.* 2003).

A modification on the standardised test was developed by Mr L. C. Bainbridge (The Pulvertaft Hand Centre). The research team at the Division of Vascular Medicine, The University of Nottingham, started validating this test in patients with RP and HAVS two years ago.

3.1.2 Repeatability of methods

Repeatability is defined as outcome consistency under the same conditions (i.e. same operator, same apparatus, within a short time interval and for the same sample). It is an important test validation requirement (Bircher *et al.* 1994).

The standardised CPT was "positive one day and negative the next day" for subjects exposed to vibration, and authors reported wide limits of agreement in vibration-exposed subjects (i.e. LOA for middle finger 5 minutes post-cooling was 2.3, 10.9 compared to 5.1, 6.9 in the control group; similar findings were noticed in the other digits) (Griffin *et al.* 1998). Similar findings were reported

elsewhere (Mason *et al.* 2003). Other formats of the test exist but repeatability evidence remains lacking (Coughlin *et al.* 2001).

The use of LDI in the assessment of a provoked microvascular response minimised the importance of point-to-point variability and preserved the representation of the blood flow map in day-to-day measurements (Nilsson 1997; Fullerton *et al.* 2002). Evidence supporting LDI repeatability exists in the forearm (coefficient of variation <10% for ACH iontophoresis and 10-20% for SNP) (Kubli *et al.* 2000) and the gaiter area (Klonizakis *et al.* 2003). Evidence of LDI repeatability in the hand is lacking.

The aims of this chapter are: firstly, to present the data analysis I have undertaken on CPT data collected by members of the research team to identify characteristics in the re-warming curve that differentiates between subjects with PRP, HAVS and controls; secondly, to investigate the modified CPT repeatability; thirdly, to investigate the repeatability of LDI in the hand.

3.2 METHODS

3.2.1 CPT modification and repeatability

Subject recruitment and demographical data collection is outlined in Sections 2.4 and 2.6 respectively. The modified CPT is described in detail in Section 2.11. Subjects participating in the study were asked to re-attend for a repeat test after 12-14 days.

Three groups were recruited:

[1] A control (C) group with no history of RP, cold intolerance symptoms, history of peripheral vascular disease or exposure to vibration.

[2] A HAVS group with a history of exposure to vibration for more than five years and stage (V2) or more on the Stockholm Workshop Score (McGeoch *et al*. 2005) (Section 1.2.4).

[3] Subjects with Primary RP (PRP), no history of connective tissue disease or exposure to vibration.

Exclusion criteria:

[1] Smoked within the last 6 hours.

[2] Currently taking medication for cardiac disease or hypertension including ß-Blockers, vasodilators, ACE inhibitors.

[3] Currently taking long-term medication for migraine or RP.

[4] A history of a significant finger or limb injury.

[5] Under 18 years of age.

[6] Showed clinical evidence of central or peripheral cyanosis (not related to cold weather).

[7] Have a prolonged timed Allan's test.

[8] Failed to maintain their hands in the water for the necessary period.

3.2.2 LDI repeatability

Non-smoking healthy male and female volunteers aged 18 years or over were recruited to undergo two LDI scanning sessions 12-14 days apart. In each session the back of the hand was scanned nine times and the vascular challenge delivered using iontophoresis following the third scan. Details of the recruitment, LDI and iontophoresis methodology are covered in Chapter 2.

Three operators (myself, a PhD student and a senior research technician) each performed the study on 20 subjects.

Subjects were excluded if they were taking vasoactive medication or gave a history of Raynaud's phenomenon, exposure to vibration, hand injury or carpal tunnel syndrome.

3.3 DATA ANALYSIS

Data analysis followed the methods outlined in Section 2.8. Additional statistical tests are explained where appropriate.

3.3.1 CPT modification

The following measurements were obtained: baseline temperature (defined as the difference between the pre-cooling digit temperature and the ambient temperature), temperature rise in the first 30 seconds (T_{30secs}), time taken for the hands to re-warm by 5°C ($T_{5°C}$) and the time variability in re-warming between digits within the hand (defined as the time difference between the fastest and slowest digit to re-warm to room temperature after cooling within the hand). The latter was felt to be of particular importance in patients with vibration exposure as the effect is expected to vary between digits in the same individual. To study this observation the patients within each group were stratified in one of five subgroups.

Group 1 0–1 minutes

Group 2 >1–2 minutes

Group 3 >2–3 minutes

Group 4 >3–4 minutes

Group 5 >4 minutes

Thumbs were excluded from all calculations to allow comparison with published literature (Proud *et al*. 2003). It was estimated that a sample size of 60 subjects in each group would allow the detection of 10% difference between the groups

with a power of 80% and a beta error of <0.05. Univariate linear regression was used to study the effect of age, gender and smoking. Odds ratio analysis for the effect of gender and Receiver Operator Curves (ROC) analysis for the sensitivity and specificity of the CPT was provided by the trust statistician (Dr Rachel Hilliam).

3.3.2 Test repeatability

Repeatability of the data was investigated using a random one-way intra-class correlation (Howell 2002) and Bland-Altman Plots (Bland *et al.* 1986). To facilitate the comparison with previously published literature, the correlation coefficient (*r*) and the coefficient of variation (CoV) was also calculated. The following parameters were investigated: baseline, T_{30secs} and $T_{5°C}$.

3.3.2.1 Repeatability of LDI in the hand

The repeatability of three parameters was investigated: (**LDI^{0}**) (the mean perfusion prior to the delivery of the iontophoresis charge), (**LDI^{Max}**) (maximum post-iontophoresis perfusion readings) and (**LDI^{Mean}**) (mean perfusion values of the first three images post-delivery of iontophoresis). Further analysis was undertaken to investigate operator repeatability variations.

3.4 RESULTS

3.4.1 CPT modification

One hundred and seventy-six subjects were included in the study: 86 controls, 31 PRP and 59 HAVS (Table 3.1). None of the recruited subjects failed to complete the study.

Age and smoking had no effect on the individual response to cooling ($p>0.05$, Linear Regression). The effect of gender was only significant at T_{30secs}; males

demonstrated a higher mean temperature rise compared to females (e.g. Right hand males 2°C (0.9), females 1.4°C (0.8); p = 0.003. Left hand males 1.9°C (0.9), females 1.5°C (0.6); p = 0.001) (Table 3.2). Additionally, no significant effect of gender was demonstrated when the odds ratio was calculated for baseline, T_{30sec} and $T_{5°C}$ (Appendix 3.1).

	Sample size(n)	Gender		Age (years)	Height (M)	Weight (kg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Smokers %	Right Hand Dominance
		Male	Female							
Control	86	41%	59%	40.7 (19-69)	1.7 (1.5-1.9)	72.4 (48-128)	125.5 (86-171)	81.4 (61-119)	16.5%	93.0%
PRP	31	19%	81%	48.9 (23-82)	1.7 (1.5-1.9)	65.5 (48-94)	125 (107-168)	82.5 (65-106)	35.5%	90.4%
HAVS	59	97%	3%	49.4 (28-76)	1.7 (1.6-1.8)	84.6 (70-91)	143 (172-125)	87.4 (99-79)	24.1%	95.2%

Table 3.1 Characteristics of the three groups (PRP: Primary Raynaud's Phenomenon, HAVS: Hand Arm Vibration Syndrome)

Effect of Gender, smoking and age (p-values)								
	Baseline		T_{30secs}		$T_{5°C}$		Time variability in finger re-warming within the hand	
	Right hand	Left hand	Right hand	Left hand	Right hand	Left hand	Right hand	Left hand
Gender	0.20	0.54	0.003	0.001	0.07	0.26	0.20	0.70
Smoking	0.34	0.28	0.75	0.76	0.34	0.73	0.90	0.70
Age	0.18	0.13	0.45	0.91	0.06	0.04	0.35	0.50

Table 3.2 Effect of gender, smoking and age on CPT response (Linear Regression)

Baseline Temperature

The baseline temperature was significantly higher in the control group compared to the PRP and HAVS groups ($p < 0.001$ for both the right and left hands, one-way ANOVA) (Figure 3.1).

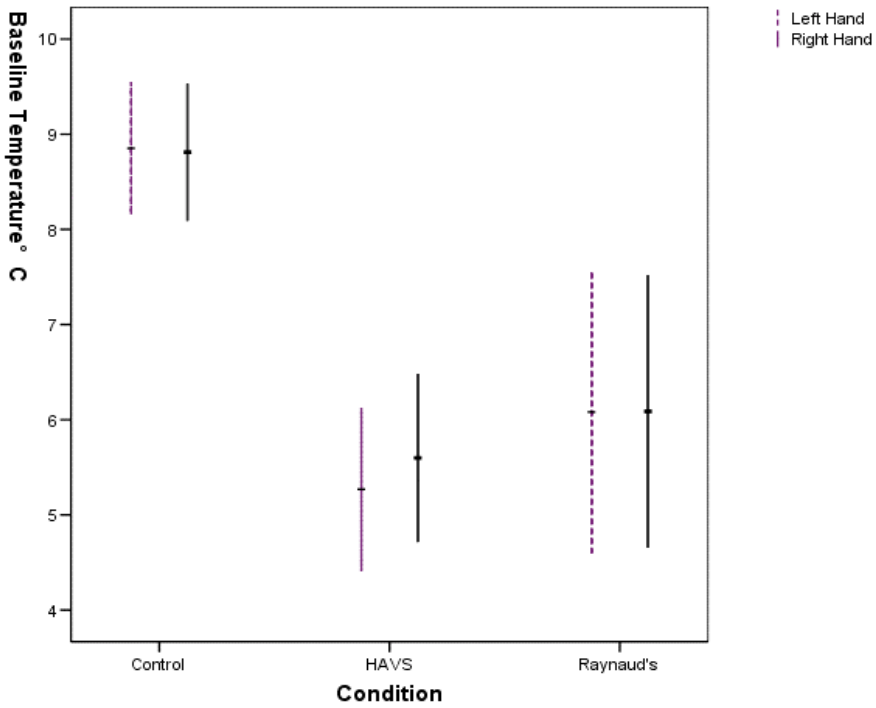


Figure 3.1 Graph demonstrating the mean with 95% error bars for baseline temperature of the three groups for each hand (statistically significant $p < 0.05$, ANOVA)

Based on the 95% CI, a PRP or HAVS patient is unlikely to have a baseline temperature greater than 7.5°C (Table 3.3). This may be a useful finding for case screening.

Baseline temperature				
Side	Group	Mean °C (SD)	95% CI of the mean	
			Lower bound	Upper bound
Left Hand	Controls	8.8(3.3)	8.0	9.6
	PRP	5.9(3.8)	4.6	7.2
	HAVS	5.2(3.2)	4.4	6.0
Right Hand	Controls	8.7(3.5)	7.9	9.5
	PRP	5.9(4.0)	4.0	7.9
	HAVS	5.6(3.4)	4.8	6.4

Table 3.3 Data analysis of baseline temperature (data shown as mean (SD))

Temperature rise in the first 30 seconds (T_{30secs})

The T_{30secs} rise in the HAVS group was significantly higher than the other two groups ($p < 0.001$ for both the right and left hands, ANOVA) (Figure 3.2).

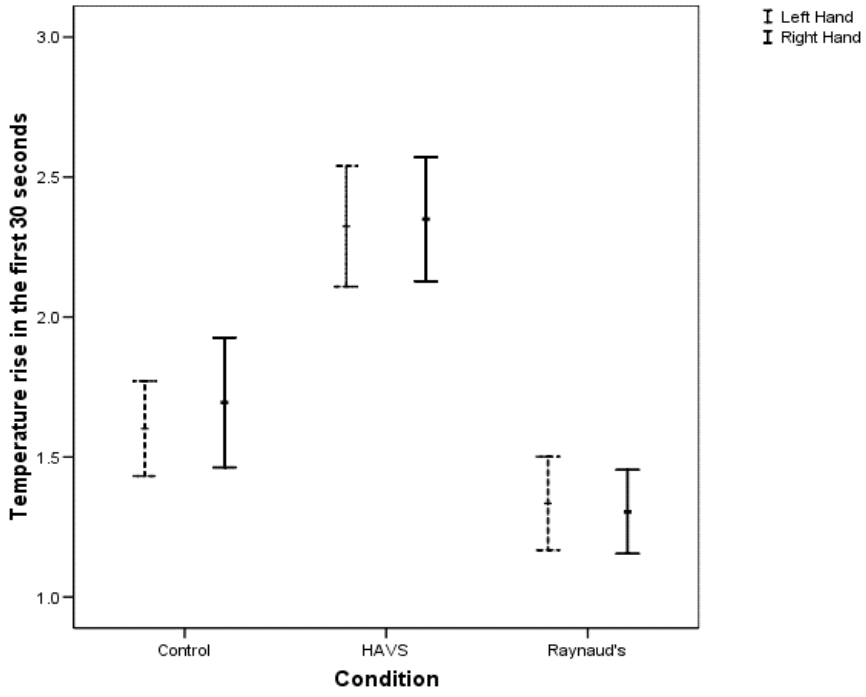


Figure 3.2 Graph demonstrating the mean with 95% error bars for T_{30sec} of the three groups for each hand (statistically significant $p < 0.05$, ANOVA)

Extrapolating from the confidence intervals (Table 3.4), a temperature gain of 2.2°C or higher in combination with a low baseline temperature may help identify HAVS patients.

Descriptive data on the Temperature rise in first 30 secs (T_{30secs})				
Side	Group	Mean °C (SD)	95% CI of the mean	
			Lower bound	Upper bound
Left Hand	Controls	1.6(0.7)	1.4	1.8
	PRP	1.3(0.5)	1.1	1.5
	HAVS	2.4(0.9)	2.2	2.6
Right Hand	Controls	1.7(1.0)	1.5	1.9
	PRP	1.3(0.4)	1.2	1.4
	HAVS	2.4(1.0)	2.2	2.6

Table 3.4 Data analysis at T_{30sec} (data shown as mean (SD))

Time to re-warm by 5°C ($T_{5°C}$)

$T_{5°C}$ was significantly longer in the PRP group compared to the other two groups ($p < 0.001$ for both the right and left hands, one-way ANOVA) (Table 3.5 and Figure 3.3).

Descriptive data on the Time to re-warm by 5°C ($T_{5°C}$)				
Side	Group	Mean Sec(SD)	95% CI of the mean	
			Lower bound	Upper bound
Left Hand	Controls	241(15)	211	271
	PRP	415(38)	339	491
	HAVS	262(20)	222	302
Right Hand	Controls	258(18)	222	294
	PRP	411(35)	341	481
	HAVS	255(20)	215	295

Table 3.5 Data analysis at $T_{5°C}$ (data shown as mean (SD))

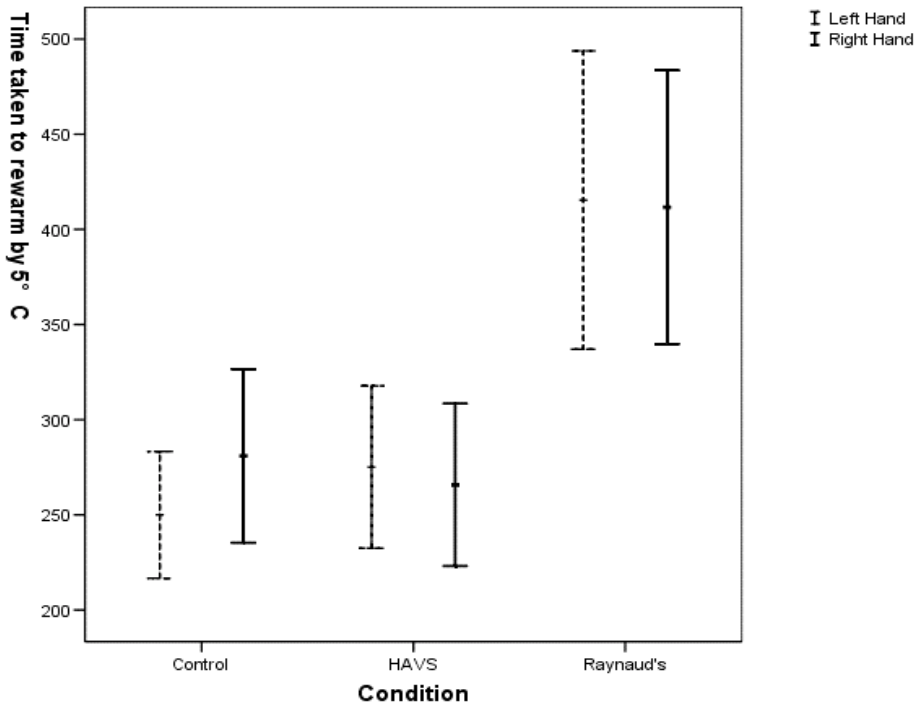


Figure 3.3 Graph demonstrating the mean with 95% error bars for $T_{5°C}$ of the three groups for each hand (statistically significant $p < 0.05$, ANOVA)

Time variability in finger re-warming within the hand between the groups

There was no significant distinctive re-warming pattern in the digits between the groups ($p = 0.21$, X^2 test).

In testing sensitivity and specificity, the limits of the confidence intervals were used to allow for the better sensitivity while maintaining an acceptable specificity; we considered baseline temperature (≥ 6°C) to be representative of the control group compared to the HAVS and PRP groups, T_{30sec} (≥1.8°C/30 sec.) to indicate a HAVS response compared to the other two groups, and $T_{5°C}$ of 300 sec. or longer to be a PRP response compared to the other two groups (Table 3.6).

	Baseline Temperature	T_{30secs}	$T_{5°C}$
Control	>6°C	<1.8°C	<300 sec.
HAVS	<6°C	>1.8°C	<300 sec.
PRP	<6°C	<1.8°C	>300 sec.

Table 3.6 Summary of CPT findings

ROC analysis for sensitivity and specificity of the modified CPT

ROC curve analysis showed a test sensitivity between 61% and 79% and specificity between 43% and 79%. T_{30sec} and $T_{5°C}$ both have >60% sensitivity and specificity (Tables 3.7-3.9).

Baseline		
	Left mean baseline	Right mean baseline
Sensitivity	0.795 (0.696, 0.868)	0.786 (0.687, 0.860)
Specificity	0.433 (0.336, 0.536)	0.456 (0.357, 0.558)
PPV	0.564 (0.474, 0.651)	0.574 (0.483, 0.660)
NPV	0.696 (0.567, 0.801)	0.695 (0.569, 0.797)
LR+	1.403 (1.136, 1.733)	1.443 (1.159, 1.797)
LR-	0.473 (0.291, 0.768)	0.470 (0.295, 0.751)

Table 3.7 Sensitivity and specificity of baseline measurement

$T_{5°C}$		
	Left mean baseline	Right mean baseline
Sensitivity	0.645 (0.469, 0.789)	0.613 (0.438, 0.763)
Specificity	0.709 (0.630, 0.778)	0.641 (0.561, 0.715)
PPV	0.328 (0.223, 0.453)	0.268 (0.179, 0.381)
NPV	0.901 (0.831, 0.944)	0.886 (0.811, 0.933)
LR+	2.219 (1.537, 3.202)	1.709 (1.199, 2.436)
LR-	0.500 (0.308, 0.814)	0.604 (0.381, 0.955)

Table 3.8 Sensitivity and specificity of $T_{5°C}$ measurement

T_{30sec}		
	Left mean baseline	Right mean baseline
Sensitivity	0.707 (0.580, 0.808)	0.712 (0.586, 0.812)
Specificity	0.763 (0.677, 0.832)	0.795 (0.711, 0.859)
PPV	0.603 (0.484, 0.711)	0.646 (0.525, 0.751)
NPV	0.837 (0.754, 0.895)	0.840 (0.758, 0.897)
LR+	3.689 (2.292, 5.935)	4.029 (2.515, 6.455)
LR-	0.475 (0.350, 0.644)	0.421 (0.300, 0.591)

Table 3.9 Sensitivity and specificity of T_{30sec} measurement

3.4.2 Repeatability of the modified CPT

The demographics are summarised in Table 3.10. No statistically significant differences were found between the two visits at baseline, T_{30secs} and $T_{5°C}$ ($p > 0.05$, Wilcoxon Signed Rank Sum). The CoV values were large (38-56%) and *r* was only >0.5 *at* $T_{5°C}$. The ICC identified $T_{5°C}$ to have the highest reproducibility for both right and left hands (ICC = 0.7 in both the right and left hands) compared to baseline and T_{30sec} (Tables 3.11 and 3.12). The repeatability of T_{30secs} was lower than baseline and $T_{5°C}$ for both hands and noticeably low in the left hand (ICC for T_{30secs} = 0.4 for right hand and 0.03 for left hand).

The results for baseline and $T_{5°C}$ are displayed as Bland-Altman Plots in Figures 3.4-3.7; the plots identify a tendency for the repeatability to be (higher clustering tendency around the mean) at higher baseline temperatures and in subjects with faster re-warming.

Analysis of other segments of the curve at various time points demonstrated a consistently repeatable test (Figures 3.8 and 3.9, and Appendix 3.2).

Condition	Size	Age	Female	Male
Controls	32	38.5 (11.7)	21 (65.6%)	11 (34.4%)
PRP	27	49.9 (15.3)	20 (74.1%)	7 (25.9%)
HAVS	3	54.7 (13.3)	0	3 (100%)
Total	62	44.3 (14.5)	41 (66.1%)	21 (33.9%)

Table 3.10 Demographics of the CPT repeatability sample

	Baseline(^{o}C)	T_{30secs} (^{o}C)	$T_{5°C}$ (Sec.)
Median Visit 1	8.8 (3.1, 10.0)	1.5 (1.1, 1.9)	300 (172, 455)
Median Visit 2	8.2 (1.0, 10.3)	1.3 (1.0, 1.8)	305 (154,457)
P value	0.27	0.11	0.60
r	0.40	0.11	0.51
CoV	56%	38%	51%
ICC	0.49	0.4	0.7

Table 3.11 Repeatability of measurements in the **Right hand**

	Baseline Temp(^{o}C)	T_{30secs} (^{o}C)	$T_{5°C}$ (Sec.)
Median Visit 1	9.0 (3.7, 10.3)	1.5 (1.2, 1.9)	287 (165, 415)
Median Visit 2	7.6 (0.9, 10.4)	1.2 (0.9, 1.6)	326 (158,511)
P value	0.19	0.07	0.20
r	0.35	0.15	0.54
CoV	57%	27%	55%
ICC	0.53	0.03	0.7

Table 3.12 Repeatability of measurements in the **Left hand**

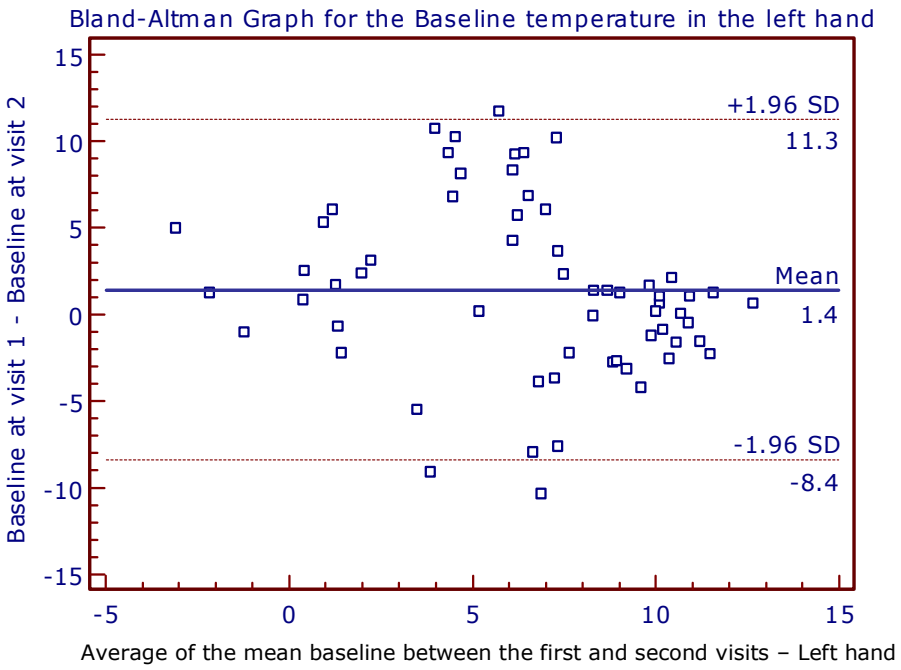


Figure 3.4 Bland-Altman Plots for Baseline temperature (**Left hand**)

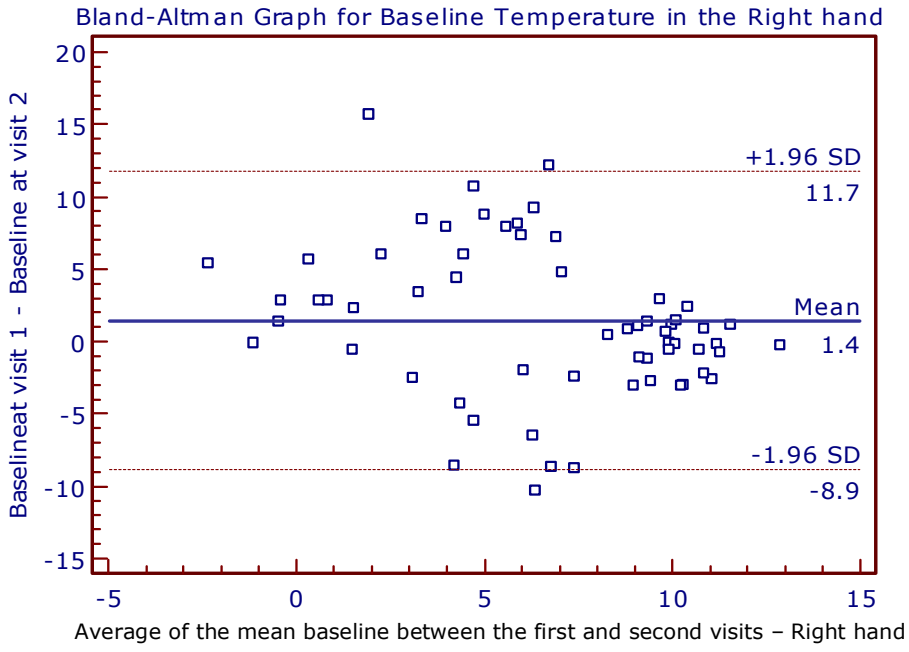


Figure 3.5 Bland-Altman Plots for Baseline temperature (**Right hand**)

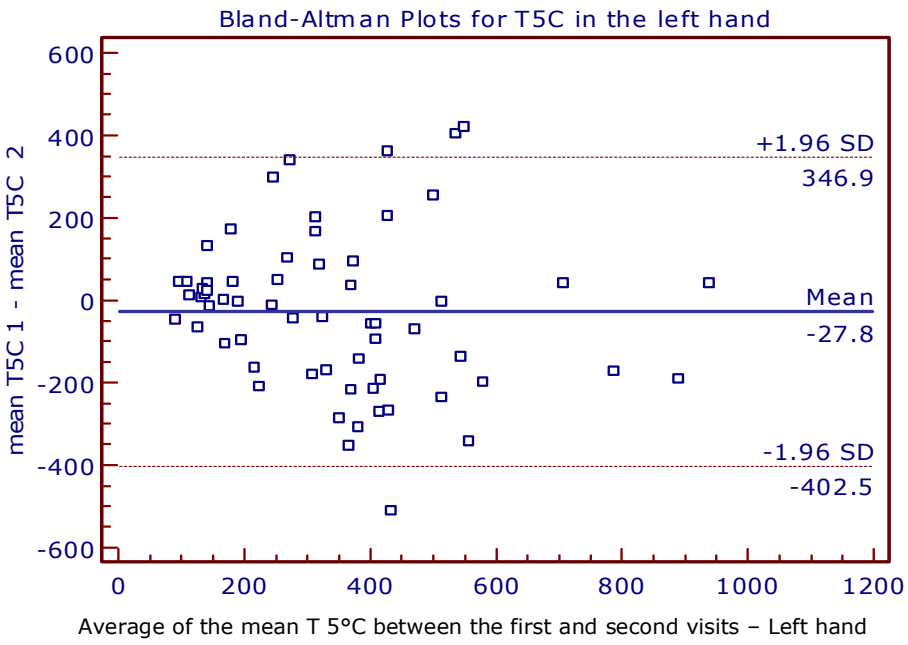


Figure 3.6 Bland-Altman Plots for $T_{5°C}$ (**Left hand**)

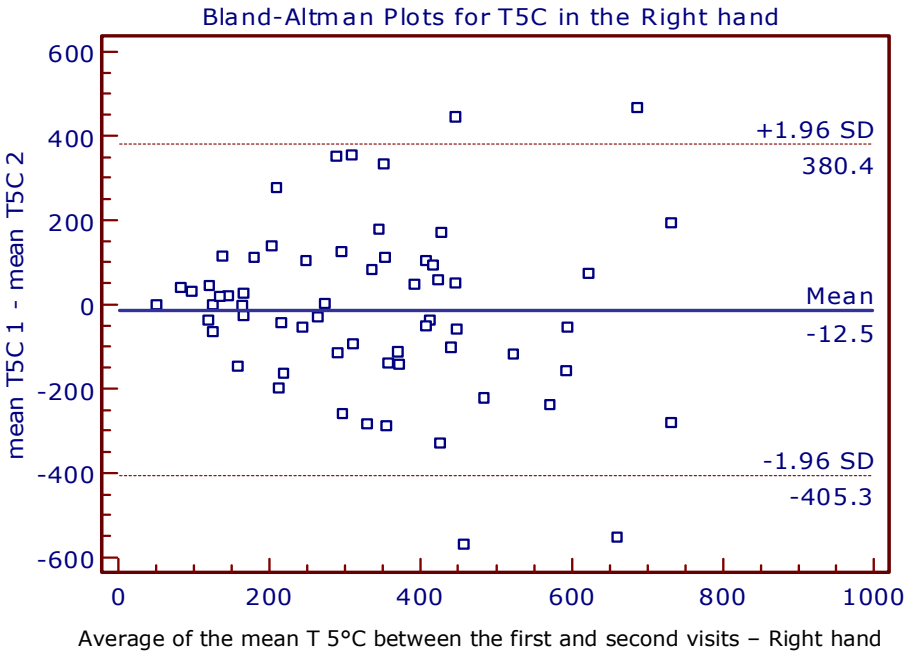


Figure 3.7 Bland-Altman Plots for $T_{5°C}$ (**Right hand**)

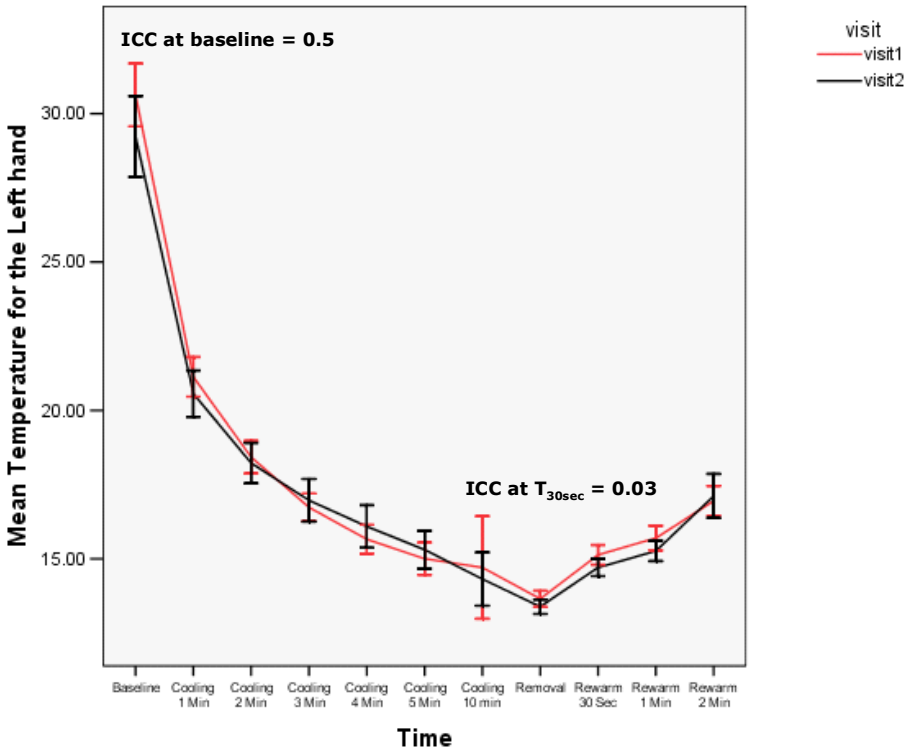


Figure 3.8 The graph represents the mean values (95% CI error bars) at sequential time points during the CPT in the **Left hand**

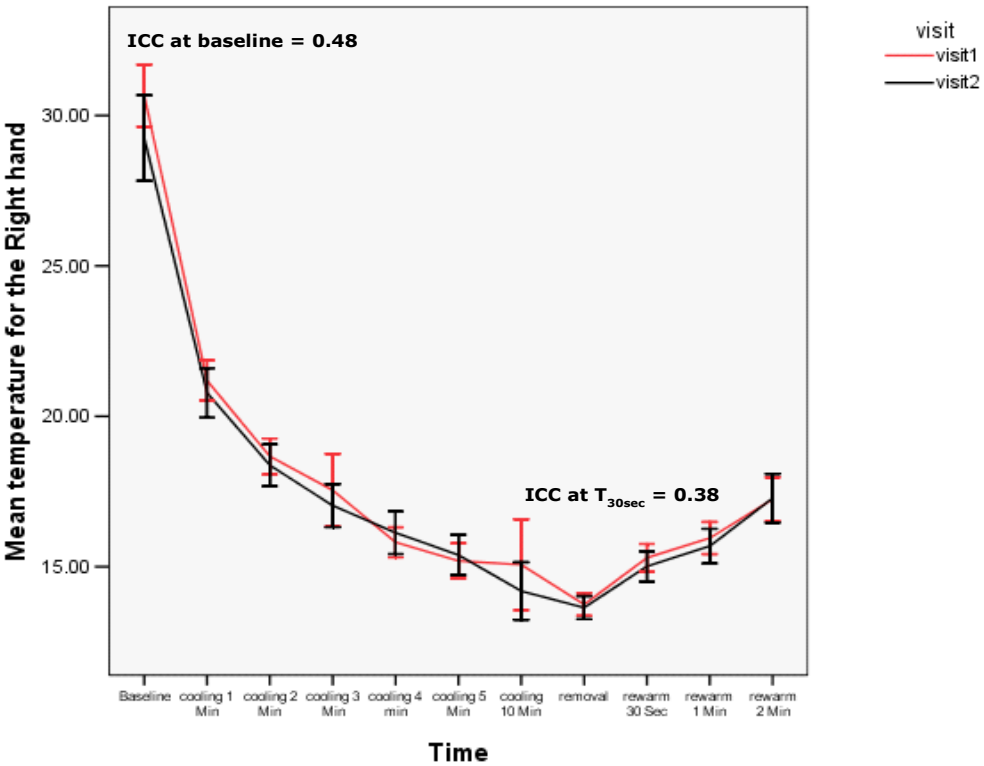


Figure 3.9 The graph represents the mean values (95% CI error bars) at sequential time points during the CPT in the **Right hand**

3.4.3 Repeatability of LDI in the hand

The data of 60 subjects were analysed: the mean age of the sample was 48.51(17.9) years, Height (cm) 170.5(10), Weight (Kg) 78.01(14), mean systolic BP (mmHg) 127(17) and mean diastolic BP (mmHg) 78(9). Fifty-one (85%) subjects were right-handed.

The mean values in LDI^{Max} had the highest ICC (ICC = 0.49 for SNP and 0.48 for ACH); those of the LDI^{Mean} had lower repeatability (ICC = 0.41 for SNP and 0.42 for ACH) (Tables 3.13-3.16).

When maximum, minimum and mean values for the LDI^{Max} and LDI^{Mean} data sets were compared, a statistically significant difference ($p < 0.05$) was found for all parameters. The correlation (*r*) between the two visits was weak (i.e. $r < 0.15$ for SNP and $r = 0.19$ -0.35 for ACH) and the CoV was wide more so for the SNP (37-44%) than the ACH (48-69%). Bland-Altman plots revealed higher repeatability at lower perfusion values (Figures 3.10 and 3.11).

Parameters at LDI^{0} were not reproducible for either SNP or ACH (Tables 3.17 and 3.18).

There was observed variation in test repeatability between the three operators for each of the drugs and with the same operator when comparing the two iontophoresis drugs (Tables 3.19 and 3.20, Appendices 3.3-3.5).

Stage	Variable	Mean(SD)	95%CI	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
LDI^{Max}	Minimum 1	0.44 (0.21)	0.40, 0.48	0.009	0.090	0.12 (0.1)	60.0%	0.15
	Minimum 2	0.50 (0.24)	0.46, 0.55	0.19				
	Maximum 1	1.42 (0.53)	1.33, 1.52	0.01	0.030	0.30 (0.001)	48.3%	0.23
	Maximum 2	1.65 (1.00)	1.47, 1.83	0.06				
	Mean 1	0.82 (0.28)	0.77, 0.87	0.20	0.016	0.30 (0.001)	40.5%	0.49
	Mean 2	0.90 (0.33)	0.84, 0.96	0.06				

Table 3.13 Visit comparison at LDI^{Max} **for SNP**

Stage	Variable	Mean(SD)	95%CI	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
LDI^{Max}	Minimum 1	0.43 (0.22)	0.39, 0.47	<0.0001	0.009	0.13 (0.15)	76.2%	0.19
	Minimum 2	0.52 (0.25)	0.47, 0.56	<0.0001				
	Maximum 1	1.49 (0.66)	1.37, 1.61	0.001	0.663	0.23 (0.013)	69.5%	0.29
	Maximum 2	1.51 (0.71)	1.38, 1.64	0.200				
	Mean 1	0.84 (0.31)	0.78, 0.89	<0.0001	0.032	0.22 (0.015)	52.3%	0.48
	Mean 2	0.91 (0.35)	0.84, 0.97	0.028				

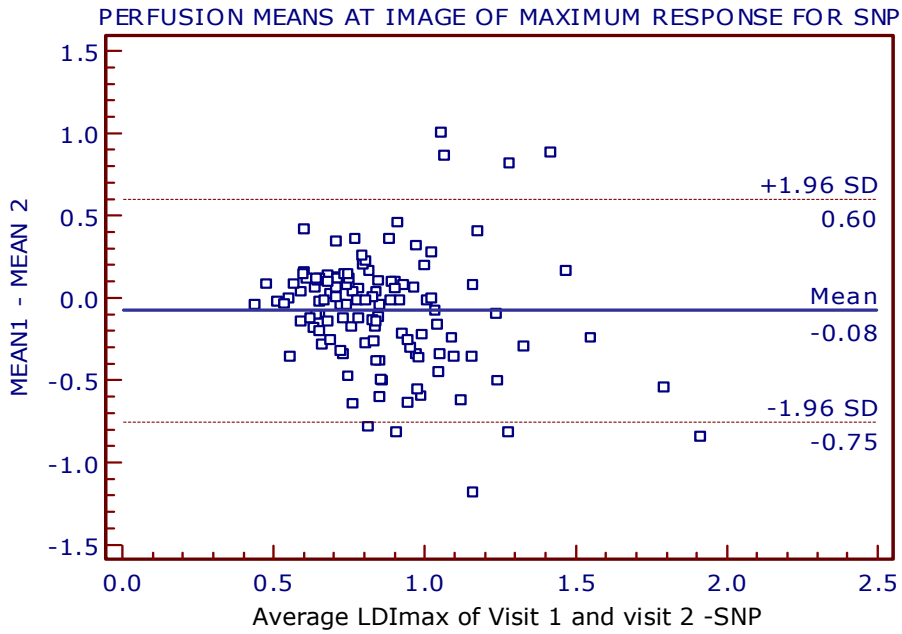
Table 3.14 Visit comparison at LDI^{Max} **for ACH**

Stage	Variable	Mean(SD)	95%CI	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
LDI^{Mean}	Minimum 1	0.40 (0.18)	0.37, 0.44	0.008	0.031	0.15 (0.1)	56.5%	0.18
	Minimum 2	0.47 (0.20)	0.43, 0.50	<0.0001				
	Maximum 1	1.25 (0.42)	1.17, 1.32	<0.0001	0.113	0.30 (0.001)	44.0%	0.49
	Maximum 2	1.34 (0.52)	1.25, 1.44	0.004				
	Mean 1	0.74 (0.23)	0.70, 0.78	0.001	0.021	0.22 (0.015)	43.7%	0.41
	Mean 2	0.81 (0.29)	0.76, 0.86	<0.0001				

Table 3.15 Visit comparison at LDI^{Mean} **for SNP**

Stage	Variable	Mean(SD)	95%CI	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
LDI^{Mean}	Minimum 1	0.40 (0.19)	0.37, 0.44	<0.0001	0.004	0.13 (0.16)	66.4%	0.09
	Minimum 2	0.48 (0.23)	0.44, 0.53	<0.0001				
	Maximum 1	1.29 (0.49)	1.20, 1.38	0.001	0.550	0.35 (<0.0001)	56.1%	0.41
	Maximum 2	1.31 (0.50)	1.22, 1.40	<0.0001				
	Mean 1	0.74 (0.25)	0.70, 0.79	<0.0001	0.017	0.19 (0.036)	48.2%	0.42
	Mean 2	0.82 (0.31)	0.77, 0.88	<0.0001				

Table 3.16 Visit comparison at LDI^{Mean} **for ACH**



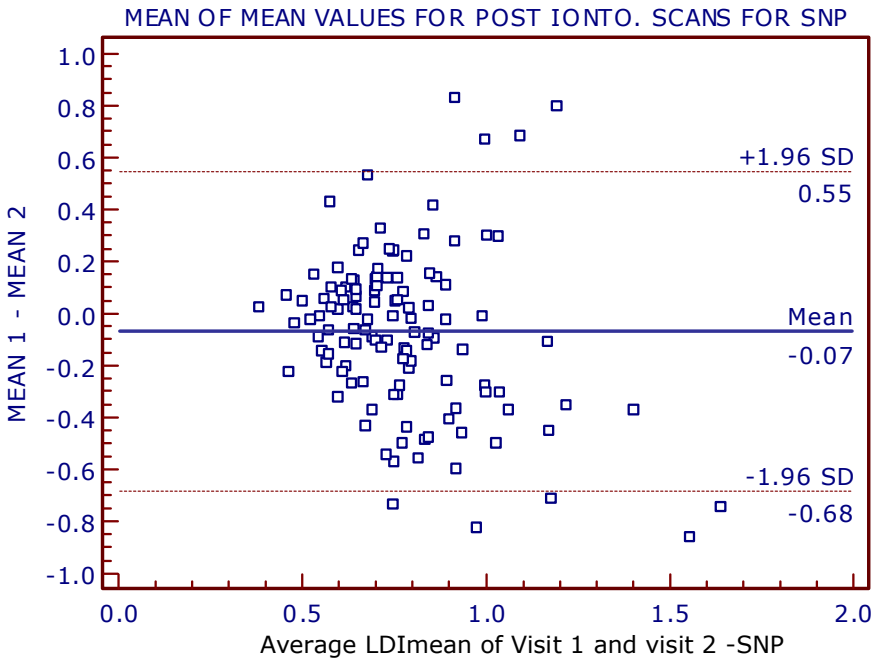
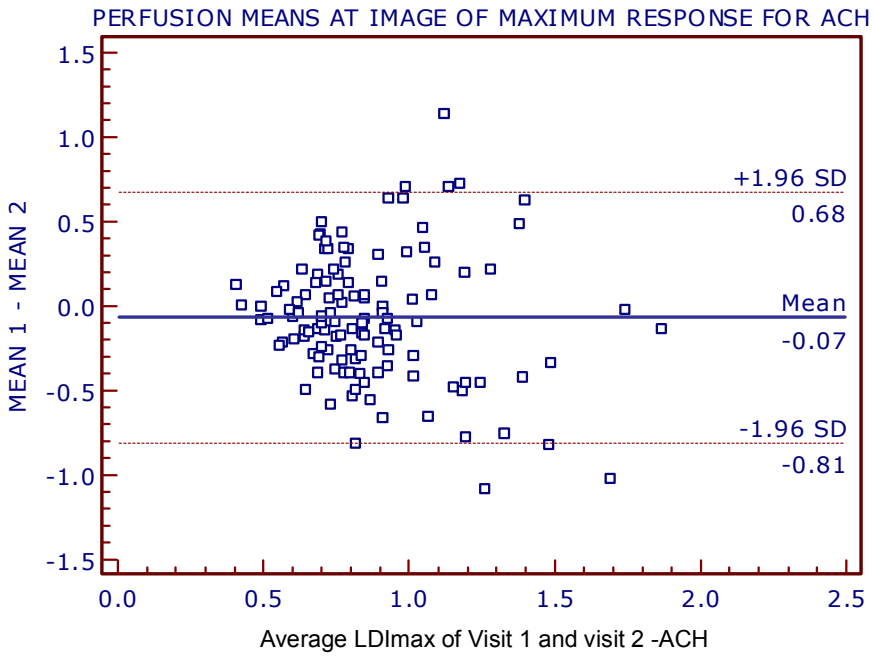


Figure 3.10 Bland-Altman plots **for SNP**



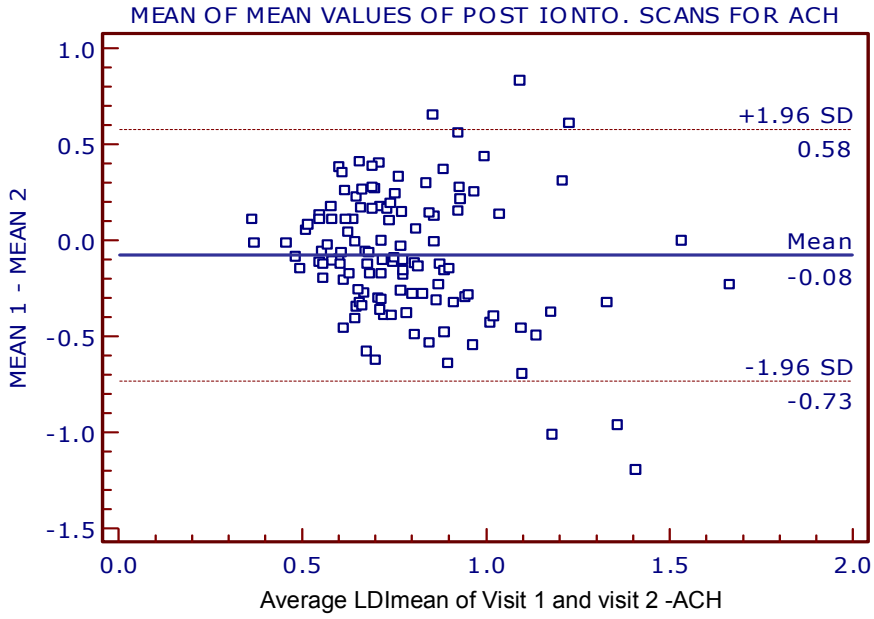


Figure 3.11 Bland-Altman plots **for ACH**

Stage	Variable	Mean(SD)	95%CI	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
LDI^0	Minimum 1	0.35 (0.14)	0.33, 0.38	0.04	0.015	0.15 (0.09)	58.6%	0.19
	Minimum 2	0.40 (0.15)	0.37, 0.43	0.00				
	Maximum 1	0.95 (0.31)	0.89, 1.00	0.005	0.116	0.31 (0.001)	40.9%	0.32
	Maximum 2	0.95 (0.21)	0.92, 0.99	0.001				
	Mean 1	0.61 (0.15)	0.58, 0.63	0.008	0.007	0.22 (0.01)	35.0%	0.25
	Mean 2	0.65 (0.16)	0.62, 0.68	0.00				

Table 3.17 Visit comparison at LDI^0 for **SNP**

Stage	Variable	Mean(SD)	95%CI	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
LDI^0	Minimum 1	0.34 (0.14)	0.31, 0.36	0.015	0.001	0.11 (0.22)	66.3%	0.18
	Minimum 2	0.39 (0.28)	0.37, 0.42	0.200				
	Maximum 1	0.90 (0.21)	0.86, 0.93	0.004	0.020	0.10 (0.26)	37.0%	0.49
	Maximum 2	0.98 (0.28)	0.93, 1.03	0.009				
	Mean 1	0.58 (0.15)	0.55, 0.61	<0.0001	0.001	0.09 (0.3)	42.1%	0.41
	Mean 2	0.64 (0.16)	0.61, 0.67	<0.0001				

Table 3.18 Visit comparison at LDI^0 for **ACH**

Stage	Variable	Operator 1	Operator 2	Operator 3
LDI^0	Minimum	0.1	0.6	-0.6
	Maximum	0.1	0.5	0.6
	Mean	0.2	0.4	0.3
LDI^{Max}	Minimum	-0.3	0.5	-0.01
	Maximum	0.2	0.3	0.7
	Mean	0.1	0.3	0.6
LDI^{Mean}	Minimum	-0.2	0.5	0.04
	Maximum	0.3	0.2	0.7
	Mean	0.1	0.1	0.7

Table 3.19 LDI repeatability variation between operators for **SNP**

Stage	Variable	Operator 1	Operator 2	Operator 3
LDI^0	Minimum	-0.1	0.3	-0.1
	Maximum	0.2	0.3	0.1
	Mean	-0.1	0.3	0.7
LDI^{Max}	Minimum	0.4	0.1	-0.002
	Maximum	0.5	0.1	0.1
	Mean	0.5	0.1	0.6
LDI^{Mean}	Minimum	0.2	0.1	-0.02
	Maximum 1	0.4	0.1	0.5
	Mean 1	0.3	0.1	0.6

Table 3.20 LDI repeatability variation between operators for **ACH**

3.5 DISCUSSION

3.5.1 The modified CPT

The CPT method (thermocouple temperature measurement, LDI, thermography), study protocol (water bath temperature and period of immersion) and seasonal variation were linked to variations in the outcome of the CPT (Harada *et al.* 1998; Coughlin *et al.* 2001; Harada 2002; Proud *et al.* 2003b). Given the variation between CPT tests and patients, it is exaggerated to deem the test as of no value. Understanding disease pathophysiology is

important when designing a diagnostic test for it (Stoyneva *et al.* 2003; Herrick 2005). Knowledge gaps still exist in our understanding of changes in RP and HAVS, which makes it difficult to develop a validated test.

In 2000, Coughlin *et al*. reported a good sensitivity, specificity, and positive and negative predictive values (100%, 88%, 95% and 100%, respectively at 8 minutes post-cold challenge). Their CPT used thermal imaging and a cooling challenge of 5°C for 1 minute in 21 HAVS patients and 10 controls (Coughlin *et al.* 2001). A wide range of sensitivities and specificities (sensitivity 22-73% and specificity 43-100%) has been reported by other investigators (Hack *et al.* 1986; Bovenzi 1987; Gautherie 1995). The modified CPT applied an adequate challenge (water temperature = 12°C, hands must cool down to 15°C) whilst avoiding the risk of reactive hyperaemia (Coughlin *et al.* 2001). Frequent (every 6 seconds) temperature measurements allowed accurate curve assessment at various points.

The modified CPT identified a significantly lower baseline temperature amongst the HAVS and PRP groups. This could be a useful screening tool for RP. The test suggests normality when baseline is >7.5°C above the ambient temperature; this excluded PRP and HAVS with a Stockholm Workshop Vascular score of V2 or more. The lower baseline skin blood flow secondary to a high sympathetic activity in the RP group is a possible cause for the low baseline temperature and smaller response to vaso-constrictive stimuli (Wollersheim *et al.* 1991). Cherkas *et al*. reported a similar observation suggesting baseline temperature can help identify RP sufferers from the general population with reservations on its low predictive power and the inability of the test to stage the disease (Cherkas *et al.* 2003).

The modified CPT can help differentiate between PRP and HAVS. A T_{30sec} >2.2°C is indicative of HAVS and, combined with a low baseline temperature,

suggests HAVS as the diagnosis; this was not reported before. The HAVS' response at T_{30sec} is probably due to disturbed local vascular response to the cold secondary to an underlying aberrant autonomic reflex. The pattern of re-warming in HAVS after T_{30sec} followed a normative course compared to PRP. PRP had a slower re-warming time ($T_{5°C}$ >330 seconds), which in this study helped to differentiate them from HAVS. This pattern of re-warming has not been reported before.

3.5.2 The repeatability of methods

There are inherent limitations in the consistency of repeated measurements of physiological variables. This applies to skin temperature and laser Doppler microcirculation measurements (Bartelink *et al.* 1993; Bircher *et al.* 1994; Beevers *et al.* 2001; Williams *et al.* 2004).

3.5.2.1 Repeatability of the modified CPT

Using ICC allowed the amalgamation of the three groups into one large sample to reflect the repeatability of the test without making specific conclusions relating to any particular group. ICC is designed to test the repeatability based on the variation between the two visits within the same subject (Fleiss *et al.* 1973; Howell 2002). This method of analysis allowed the use of the test's repeatability outcome as a guide in choosing the parameters helpful in the assessment of patients with hand injuries and CTS for which the repeatability of the test has not been previously determined. The analysis of the three parameters used in the differentiation between the groups (baseline, T_{30sec} and $T_{5°C}$) revealed $T_{5°C}$ to be the most repeatable curve segment (ICC = 0.7 for both hands). Baseline measurement had moderate repeatability (ICC = 0.49 on the left and 0.53 on the right); henceforth, baseline and $T_{5°C}$ were used in subsequent studies.

CPT repeatability has been reported as acceptable in controls. This was demonstrated using a 15°C challenge for 5 minutes (Griffin *et al.* 1998), a 5-7°C challenge for 15 minutes (Hack *et al.* 1986) and with a 16°C challenge for 5 minutes (Bartelink *et al.* 1993). Bartelink *et al*. also reported a good repeatability in the RP group (Bartelink *et al.* 1993). In the standardisation report for CPT, a recommendation for a repeat CPT test if the symptoms and CPT findings did not match was made based on larger LOA in the HAVS group. This variation in the repeatability between the two groups (control and HAVS) was thought to be due to a larger inconsistency in the response of the central sympathetic nervous system to the cold provocation in the HAVS group (Griffin *et al.* 1998).

Apart from some similarities in the clinical history and presentation of RP and HAVS, the evidence to support a pathophysiological link between these conditions is lacking (Pyykko *et al.* 1987; Noel 2000; Block *et al.* 2001). Conclusions on the CPT repeatability in HAVS should not be made comparable to these of RP. The evidence for CPT repeatability in HAVS is lacking. The small sample size, lack of objective diagnostic gold standard and weak staging tools make the available evidence questionable. Due to the small number of HAVS in our repeatability study, no conclusions could be drawn regarding the CPT repeatability in this group.

3.5.2.2 Repeatability of LDI in the hand

Early techniques utilising laser Doppler technology had poor repeatability (Schabauer *et al.* 1994). The spatial variation within the microvascular network is partly to blame (Kubli *et al.* 2000; Fullerton *et al.* 2002). Additionally, the mechanical contact of the instruments modified the vascular response leading to significant variations in repeat measurements (Obeid *et al.* 1990; Kernick *et al.* 2000; Fullerton *et al.* 2002). LDI overcame these limitations (Section 1.5).

LDI repeatability in the forearm (Morris *et al.* 1996; Kubli *et al.* 2000) and gaiter area (Klonizakis *et al.* 2003) has been explored. A good day-to-day repeatability was reported for ACH and SNP in the forearm (CoV <10%, 10-20%, 23%, 31% (Morris *et al.* 1996; Kubli *et al.* 2000)) and the gaiter area (10-20%, 10-20% (Kolonizakis 2004)). Our study revealed a wider CoV for both SNP and ACH (40-43% and 48-52% respectively) despite using identical LDI methodology to that adopted in previous house studies (Klonizakis *et al.* 2003; Klonizakis *et al.* 2006). The ICC for the test was not high (0.41-0.49) confirming this finding.

Our findings might be explained by a possible inconsistency in the methodology between the various operators (Appendices 3.3-3.5), difficulty in accurately identifying the same areas of interest (AOI) on repeat testing, participant in compliance with alcohol and cigarette abstinence and the lack of noise levels control. Marking the AOI for two weeks was not practical; the use of anatomical land marks was not always feasible while trying to avoid the variable superficial venous anatomy and the large size of the iontophoresis electrode in relation to the AOI was also a difficulty. Acceptable noise levels were not defined in the literature; during the study, a conversation was held to answer queries from some of the subjects and the effect of this on the outcome cannot be determined. The position of the AOI in the hand might have played a bigger role than expected; perfusion values for distal forearm measurements were reported as higher than proximal forearm measurements using LDF in normal healthy volunteers (de Boer *et al.* 1989; Bircher *et al.* 1994).

The list of factors influencing the results of the LDI test is long (Section 1.5.4). This study adds to this list the influence of the operator. We were able to demonstrate repeatability variations between the operators and within different vasoactive challenges. The protocol was standardised but the approach to the AOI selection and the skin handling was not. Perfusion values for distal forearm measurements were reported to be higher than proximal forearm

measurements using LDF in normal healthy volunteers (de Boer *et al.* 1989; Bircher *et al.* 1994). This prompts questions on whether the responsiveness of the microcirculatory bed in the upper limb is higher distally than proximally requiring a more specific LDI protocol taking into account the above-mentioned limitations.

3.6 CONCLUSION

The use of CPT and LDI is influenced by environmental, technical and biological variations. LDI and CPT in the hand have limited value in the assessment of individual cases due to their moderate repeatability but are useful tools in detecting group trends. The modified CPT can differentiate between PRP, HAVS and healthy volunteers groups. The LDI repeatability in the hand needs to be revisited with revised methodology and using smaller iontophoresis electrodes.

CHAPTER 4: THE EFFECT OF CARPAL TUNNEL SYNDROME ON THE MICROVASCULAR RESPONSE TO COLD IN THE HAND

4.1 INTRODUCTION

Autonomic dysfunction associated with CTS has been reported as early as 1957 (Garland *et al.* 1957). Phalen suggested that the median nerve carries autonomic nerve fibres which are affected in CTS resulting in vasomotor control disturbances (Phalen 1966).

The prevalence of autonomic symptoms in CTS has gradually increased with heightened awareness and better documentation. In a retrospective review of 2,800 CTS patients, only 28 reported autonomic symptoms (Linscheid *et al.* 1967). More recently, the prevalence has been reported to be as high as 55-60% (Chung *et al.* 1999; Verghese *et al.* 2000) and the symptoms seem to respond favourably to CTR (Chung *et al.* 1999; Chung *et al.* 2000), but the high prevalence has not yet helped unveil the underlying pathology.

4.2 AIMS

Firstly, to investigate the microvascular response in the hands of both normal volunteers and patients with CTS to a cold challenge and, secondly, to investigate the effect of CTR on the CPT in CTS patients.

4.3 METHODS

After obtaining the required ethical approval, subject recruitment and demographic data collection were carried out as outlined in Chapter 2. A data collection sheet was used (Appendix 5.1). Subjects were asked to complete a vibration white finger (VWF) screening questionnaire (Appendix 4.5).

We recruited two groups:

1- CTS patients awaiting surgery

2- Normal controls (NC)

Inclusion criteria

- Male or female aged $\geq$ 16 years
- No history of vibration exposure or history of RP prior to the development of CTS
- CTS patients awaiting surgery

or

- Normal control (NC) subject with no history of hand injury or CTS
- Subjects who give written informed consent after reading the information sheet for volunteers

Exclusion criteria

- Smoked within the last 6 hours
- Treatment with vasodilating medication including but not restricted to α-blockers, β-blockers, calcium channel antagonists, ace inhibitors, angiotensin II blockers, nitrates
- Intake of alcohol or caffeine-containing drinks within the last 12 hours
- Central or peripheral cyanosis on arrival at the examination
- Type I or Type II DM
- Subjects failing to maintain their hands in the water until the end of the test

All subjects underwent LDI of both hands at baseline followed by CPT (Sections 2.10 and 2.11). During the CPT re-warming phase, LDI was repeated on the affected hand in CTS patients and on a randomly selected side in the NC based on a randomisation table provided by the Trust statistician.

Subjects with CTS were asked to re-attend for a repeat test 5-7 months post-CTR. For descriptive purposes the following definitions were used; left hand control group (NC^{Left}), right hand control group (NC^{Right}), CTS affected hand ($CTS^{Affected}$), CTS unaffected hand (CTS^{C}).

4.4 SAMPLE SIZE AND DATA ANALYSIS

It was estimated that a sample size of 60 subjects in each group would allow the detection of 10% difference between the groups with a power of 80% and a beta error <0.05. During analysis, each hand was treated as a data unit (Garland *et al.* 1957).

In the control group (NC), the data from NC^{Left} and NC^{Right} was compared to allow the amalgamation of the sample into one NC group. Unpaired data analysis was used to compare the groups, except when the effect of CTR was studied where paired data analysis methods were utilised. The data are given as mean (SD) unless otherwise stated. Statistical advice was provided by the Trust statistician. Data analysis was conducted as outlined in Section 2.8.

4.5 RESULTS

Recruitment was complete with 60 subjects in each group. To date, 40 CTS subjects completed a 5-7 months post-surgery re-test. Recruitment history is outlined in Appendix 4.1. Demographics are summarised in Table 4.1.

The VWF screening questionnaire identified four subjects with white finger discoloration on exposure to cold in the CTS group and two in the control group. The questionnaire lacked the ability to identify patients with cold intolerance symptoms (Section 1.2.2) and was therefore not used in further analysis.

Group	Sample Size	Age (years)	Sex (Males)	Weight (Kg)	Height	Systolic BP (mmHg)	Diastolic BP (mmHg)	Dominance (Right handedness)
NC	60	48(21)	28(47%)	74(12)	171(8)	126(19)	77(11)	55(92%)
CTS	60	56(13)	20(33%)	79(14)	166(8)	131(16)	84(9)	58(97%)

Table 4.1 Demographics of the groups

4.5.1 Control group

Cold Provocation Testing

There was no statistically significant difference between the NC^{Left} and NC^{Right} at baseline or $T_{5^{\circ}C}$ (p-value >0.05 (Mann-Whitney U)) (Appendix 4.2.A).

Laser Doppler Imaging

Perfusion values for NC^{Left} and NC^{Right} in response to ACH and SNP were compared. There was no statistical difference between the two sides (p-value >0.05 (Mann-Whitney U)) when LDI_{Max}, LDI_{Mean}, Post-cooling LDI_{Max}, Post-cooling LDI_{Mean} were compared (Appendices 4.2.B & C).

The data from NC^{Left} and NC^{Right} were amalgamated and are referred to collectively as NC (Table 4.2).

	ACH		SNP	
	Median	Interquartile range	Median	Interquartile range
Mean LDI_{Max}	0.84	0.65, 1.10	0.84	0.67, 1.02
Mean LDI_{Mean}	0.77	0.59, 0.90	0.78	0.62, 0.94
Post-cooling Mean LDI_{Max}	0.72	0.62, 0.84	0.74	0.61, 0.85
Post-cooling Mean LDI_{Mean}	0.67	0.58, 0.78	0.70	0.58, 0.82

Table 4.2 LDI response in the control group (n=120)

The microvascular response to a cold challenge in NC was assessed. Cold cause suppression of the endothelial-dependent and -independent response in the control group (Table 4.3 and Figures 4.1 & 4.2).

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	p-value (Wilcoxon Signed Ranks Test)
For ACH					
Mean LDI_{Max}	Pre-cooling	0.039	0.87	0.68, 1.06	*0.002
	Post-cooling	0.003	0.72	0.62, 0.84	
Mean LDI_{Mean}	Pre-cooling	0.200	0.79	0.65, 0.91	0.002
	Post-cooling	0.157	0.67	0.58, 0.78	
For SNP					
Mean LDI_{Max}	Pre-cooling	0.009	0.81	0.67, 1.0	0.005
	Post-cooling	0.002	0.74	0.61, 0.85	
Mean LDI_{Mean}	Pre-cooling	0.019	0.76	0.62, 0.93	0.015
	Post-cooling	0.067	0.7	0.58, 0.82	

Table 4.3 The microvascular response to a cold challenge in the control group (n=120) (* Paired T-Test)

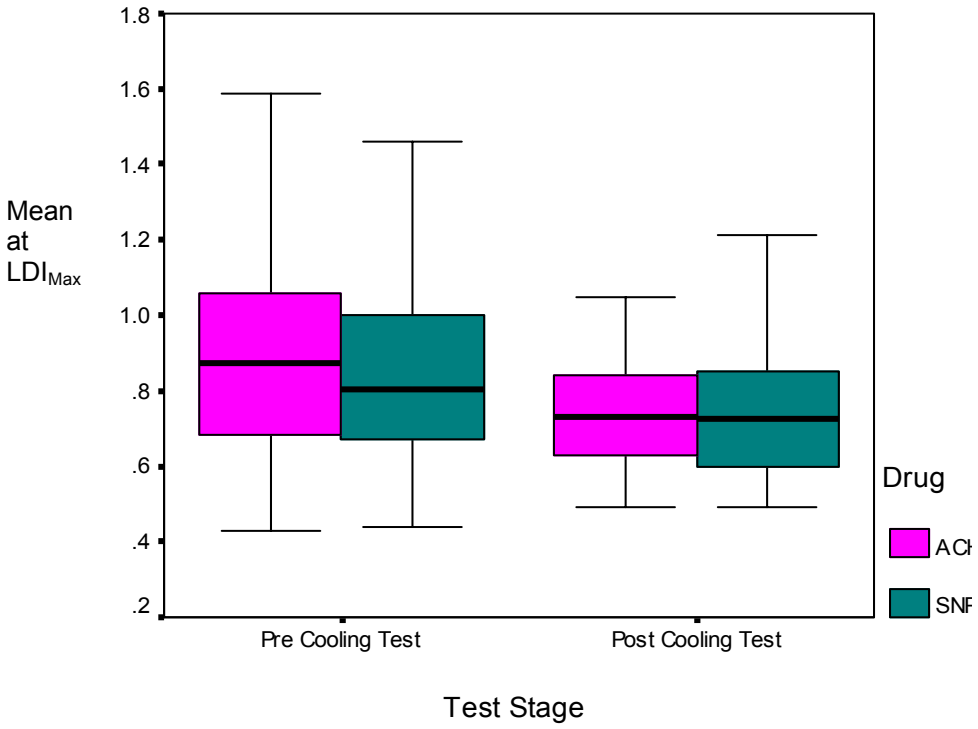


Figure 4.1 LDI_{max} in NC. Change post-cooling for ACH and SNP (p-value = 0.002 and 0.005, respectively)

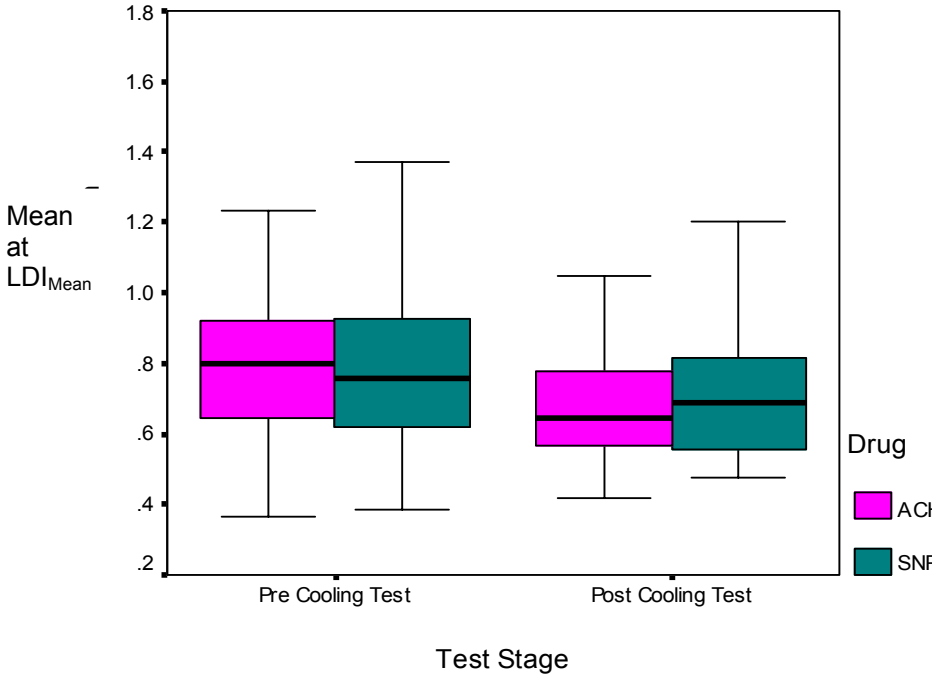


Figure 4.2 LDI_{Mean} in NC. Change post-cooling for ACH and SNP (p-value = 0.002 and 0.15, respectively)

The CPT and LDI findings for NC and CTS^{C} were compared and no significant difference observed (p-value >0.05 (Mann-Whitney U)) (Appendix 4.3). CTS^{C} was used as a control against $CTS^{Affected}$.

4.5.2 The effect of CTS on the microvascular and rewarming response of the hand

The CPT and LDI data for $CTS^{Affected}$ and CTS^{C} were compared and no significant difference observed (Tables 4.4 A, B, C).

		Normality (Shapiro-Wilk)	Median	Interquartile range	p-value (Mann-Whitney U)
Baseline	CTS^{C}	0.2	7.7	5.2, 9.3	0.97
	$CTS^{Affected}$	<0.0001	7.7	4.7, 9.7	
$T5^{o}C$	CTS^{C}	0.2	330	206, 512	0.27*
	$CTS^{Affected}$	0.2	372	191, 591	

Table 4.4.A **CPT** comparison between $CTS^{Affected}$ and CTS^{C} (* T-Test)

		Normality (Shapiro-Wilk)	Median	Interquartile range	p-value (Mann-Whitney U)
Mean LDI_{Max}	CTS^{C}	0.02	0.76	0.59, 0.98	0.4
	$CTS^{Affected}$	0.002	0.79	0.65, 0.99	
Mean LDI_{Mean}	CTS^{C}	0.2	0.68	0.54, 0.92	0.3
	$CTS^{Affected}$	<0.0001	0.73	0.62, 0.89	
Post-cooling Mean LDI_{Max}	CTS^{C}	0.002	0.68	0.58, 0.8	0.3
	$CTS^{Affected}$	<0.0001	0.73	0.62, 0.84	
Post-cooling Mean LDI_{Mean}	CTS^{C}	0.001	0.63	0.54, 0.76	0.3
	$CTS^{Affected}$	0.004	0.68	0.59, 0.78	

Table 4.4.B LDI response to ACH between $CTS^{Affected}$ and CTS^{C}

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	p-value (Mann-Whitney U)
Mean LDI_{Max}	CTS^{C}	0.04	0.75	0.64, 0.96	0.2
	$CTS^{Affected}$	<0.0001	0.84	0.69, 1.05	
Mean LDI_{Mean}	CTS^{C}	0.01	0.7	0.61, 0.9	0.1
	$CTS^{Affected}$	0.003	0.78	0.64, 0.97	
Post-cooling Mean LDI_{Max}	CTS^{C}	<0.0001	0.7	0.62, 0.81	0.09
	$CTS^{Affected}$	0.09	0.79	0.65, 0.98	
Post-cooling Mean LDI_{Mean}	CTS^{C}	<0.0001	0.63	0.57, 0.78	0.09
	$CTS^{Affected}$	0.2	0.76	0.58, 0.89	

Table 4.4.C No statistical significant difference in the LDI response to SNP between $CTS^{Affected}$ and CTS^{C}

4.5.3 The microvascular response following CTR

Forty CTS subjects completed two visits (i.e. pre- and post-operative). The pre- and post-CTR, CPT and LDI were compared. Baseline temperature was significantly higher following CTR (Table 4.5, Figure 4.3). There was no statistically significant difference in the LDI pre- and post-operatively (Tables 4.6 A & B).

		Normality (Shapiro-Wilk)	Median	Interquartile range	p-value (Wilcoxon Signed Ranks Test)
Baseline	Pre-op	0.012	7.7	5.96, 9.6	0.016
	Post-op	0.001	9.6	6.2, 10.5	
$T_{5°C}$	Pre-op	0.098	474	264, 593	0.063
	Post-op	0.02	348	144, 534	

Table 4.5 CPT changes in response to a surgery in $CTS^{Affected}$ (n=40)

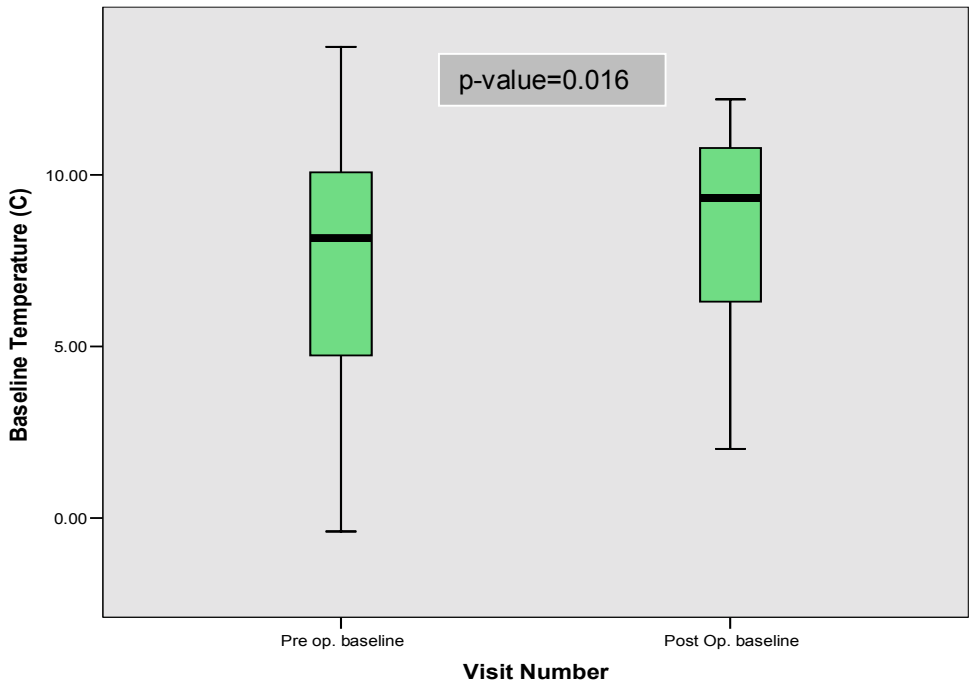


Figure 4.3 The change in the baseline temperature in the CTS-affected hand post-surgery (n=40)

		Normality (Shapiro-Wilk)	Median	Interquartile range	p-value (Wilcoxon Signed Ranks Test)
Mean LDI_{Max}	Pre-op	0.001	0.79	0.64, 1.1	0.9
	Post-op	0.005	0.82	0.66, 1.18	
Mean LDI_{Mean}	Pre-op	0.001	0.73	0.62, 0.94	0.7
	Post-op	0.007	0.75	0.59, 1.09	
Post-cooling Mean LDI_{Max}	Pre-op	0.001	0.73	0.6, 0.84	0.7
	Post-op	0.001	0.73	0.65, 0.86	
Post-cooling Mean LDI_{Mean}	Pre-op	0.001	0.70	0.56, 0.77	0.8
	Post-op	<0.0001	0.64	0.58, 0.78	

Table 4.6.A Pre- and post-CTR perfusion data (**ACH**) (n=40)

		Normality (Shapiro-Wilk)	Median	Interquartile range	p-value (Wilcoxon Signed Ranks Test)
Mean LDI_{Max}	Pre-op	<0.0001	0.86	0.71, 1.1	0.8
	Post-op	0.006	0.81	0.69, 1.2	
Mean LDI_{Mean}	Pre-op	<0.0001	0.78	0.68, 1.0	0.9
	Post-op	0.014	0.75	0.65, 1.1	
Post-cooling Mean LDI_{Max}	Pre-op	0.02	0.79	0.62, 0.88	0.09
	Post-op	0.002	0.80	0.69, 1.0	
Post-cooling Mean LDI_{Mean}	Pre-op	0.03	0.75	0.57, 0.82	0.1
	Post-op	0.003	0.75	0.67, 0.94	

Table 4.6.B Pre- and post-CTR perfusion data (**SNP**) (n=40)

The re-warming data of the index and middle fingers on the $CTS^{Affected}$ side (digits supplied by the median nerve) were compared pre- and post-operatively (Table 4.7). In these digits, CTR significantly raised baseline temperature and shortened $T_{5°c}$ (Figures 4.4 & 4.5, Appendix 4.4).

		Normality (Shapiro-Wilk)	Median	Interquartile range	p-value (Wilcoxon Signed Ranks Test)
Baseline	Pre-op	0.054	7.7	3.7, 9.8	0.003
	Post-op	<0.0001	9.4	5.8, 10.5	
$T_{5°C}$	Pre-op	0.2	468	288, 675	0.013
	Post-op	0.01	273	144, 558	

Table 4.7 The effect of CTR on the CPT findings in the median nerve-supplied digits (n=40)

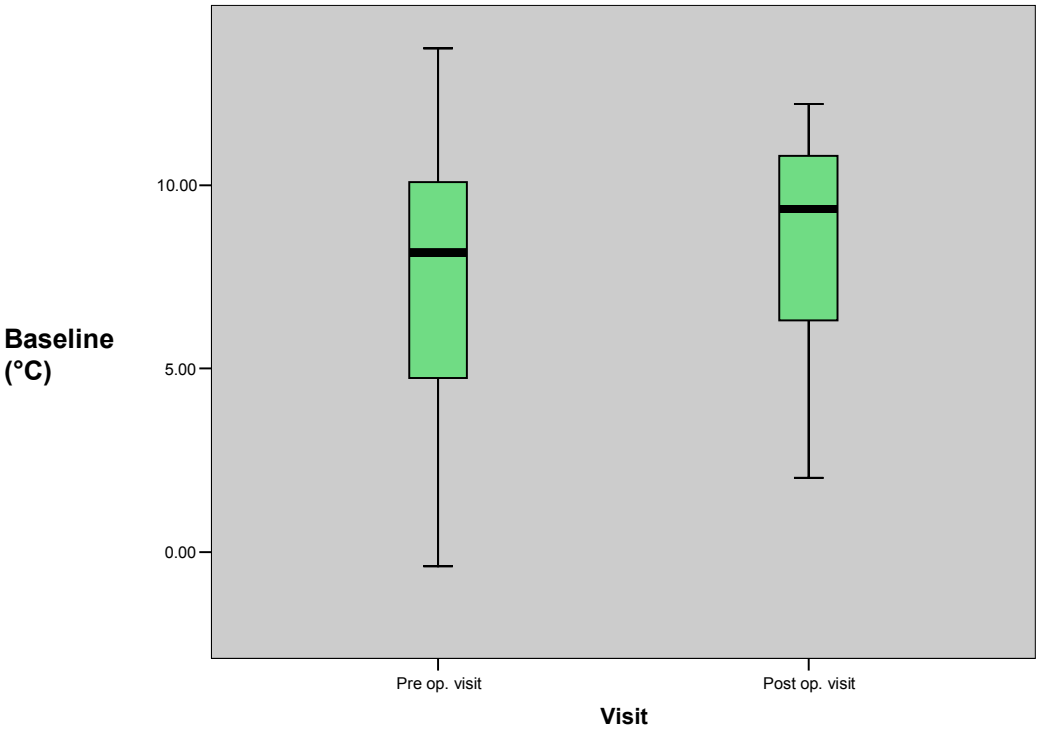


Figure 4.4 The effect of CTR on the CPT findings in the median nerve-supplied digits at baseline (n=40)

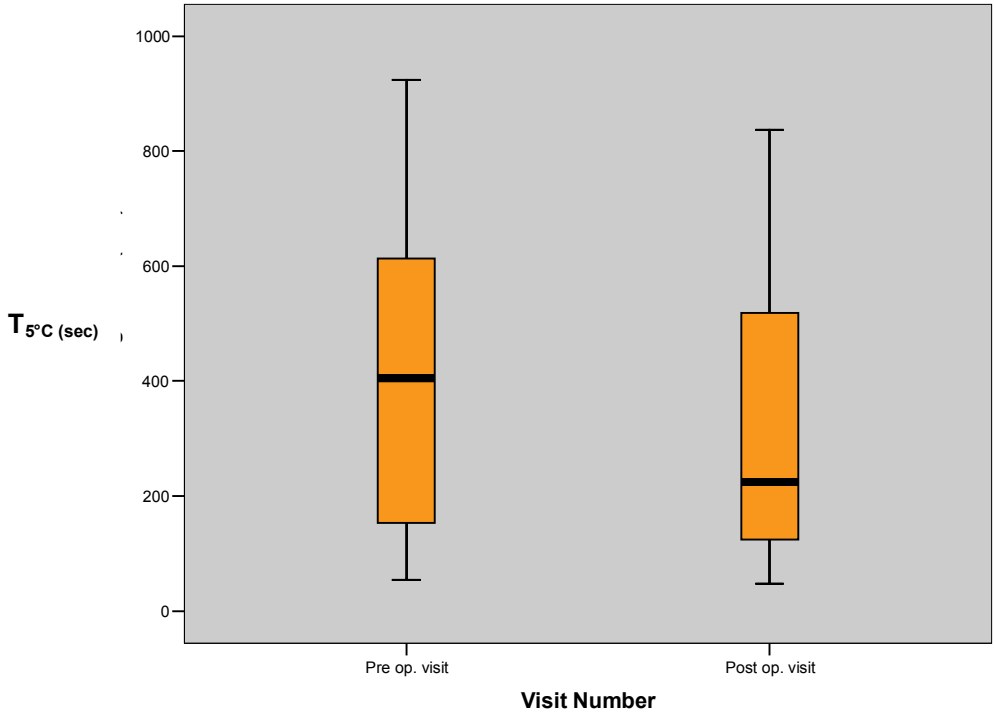


Figure 4.5 The effect of CTR on the CPT findings in the median nerve-supplied digits at $T_{5°C}$ (n=40)

4.6 DISCUSSION

This study identified a significant rise in the digital baseline temperature (>1.5°C) 5-7 months post-CTR, and a faster $T_{5°C}$ post-CTR particularly in the median nerve-supplied digits. The study identified the effect of cold on suppressing the response of both the endothelial-dependent and -independent mechanisms to stimulation in the control group.

Following a series of publications documenting the autonomic symptoms amongst CTS patients (Linscheid *et al.* 1967; Pal *et al.* 1996; Chung *et al.* 1999; Chung *et al.* 2000; Verghese *et al.* 2000), the American Academy of Neurology included dry skin, swelling and colour changes as part of the CTS picture (AAN 1993). Some authors considered this presentation a variant of RP (Linscheid *et al.* 1967). Gradually the prevalence of such symptoms increased up to 60% amongst CTS suffers.

A rise in the baseline temperature post-CTR is not a novel finding. Despite the small sample size, unclear methodology and the lack of statistical significance, Chung *et al*. evaluated the improvement of the autonomic (RP-like) symptoms subjectively and objectively (using photoplethysmography following CPT) in a group of CTS suffers pre- and post-operatively; they reported a 78% improvement in 18 patients post-CTR (all bilateral, and three out of seven unilateral CTRs improved) with a mean recovery time of 4 months (Chung *et al.* 1999; Chung *et al.* 2000). The faster $T_{5°C}$ post-CTR is a novel finding in our study and once again recovery of the vasomotor sympathetic fibres to the fingers carried by the median nerve might be the cause.

Endothelial function is mediated mainly by Nitrous Oxide (NO) with variable contribution from substances such as prostaglandins and an endothelial-derived hyperpolarisation factor (Furchgott *et al.* 1980; Vallance *et al.* 1989; Garland *et*

al. 1995; Kvandal *et al.* 2003). Whereas SNP acts directly on the smooth muscle cells (Rapoport *et al.* 1983; Kvandal *et al.* 2003), ACH-induced vasodilatation depends on an intact vascular endothelium to stimulating NO synthesis in the endothelial cells. Therefore, endothelial function can be evaluated by comparing the ACH- and SNP-induced vasodilatation (Griendling *et al.* 1996). Our study clearly identified the effect of cold on suppressing the endothelial function in normal controls. The effect of temperature on microvascular perfusion has been reported previously (Bircher *et al.* 1994; Fullerton *et al.* 2002), resulting in a lower perfusion response to an endothelial-dependent stimulus (i.e. ACH).

Using infrared telethermography, a block-induced paralytic vasodilatation was studied in 47 subjects (15 median blocks, 15 ulnar blocks and 17 radial blocks). The authors concluded that the vasomotor supply of the skin of the hand followed the sensory supply territory (Campero *et al.* 1993). These findings might explain why CPT measured vasomotor changes post-surgery (measures the temperature of the terminal phalanx), while LDI failed to detect similar changes on the dorsum of the hand. This area receives its sensory supply from the ulnar and radial nerves, not the median nerve.

There are some shortcomings in the LDI studies. To deliver an iontophoresis challenge to the median nerve distribution region, small, easy to secure digital chambers are required. Such chambers were not available and scanning the back of the hand was a compromise. There is no evidence in the literature to suggest that local neural injury causes a systemic response when cold-related symptoms are in question (Section 1.2.3). Indirectly, these findings suggest that changes in the microvascular response post-CTR is a local phenomenon.

The use of a cold intolerance assessment tool could have strengthened this study. A vibration white finger screening questionnaire (Appendix 4.5) was used

but was not useful in screening cold intolerance. We introduced the CISS questionnaire (McCabe *et al.* 1991; Ruijs *et al.* 2006) later on in the study; this was sent by mail to the participants but the replies were incomplete and not available for analysis. The use of the CISS questionnaire should allow stratification of the subjects into subgroups which can be compared.

4.7 CONCLUSION

CTR significantly raises the baseline temperature and shortens the re-warming time in the median nerve-supplied digits. Cold blunts the endothelial response to direct and indirect stimulation. It would be interesting to investigate the effect of CTR on other cold-related conditions like RP.

CHAPTER 5: THE EFFECT OF HAND INJURY ON THE MICROVASCULAR RESPONSE IN THE HAND

5.1 INTRODUCTION

Cold-related symptoms in the injured hand are not uncommon with 50-100% prevalence. The pathophysiology is unclear but a neural cause is favoured; however, a direct correlation between the severity of symptoms and the extent of the neural injury is lacking (Section 1.2.4) (Engkvist *et al.* 1985; Kay 1985; Freedman *et al.* 1995).

Small-sized retrospective studies reported a lower digital baseline temperature in the injured hand compared to controls (Engkvist *et al.* 1985) and a lower pulse pressure (<75% of the unaffected contralateral digit), particularly in the severely affected (Gelberman *et al.* 1978).

5.2 AIMS

To investigate the CPT and perfusion response in the injured hand compared to normal controls.

5.3 METHODS

A data collection sheet was used to record demographical data (Appendix 5.1). Subjects were required to complete a vibration white finger (VWF) screening questionnaire (Appendix 4.5).

Two groups were recruited:

Group 1: Patients sustaining a hand injury (HI) in the previous three months to five years

Group 2: Normal control (NC) volunteers

Inclusion and exclusion criteria were similar to those outlined in Chapter 4. Additionally, subjects with HI to the median, ulnar or digital nerves, radial or ulnar artery, tendons or fracture of metacarpal, proximal or middle phalanges were included. The severity of the injury was classified according to the hand injury severity score (Bartelink *et al.* 1993).

All subjects were studied using LDI (both hands) followed by a CPT, as detailed in Sections 2.10 and 2.11. During the re-warming phase of the CPT, LDI was repeated on the affected hand in the HI group and on a randomly-selected side in the NC group based on a randomisation table provided by the Trust statistician.

For description purposes, the following references were used: the affected side within the hand injury group ($HI^{Affected}$), the control side of the HI (HI^{C}) and the normal control group (NC).

Sample size and data analysis

It was estimated that a sample size of 60 subjects in each group would allow the detection of a 10% difference between the groups with a power of 80% and a beta error of <0.05. Data from NC, $HI^{Affected}$ and HI^{C} were analysed using unpaired statistical tests. Pre- and post-cooling $HI^{Affected}$ data were analysed using paired statistical tests. Advice was sought from the Trust statistician when required. The data analysis was conducted as outlined in Section 2.8. Data were presented as mean (SD) unless stated otherwise.

5.4 RESULTS

5.4.1 Recruitment and demographics

Data from the NC recruited for the CTS study (Chapter 4) was used in this study. Hand injury recruitment was very challenging; details of the recruitment

are outlined in Figure 5.1. The demographics of the groups are summarised in Table 5.1.

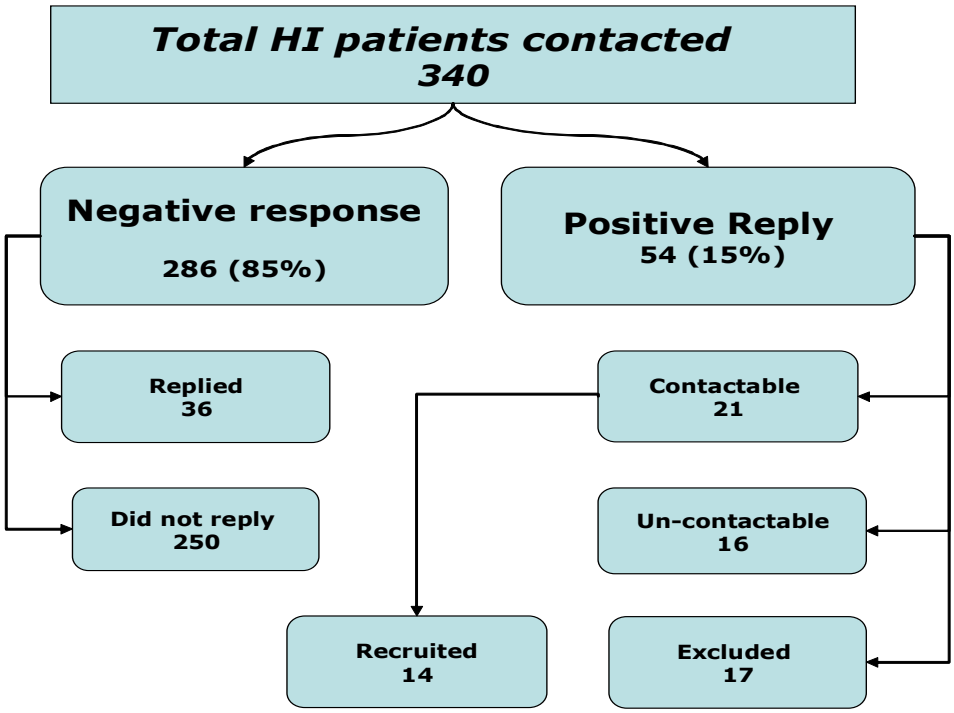


Figure 5.1 Hand Injury Recruitment

	Sample Size	Age (years)	Sex (Males)	Weight (Kg)	Height (cm)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Dominance (Right handedness)
NC	60	47.6 (21)	28 (47%)	74 (12)	171 (8)	126 (19)	77 (11)	55 (92%)
HI	14	52 (16)	12 (75%)	75 (14)	175 (7)	139 (12)	83 (8)	10 (71%)

Table 5.1 Demographical data

5.4.2 The microvascular perfusion response to iontophoresis challenge

ACH Iontophoresis

The data from NC, $HI^{Affected}$ and HI^{C} were compared. No statistically-significant difference was observed when ACH was used (Table 5.2).

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	p-value (Mann-Whitney U)
ACH Pre-cooling					
Comparing microvascular response in between NC and HI^{C}					
Mean LDI_{Max}	NC	0.2	0.79	0.66, 1.0	0.7
	HI^{C}	<0.0001	0.84	0.65, 1.1	
Mean LDI_{Mean}	NC	0.2	0.86	0.65, 1.1	0.2
	HI^{C}	0.003	0.77	0.59, 0.9	
Comparing microvascular response between HI^{C} and $HI^{Affected}$					
Mean LDI_{Max}	HI^{C}	0.2	0.79	0.66, 1.01	*0.67
	$HI^{Affected}$	0.1	0.78	0.66, 0.95	
Mean LDI_{Mean}	HI^{C}	0.2	0.86	0.65, 1.08	*0.98
	$HI^{Affected}$	0.8	0.89	0.63, 1.1	

Table 5.2 The pre-cooling microvascular response to **ACH** in hand injury (* T-Test)

SNP Iontophoresis

The data from NC, $HI^{Affected}$ and HI^{C} were compared. No statistically-significant difference was observed when SNP was used (Table 5.3).

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	p-value (Mann-Whitney U)
SNP Pre-cooling					
Comparing microvascular response in between NC and HI^{C}					
Mean LDI_{Max}	NC	0.001	0.74	0.58, 0.86	0.2
	HI^{C}	<0.0001	0.82	0.67, 1	
Mean LDI_{Mean}	NC	0.028	0.71	0.55, 1.02	0.6
	HI^{C}	<0.0001	0.78	0.62, 0.93	
Comparing microvascular response between HI^{C} and $HI^{Affected}$					
Mean LDI_{Max}	HI^{C}	0.001	0.74	0.58, 0.86	0.98
	$HI^{Affected}$	0.01	0.78	0.56, 0.91	
Mean LDI_{Mean}	HI^{C}	0.03	0.71	0.55, 1.02	0.91
	$HI^{Affected}$	0.3	0.77	0.6, 0.96	

Table 5.3 The pre-cooling microvascular response to **SNP** in hand injury

LDI findings post-cooling in hand injury

As for NC (Section 4.5), the endothelium-dependent stimulation in the $HI^{Affected}$ was blunted by cold. The independent-endothelial response did not mirror that of the NC in response to cold in this small sample (Table 5.4).

		Normality (Shapiro-Wilk)	Median	Interquartile range	p-value (Wilcoxon Signed Ranks Test)
ACH					
Mean LDI_{Max}	Pre-cooling	0.1	0.78	0.66, 0.95	0.27
	Post-cooling	<0.0001	0.68	0.59, 0.76	
Mean LDI_{Mean}	Pre-cooling	0.8	0.89	0.63, 1.1	0.01
	Post-cooling	0.001	0.65	0.55, 0.67	
SNP					
Mean LDI_{Max}	Pre-cooling	0.01	0.78	0.56, 0.91	0.08
	Post-cooling	0.8	0.92	0.8, 1.08	
Mean LDI_{Mean}	Pre-cooling	0.3	0.77	0.6, 0.96	0.2
	Post-cooling	0.4	0.84	0.79, 0.98	

Table 5.4 The effect of cold on the microvascular response to stimulation

5.4.3 The cold provocation test in hand injury

There was no significant difference in CPT findings between NC and HI when baseline and $T_{5°C}$ were compared (Table 5.5).

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	p-value (Mann-Whitney U)
CPT					
NC and HI^{C}					
Baseline	HI^{C}	0.014	9.1	3.1, 10.3	0.445
	NC	<0.0001	6.7	3.9, 9	
$T_{5°C}$	HI^{C}	0.139	253	113, 406	0.089
	NC	0.001	369	200, 623	
Within HI group					
Baseline	HI^{C}	0.015	9.1	3.1, 10.3	0.9
	$HI^{Affected}$	<0.0001	9.6	2.5, 10.5	
$T_{5°C}$	HI^{C}	0.013	253	113, 406	0.4
	$HI^{Affected}$	0.264	322	155, 633	

Table 5.5 The CPT response in hand injury

5.4.4 The hand injury severity score (HISS) and vibration white finger (VWF) questionnaire

HISS was used to classify patients according to their injury severity and allow for a correlation between the injury severity and the degree of the microvascular response to be evaluated. The injury details of 11 subjects were available. HISS scores from subjects recruited reflected extremes on the spectrum of severity (Appendix 5.3) with a mean score of 51 (64). The wide range in a small sample size made the use of this scoring system of limited value in stratifying subjects into groups (mild, moderate, severe HI); therefore, it was not incorporated in the analysis. Using the VWF questionnaire, only two subjects reported blanching (Appendix 5.2).

5.5 DISCUSSION

In this study I was unable to identify statistically-significant changes in the CPT or skin perfusion in HI patients in response to cold. This may reflect the small sample size and wide variation in injury severity between the study subjects. Bearing in mind that CPT is a technique better suited for the detecting trends in a large sample size, the lack of significant findings is expected (Bartelink *et al.* 1993).

Recruitment was a major hurdle. Postal recruitment rates as low as 20% have been reported (Hewison *et al.* 2006) but the recruitment rate in this study was as low as 4%. Hand injury patients are usually young and may not be motivated to participate in research, particularly in the absence of a financial incentive. Additionally, the Pulvertaft Hand Unit's catchment area is very wide; therefore, the commute distance in some cases can be too far to attend.

During the study period, a number of limitations were noted. A tool to identify subjects with cold-related symptoms and objectively quantify the symptoms was not incorporated within the protocol (Section 4.6). The VWF questionnaire was not useful in the identification of CI symptoms as it only screened for white discoloration of the digits and the hand. The iontophoresis was delivered to the back of the hand rather than the affected digits; this was a compromise to accommodate for the inability to secure the available iontophoresis chambers on the affected digits.

5.6 CONCLUSION

It is vital to improve the recruitment technique (perhaps by providing a financial incentive) to achieve an adequate sample size and get meaningful conclusions. The spectrum of hand injuries is vast and a validated repeatable cold

intolerance assessment tool has to be incorporated in any future study of this condition to facilitate patient grouping. This study is a start for future work on the microvascular response of the injured hand to cold and the limitations faced here will hopefully be recognised and avoided in the future.

CHAPTER 6: THE MANAGEMENT OF CTS IN A COMMUNITY HOSPITAL – AN AUDIT STUDY

6.1 INTRODUCTION

CTS is the commonest entity seen by hand surgeons (Palmer *et al.* 1995). Despite the classic symptoms and signs, the diagnosis can occasionally be challenging due to atypical sensory symptoms, the absence of physical findings and the lack of an objective gold standard test for the diagnosis (Rempel *et al.* 1998; Michelsen *et al.* 2002).

In short-term follow-up randomised trials, steroid injection treatment seems to give better results compared to other non-operative treatments but on longer follow-up surgery appears to give the best outcome (injection success rate is 8% at two years) (Dammers *et al.* 1999a; Viera 2003; Hui *et al.* 2005).

Both conservative and surgical modalities are available for the treatment of CTS (Section 1.1.5). There is convincing evidence through randomised trials of the short-term benefits of injectable steroid compared to other modalities of non-operative treatment, but the long-term success rate remains very disappointing and surgery remains the superior option.

In a local community hospital, a fortnightly nurse-led CTS management clinic (a maximum of five new patients reviewed per clinic) with direct access to the lead consultant's consulting rooms was established in 2002. A nurse practitioner was trained by a senior hand surgeon. In this clinic, patients were assessed based on a set proforma and those diagnosed with CTS received initial conservative treatment (night splint and steroid injection). Nerve conduction studies were requested for the atypical cases and reviewed at a later date by the consultant.

In 2005, the nurse-led CTS clinic was replaced by a registrar-led hand clinic twice weekly (a maximum of seven new patients per week) covering a spectrum

of hand referrals, mainly compressive neuropathy, base of thumb OA and hand lumps.

6.2 AIMS

The aims of this work are: firstly, to assess the success rate of conservative treatment for CTS in the nurse- and registrar-led clinics; secondly, to identify predictors of non-operative treatment success; thirdly, to determine the impact of time on the severity of symptoms; fourthly, to compare the conservative with the surgical treatment of CTS; and, finally, to determine the impact of these clinics on the consultant clinic waiting time.

6.3 METHODS

6.3.1 An audit of the nurse-led CTS clinic

Approval from the Primary Care Trust Clinical Governance office was obtained. The notes of all patients treated for CTS through the nurse-led CTS clinic over a period of 18 months were audited.

Data collection was based on the assessment proforma used in the clinic and included age, gender and hand dominance. Additionally, relevant clinical history, such as the symptomatic side, the time at which worse symptoms were noted, digits affected, nocturnal symptoms and the duration of the complaint, was also documented. Symptom severity score was determined (Levine Katz Questionnaire (Levine *et al.* 1993)). Details of the clinical examination, including evidence of thenar wasting, the response to provocation i.e. Phalen's (Werner *et al.* 1994), reverse Phalen's (Bowles *et al.* 1983), Tinel's (Bowles *et al.* 1983) McMurtry's and Durkan's tests, NCS and management plan information, were also available for analysis.

6.3.2 Registrar-led CTS clinic audit

Data on patients managed in this clinic over a period of 18 months were collected from patient follow-up sheets (Appendix 6.1). Up to 6 months follow-up data were available for subjects treated non-operatively (splint and steroid injection) while up to 12 months follow-up data were available for the surgery group.

In both clinics, steroid injections were prepared in clinic (40 mg of Kenalog® (Triamcinolone Acetate) and 1 ml of Lignocaine 1%) and delivered at the level of the proximal wrist crease half-way between the Palmaris Longus and Flexor Carpi Ulnaris tendons using a 22-gauge needle angled 45° distally into the carpal tunnel. A repeat injection was offered once at 2 months.

Exclusion criteria:

- Diabetes mellitus
- Concurrent compressive neuropathy (i.e. double-crush syndrome or cubital tunnel syndrome) or a systemic neuropathy (i.e. multiple sclerosis)

After the diagnosis of CTS was established, the options of management (conservative and surgical) were discussed. Patients conservatively treated were reviewed at 2, 4 and 6 months; patients remaining asymptomatic were discharged at 6 months. A repeat injection was offered once at 2 months and all patients treated conservatively were given a night splint (FUTURA Splint). The conservative management was considered to have failed if the patient underwent CTR following conservative treatment. Patients treated surgically were followed up for a year.

6.3.3 Data analysis

The data were stored on an Excel® spread sheet and analysed as outlined in Section 2.8 using SPSS Version 13. Logistic regression was used to determine predictors of injection success.

6.4 RESULTS

6.4.1 The nurse-led CTS clinic audit

Eighty-two new patients attended the clinic over the 18 months. The notes of 74 (90%) patients (31 males, 43 females) were available. The mean age of the sample was 49 (14.4) years and 93% were right-handed. CTS was unilateral in 66 (92%) patients (right hand n=46, left hand n=20).

6.4.1.1 The success of the conservative management

Only 17 (23%) patients were successfully managed conservatively by the nurse. The remaining 57 (77%) patients were referred to the consultant clinic for further management (Figure 6.1). Of the patients who received conservative treatment, 27 (61%) failed conservative treatment and required surgical intervention.

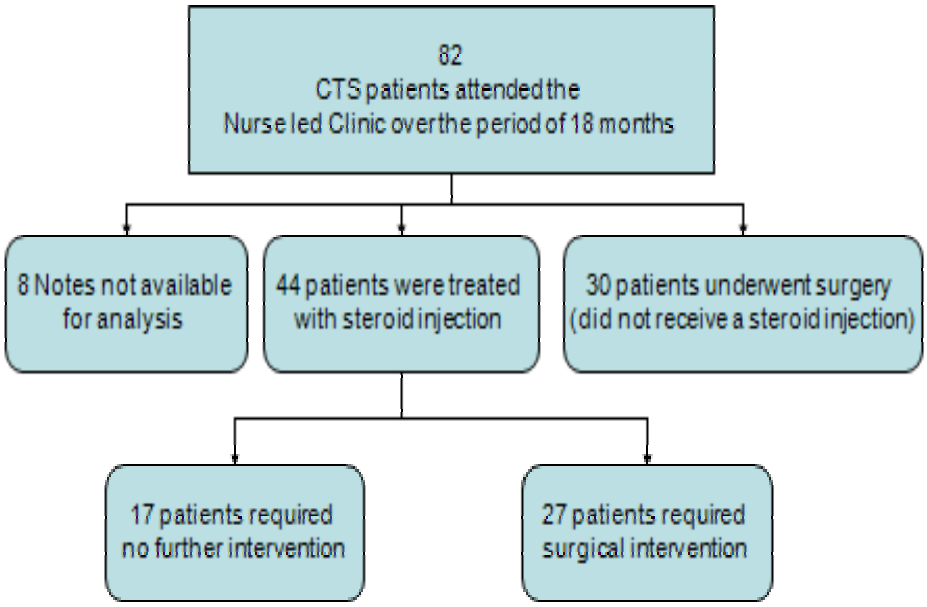


Figure 6.1 Patient treatment outcome

6.4.1.2 Predictors of the conservative treatment success

A range of clinical symptoms and investigations was analysed to determine predictors of conservative treatment success (Table 6.1, Figures 6.2 and 6.3).

Factor	p-Value (Logistic Regression)
Wake Up at Night	0.3
Duration of Symptoms	>0.1
Gender	0.9
Phalen's Test	0.9
McMurtry's Test	0.9
Reverse Phalen's Test	0.1
Durkan's Test	0.8
Tinel's Sign	0.7
Thenar Wasting	0.8

Table 6.1 Predictive significance of history and examination in determining the success of conservative treatment

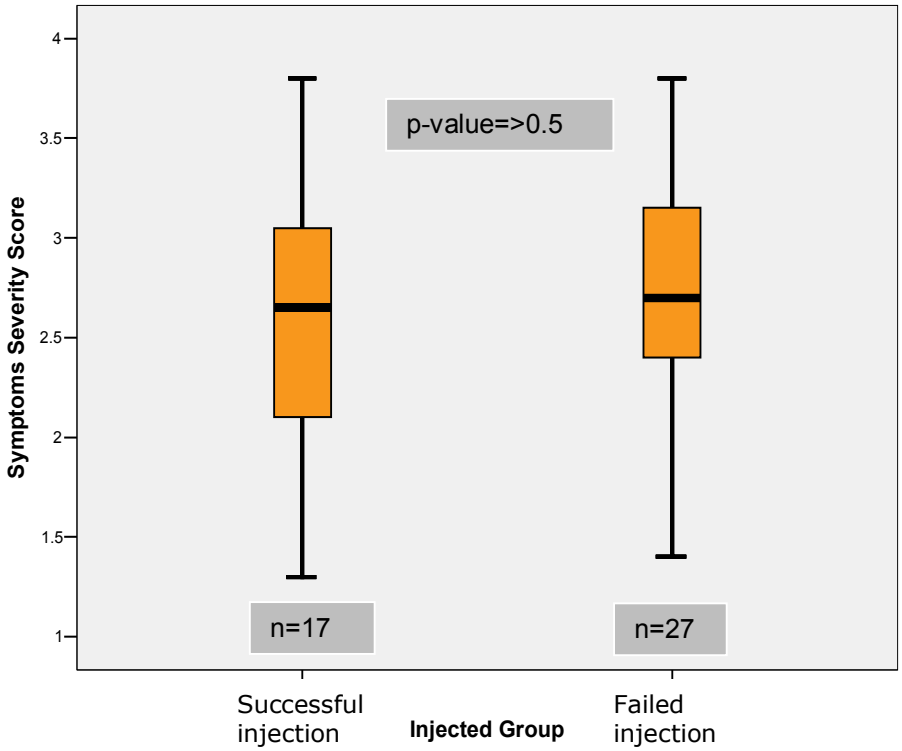


Figure 6.2 Symptom Severity Score – Nurse-led Clinic (T-Test)

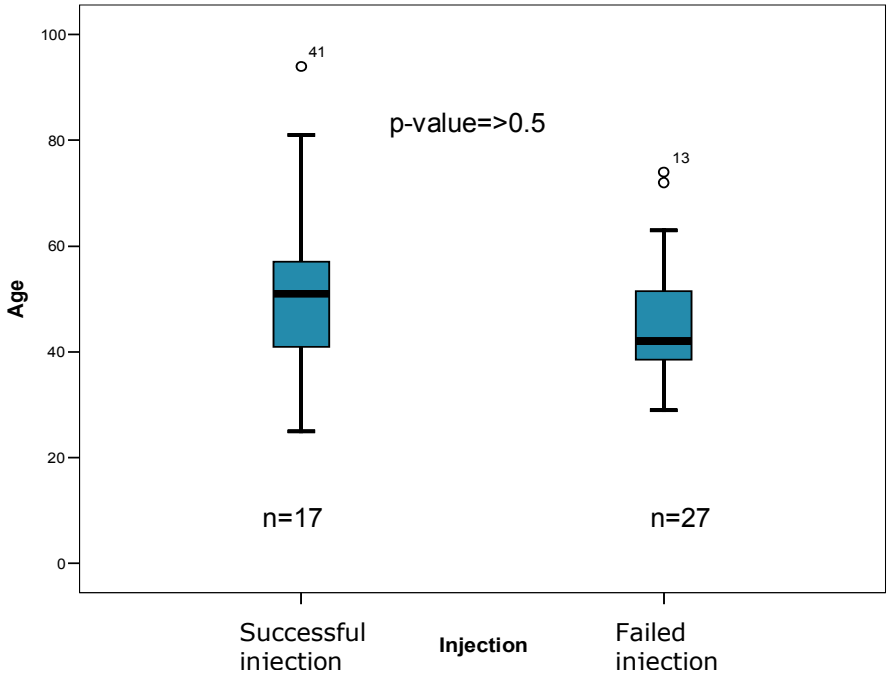


Figure 6.3 Patient Age – Nurse-led Clinic (Mann-Whitney U Test)

6.4.1.3 Disease severity and time

The severity of symptoms increased with time. This is shown as a significantly higher symptom severity score (SSS) in patients with a history >1 year (SSS at 3-6 months = 2.5(0.5), at 6-12 months = 2.4 (0.6) and >1 year = 2.9 (0.6), p = 0.01, ANOVA) (Figure 6.4). Thirty-seven per cent of the patients with a CTS history of ≥1 year reported constant symptoms (p = 0.001, X^2 test). Female patients reported more severe symptoms (SSS (males) = 2.5 (0.7) and SSS (females) = 2.8 (0.6), p = 0.03, T-Test).

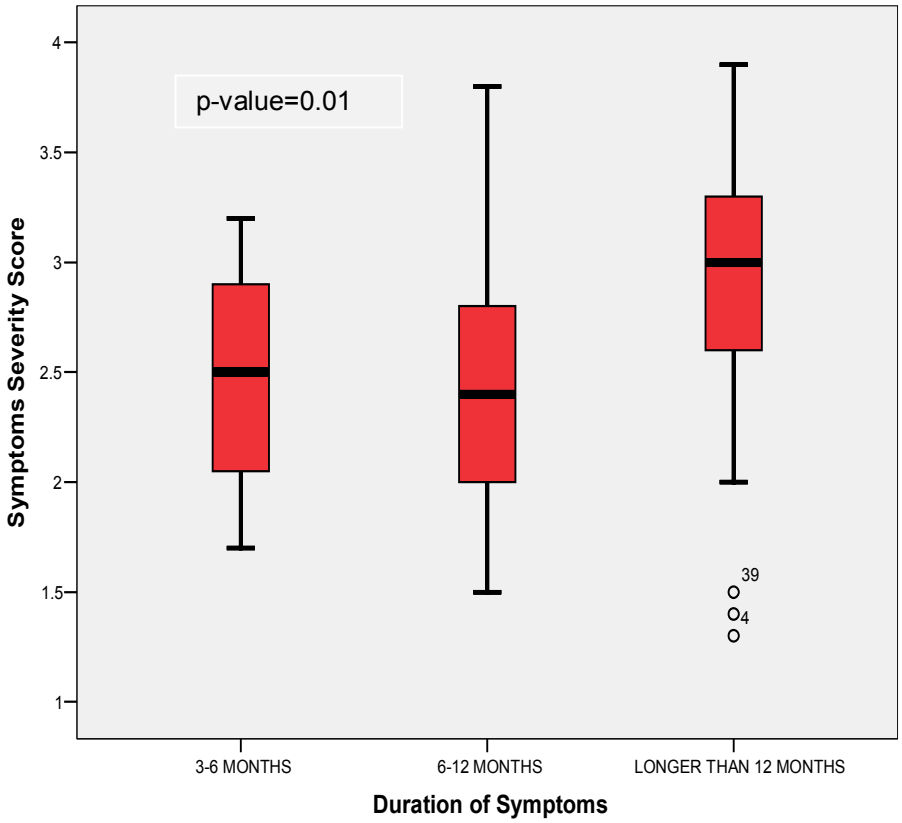


Figure 6.4 The relation between the duration of symptoms and the intensity of the disease (ANOVA) (n=74)

Night symptoms were reported by two-thirds (77%) of patients and were more prevalent amongst females (86%) versus males (35%) (p = 0.03, X^2 test), but was the worst complaint in only 23%.

6.4.1.4 The effect of a nurse-led CTS clinic on waiting times

The available databases at the hospital contained insufficient information to assess this aspect of the study. This was due to the following: firstly, all the patients were listed under the consultant's name with no reference to the nurse in the computer system in the hospital; secondly, patients seen by the nurse came from a general pool of patients and not directly from the consultant's clinic waiting list.

Service observers in the hospital management confirmed that the waiting times were not reduced by the nurse-led clinic activity (remained 27 weeks throughout the duration of the clinic service).

6.4.2 Registrar-led CTS clinic audit

The notes of 173 consecutive cases fulfilling the inclusion criteria over a period of 18 months were reviewed. Demographical data are summarised in Table 6.2. Demographically, there was no significant difference between the injection and surgery groups (Appendix 6.2). The data were skewed and are therefore presented as median (interquartile range).

		Injection Group	Surgery Group
Sample size		112	61
Age (years)		55 (20)	56 (16)
Sex	Male	33 (29%)	15 (25%)
	Female	79 (71%)	46 (75%)
Dominance	Right	92%	93%
	Left	8%	7%
Current smoking	Yes	17%	16%
	No	83%	84%
Affected side	Right	14 (23%)	16 (14%)
	Left	12 (20%)	12 (11%)
	Bilateral	35 (57 %)	84 (75%)
Duration of symptoms (months)		12 (24)	12 (30)
Off work	Yes	3%	0%
	No	97%	100%

Table 6.2 Demographical data for injection and surgery groups

6.4.2.1 Conservative management outcome

At 6 months, 51% failed non-operative treatment. The failure rate was highest at 2 months follow-up (Table 6.3).

	Total follow-up	VA score	Outcome n (%)		Total failure rate
2 months	85	4 (5.5)	Surgery	20 (24%)	18%
			Re-inject with steroid	48 (56%)	
			Not given an Injection	17 (20%)	
4 Months	54	2 (3.5)	Surgery	21 (39%)	37%
			Follow-up	33 (61%)	
6 Months	38	3 (6.5)	Surgery	16 (42%)	51%
			Discharge	22 (58%)	

Table 6.3 Conservative management group follow-up outcome

6.4.2.2 Comparison between conservatively- and surgically-managed patients

Patients opting for conservative management reported milder symptoms compared to the surgery group. Both the DASH and VA Scores were significantly lower in the conservative group ($p < 0.05$, Mann-Whitney U Test). The grip and pinch strength in the surgery group was significantly weaker ($p > 0.05$, Mann-Whitney U Test) (Tables 6.4 and 6.5).

	Injection group		Surgery Group		p-Value
	Score	Completion n (%)	Score	Completion n (%)	
LK Symptom Score	3 (0.9)/5	91 (81%)	3.2 (0.8)/5	49 (80%)	0.07
LK Function Score	2.3 (1.4)/5	89 (80%)	2.8 (1.5)/5	45 (74%)	0.08
DASH Score	36 (34)/100	71 (63%)	57 (18)/100	39 (64%)	0.004
VA Score	6 (3)/10	112 (100%)	7 (2)/10	61 (100%)	0.002

Table 6.4 Severity questionnaire scores for the conservative and surgery groups – Initial visit

		Injection Group (n=112)	Surgery Group (n=61)	p-value
Tinel's Sign	Positive	45 (40%)	30 (49%)	0.1
	Negative	67 (60%)	31 (51%)	
Phalen's test	Positive	52 (46%)	31 (51 %)	0.4
	Negative	59 (53%)	30 (49%)	
Reverse Phalen's test	Positive	41 (37%)	28 (46%)	0.2
	Negative	69 (62%)	33 (54%)	
Pinch Power		7.5 (5)	5.5 (3.5)	0.02
Grip Power		24 (16)	20.(15)	0.02
2 Point Discrimination	2	31 (28%)	7 (11.5%)	0.07
	3	39 (35%)	22 (36.1%)	
	4	29 (26%)	20 (32.8%)	
	5	6 (5%)	4 (6.6%)	
	6	5 (5%)	5 (8.2%)	
	7	0	2 (3.3%)	
	12	0	1 (1.6%)	
Monofilament test	2.83	49 (43.8%)	26 (42.6%)	0.2
	3.61	50 (44.6%)	22 (36.1%)	
	4.31	9 (8.0%)	11 (18%)	
	4.56	2 (1.8%)	1 (1.6%)	
	6.65	0	1 (1.6%)	
NCS	Yes	17%	23%	0.17
	No	83%	77%	

Table 6.5 Examination results for the surgery and conservative groups – Initial visit

At 6 months follow-up, surgery had a better outcome compared to non-operative treatment. Grip and pinch strength improved following surgery (Tables 6.6 and 6.8). No significant sensory disability was identified using the m2PDT in either group pre- and 6 months post-treatment (≤5 mm was considered normal (Section 2.12.5)). Monofilament testing was worse in the surgery group at 6 months follow-up ($p < 0.001$, χ^2 test) (Tables 6.6 and 6.7).

	Injection group		Surgery Group		
	Score	Completion n (%)	Score	Completion n (%)	p-Value
LK Symptom Score	2.2 (2)/5	30 (83%)	1.5 (1.5)/5	38 (68%)	0.1
LK Function Score	2 (1.2)/5	26 (72%)	1.5 (1.3)/5	39 (70%)	0.6
DASH Score	32 (41)/100	26 (72%)	16 (27)/5	39 (70%)	0.05
VA Score	3 (6.5)/10	36 (100%)	1 (1)/10	56 (100%)	0.002

Table 6.6 Severity questionnaire scores for the conservative and surgery groups – 6 months visit

		Injection Group (n=36)	Surgery Group (n=56)	p-value
Tinel's Sign	Positive	6 (17%)	6 (7%)	0.1
	Negative	30 (83%)	50 (93%)	
Phalen's test	Positive	10 (27%)	6 (11%)	0.04
	Negative	26 (73%)	48 (89%)	
Reverse Phalen's test	Positive	5 (14%)	3 (5.7%)	0.1
	Negative	31 (86%)	50 (94.3%)	
Pinch Power		7.5 (3.3)	6 (4)	0.053
Grip Power		25 (12)	20 (17)	0.1
2 Point Discrimination	2	16 (44%)	19 (34%)	<0.001
	3	9 (25%)	22 (39%)	
	4	2 (6%)	12 (21%)	
	5	8 (22%)	2 (4%)	
	6	0	1 (2%)	
	15	1 (3%)	0	
Monofilament test	2.83	18 (50%)	22 (42%)	<0.001
	3.61	14 (39%)	1 (2%)	
	4.31	1 (3%)	26 (49%)	
	4.56	2 (6%)	4 (8%)	
	6.65	1 (3%)	0	

Table 6.7 Examination results for the surgery and conservative groups – 6 months visit

Patients continued to improve one year post-CTR (Table 6.8).

		Surgery Group
Number		28
LK Symptom Score		1.4 (1)
LK Function Score		1.3 (0.8)
DASH Score		14 (23)
VA Score		0 (0.25)
Tinel's Sign	Positive	(3) 11%
Phalen's test	Positive	11%
Reverse Phalen's test	Positive	11%
Pinch Power		5 (3.5)
Grip Power		18 (15)
2 Point Discrimination	2	52%
	3	40%
	4	4%
	5	4%
Monofilament test	2.83	37%
	3.61	56%
	4.31	7%

Table 6.8 Post-operative results at 12 months

6.4.2.3 Surgery following conservative treatment outcome

The outcome of CTR was not significantly different when surgery was done primarily or after a period of non-operative treatment (Table 6.9).

	Surgery following failed conservative treatment (n=57)	Surgery without a trial of conservative treatment (n=61)
	p value	
LK Symptom Score	0.08	
LK Function Score	0.3	
DASH Score	0.2	
VA Score	0.7	
Tinel's Sign	*0.7	
Phalen's test	*0.5	
Reverse Phalen's test	*0.2	
Pinch Power	0.1	
Grip Power	0.1	
2 Point Discrimination	*0.7	
Monofilament test	*0.5	

Table 6.9 The surgical outcome is not affected by a failed conservative approach. Mann-Whitney U test except (* = χ^2 test).

6.4.2.4 The effect of surgery on the sensory improvement using MFT and TPD

There was no statistically-significant change in the sensory measurements when MFT and TPD were used to assess the change at 2 weeks, 6 months and one year following surgery (p-value >0.05, χ^2 test).

6.4.2.5 The effect of the registrar-led clinic on the consultant clinic waiting list

Service observers in the hospital management confirmed that the waiting time to see a consultant dropped from 27 weeks to 5 weeks while the registrar-led clinic was running.

6.5 DISCUSSION

The diagnosis and management of CTS can be challenging. The high failure rate of the conservative treatment in both the nurse and registrar clinics leads to increased clinic re-attendance suggesting surgery to be a better management option. The lack of success predictors in conservative treatment makes patient selection difficult and outcomes unpredictable. The LK symptom severity scores (SSS) was proposed as a useful triage tool with higher values favouring surgery (Boyd *et al.* 2005) but our findings did not mirror this observation as high SSS was not predictive of non-operative treatment failure.

This audit identified failure rates >50% in both nurse- and registrar-led clinics. The high failure rate of conservative treatment is in line with previously published rates of between 50% and 86% (Green 1984; Ozdogan *et al.* 1984; Weiss *et al.* 1994; Dammers *et al.* 1999; D'Arcy *et al.* 2000; Kanaan *et al.* 2001; Burke *et al.* 2003; Hui *et al.* 2004). The follow-up period seems to determine the reported failure rate. A randomised prospective study with one year follow-up of 163 patients reported 85% success rate (nocturnal symptoms improvement) amongst the injection group (Ly-Pen *et al.* 2005). This is clearly a better result than ours, but using the nocturnal symptoms as a primary indicator of success is questionable as we have noticed that not all patients have it nor is it the most concerning symptom from the patient point of view. On the other hand, Hui *et al*. reported 11% success rate (patients did not have surgery) at 80 weeks follow-up in 30 patients treated with a single Methylprednisolone acetate injection (Hui *et al.* 2004). Various types of steroid including Methylprednisolone acetate, Paramethasone acetonide and Triamcinolone acetonide have been used with various doses, which makes it difficult to compare outcomes.

CTS severity increased with time. There is no evidence in the literature clearly identifying the mechanism of steroid action in CTS, whether it is the result of the

nerve membrane stabilisation effect of steroid or a true drop in the intra-compartmental pressure of the carpal tunnel secondary to soft tissue atrophy. What is concerning is the high failure rate of non-operative treatment resulting in a delay in the delivery of the definitive treatment (CTR) and increase in the symptom severity with time.

Surgery in this study gave better symptomatic relief at 6 months. This was statistically evident in the DASH and VA Scores but not with the LK Questionnaire. This finding might be the result of significant weaknesses in the validation of the LK questionnaire as discussed earlier (Section 1.6).

Tests to evaluate the sensory function in the skin are those for the slowly adapting fibres (static two-point discrimination (sTPD) and Semmes-Weinstein monofilament (SWM) test) and for the quickly adapting fibres (vibration and moving two-point discrimination (mTPD)). SWM and vibration tests measure the sensory threshold by measuring the function of a receptor or group of receptors supplied by a single nerve fibre. mTPD and sTPD test innervations density, which requires an overlap of different sensory units and complex cortical integration (Szabo 1998). Threshold tests are more likely to detect a gradual, progressive change in the nerve function while density tests are reliable in assessing the functional nerve regeneration after nerve repair in which the brain input is radically altered. In an experimental model of acute median nerve compression, abnormalities in the SWM test were detected shortly after the appearance of subjective symptoms (reduced sensation and paresthesia) while the TPD exhibited an all-or-none phenomenon in which the abnormality was only detected after a marked or total elimination of the electrical signal (Gelberman *et al.* 1983) (Figure 6.5).

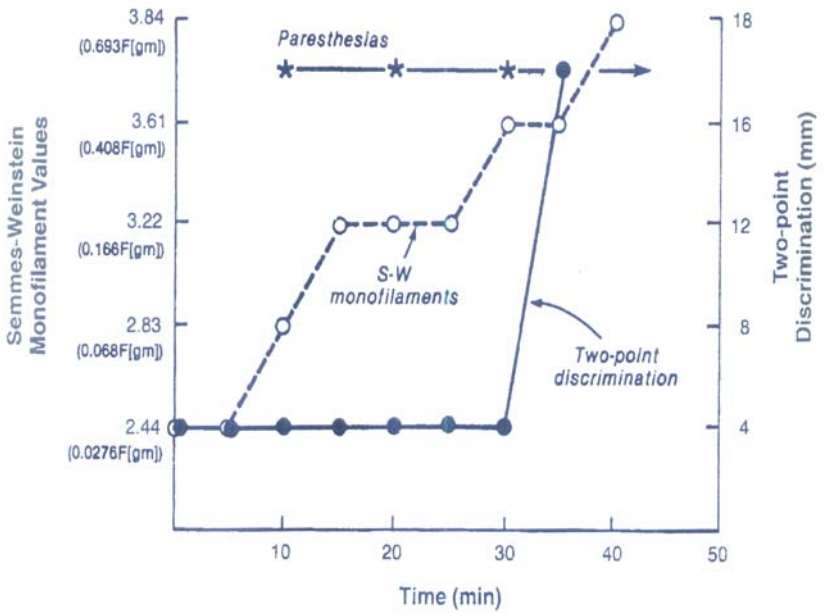


Figure 6.5 The clinical representation of neural compression with time on TPD and SWM testing (Gelberman *et al.* 1983a)

We failed to demonstrate improvement in the mTPD and SWM tests at 6 months and one year post-CTR. The mTPD findings were expected as the sensory overlap and cortical organisation remains intact in compressive neuropathy (Dellon 1978; Dellon 1981; Gelberman *et al.* 1983). The SWM test findings were unexpected but the majority of patients had normal or diminished light touch on presentation and the data does not represent the whole sample at 6 and 12 months.

The usefulness of changes in grip and pinch strength in the assessment of CTS progress and resolution is questionable. These tests are far from specific for the nerve function and are influenced by factors such as age and gender (Boatright *et al.* 1997). The abduction strength has been suggested as possibly being useful in the assessment of hand function. However, a study assessing the multidirectional power deficit in a small sample of 12 CTS patients compared to age- and sex-matched controls concluded that the commonly-used testing of thumb abduction strength may not be an effective means to evaluate the existence or severity of CTS (Boatright *et al.* 1997; Li *et al.* 2005).

The registrar-led clinics had a larger impact on the consultant's clinic due to several factors: clinics were larger and more frequent, attended to a wider spectrum of hand conditions and patients requiring surgery were directly managed in a registrar-led operating list. All this freed the consultant clinic for more cases and reduced the waiting time. A study from Leicester reported a reduction in CTR waiting time by 100 weeks within two years of the commencement of the nurse-led specialist CTS clinic (Newey *et al.* 2006). An adequately trained nurse practitioner performed approximately 400 procedures on 300 patients with comparable outcomes to the accepted standards presented in published literature. The nurse-led clinic in our study was not as successful in reducing the waiting lists. If such clinics are to have a noticeable effect, more responsibility has to be given to the nurse practitioner with adequate training to operate and review more patients, a step not all lead clinicians are happy to take (Murray 1998; Newey *et al.* 2006).

6.6 CONCLUSION

Non-operative CTS treatment has a high failure rate, surgery being the definitive treatment with better outcomes. For nurse-led clinics to have an impact, the role of the nurse has to be extended with sizable, more frequent clinics and operative responsibility.

CHAPTER 7: GENERAL DISCUSSION

7.1 MICROCIRCULATORY MEASURES

The validation of biological variables measurement tools has to accommodate for the dynamic nature of all living tissue. It is important for such tests to represent the variable measured and reflect change but, at the same time, to have reasonable repeatability. But, what is reasonable in such tests? I feel it is the ability of the test to demonstrate a trend through repeated measurements, not absolute values. Whether it is a simple blood pressure measurement of a CPT or LDI, the same rule applies.

The CPT presented in this thesis is one of many possible formats of the test, capable of detecting change. The modified CPT was able to differentiate between controls, PRP and HAVS groups. Statistically the differences were highly significant but the test repeatability was not high. This is expected. When comparing the repeatability to blood pressure measurement repeatability, it is proving to be very similar. So surely it is a very good test. It is the trend rather than the absolute value that is important and the CPT is a lengthy and an uncomfortable test which makes repeating it to determine a trend within a subject cumbersome, but makes it a very good tool for assessing groups as we have witnessed in this thesis. The baseline measurement might be useful; it is easy to measure, can be repeated frequently and a trend higher than 7.5°C suggests normality. This makes it a good screening measurement.

Pairing LDI and iontophoresis created an excellent opportunity to indirectly study the endothelial response. By eliminating a lot of the LDF limitations it is an ideal non-invasive technique but its repeatability in the hand appears to be weaker compared to the forearm or gaiter. There is evidence suggesting its repeatability to weaken, the more distal the target organ. This was noticed in the hand and should be kept in mind when sample sizing for such studies.

7.2 CTS, HI AND COLD INTOLERANCE

Autonomic symptoms are increasingly reported with CTS and evidence suggests they improve following CTR. Treatment for CTS is either operative or non-operative; amongst non-operative options, steroid injections appear to give the best results but they have a high failure rate. Surgery (open or endoscopic) remains the preferred treatment option with better symptom and function recovery.

It remains unclear why cold intolerance is highly prevalent amongst patients with hand injury. Neural and vascular causes have been explored but the neural hypothesis is favoured. The link between PRP, cold intolerance and the autonomic symptoms amongst CTS patients is frequently eluded but not supported by convincing evidence.

CPT findings post-CTR identified a significant rise in the digital baseline temperature and a faster re-warming time in the median nerve-supplied digits. This was an absolute rise in the digital temperature as pre-op testing identified no difference between the affected and control hand in patients. The role of CTR in RP would be an interesting aspect to explore.

It became evident during this work that cold intolerance severity measurement tools are weak and improperly validated. A validated tool is important in grouping subjects, particularly HI patients as the injury spectrum is very wide. The recruitment of HI subjects is difficult. I feel that, in the young, active working group, a financial incentive is of paramount importance for recruitment.

7.3 CTS CLINICS

For such clinics to be effective, they should be frequent, sizeable (>7 patients/ clinic) and run by a professional capable of managing CTS for diagnosis to CTR if required. If such requirements are not available, the workload will only be shifted but not managed. The debate on the role of nurse practitioners is such that clinics remain controversial but a well-trained nurse should be able to cover such responsibility successfully.

7.4 AREAS OF FUTURE RESEARCH

1- Identification of variation in the re-warming response in common variants of RP such as SSc, Lupus and Dermatomyositis compared to the idiopathic variant and controls. This may be aided by further analysis of more segments in the available re-warming curves for the controls and PRP to identify further segments with distinct disease representation and acceptable repeatability.

2- Validation of CISS scoring as a tool in the assessment and classification of cold-intolerant subjects.

3- A repeat of the assessment of the microvascular changes in the median nerve distribution (using appropriate iontophoresis chambers), especially comparing the pre- and post-operative response.

4- Study on the effect of carpal tunnel release in patients with PRP complicated by carpal tunnel syndrome, assessing the symptomatic and microvascular improvement post-operatively.

5- Study the effect of steroid injection therapy on the ICTP using a pressure transducer pre- and 2-4 weeks post-injection to determine whether steroid effect is due to its membrane stabilising capability or due to a true effect on the ICTP possibly as a result of soft tissue atrophy.

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APPENDICES

APPENDIX 1.1 THE LEVINE KATZ SELF-ADMINISTERED QUESTIONNAIRE

Study ID

Levine Katz self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome

Today's date:

SYMPTOM SEVERITY SCALE

The following questions refer to your symptoms for a typical 24-hour period during the past two weeks (circle on answer to each question)

How severe is the hand or wrist pain that you have at night?
1 I don't have hand or wrist pain at night
2 mild pain
3 moderate pain
4 severe pain
5 very severe pain

How often did hand or wrist pain wake you up during a typical night in the past 2 weeks?
1 never
2 once
3 two or three times
4 four or five times
5 more than five times

Do you typically have pain in your hand or wrist during the daytime?
1 I never have pain during the day
2 I have mild pain during the day
3 I have moderate pain during the day
4 I have severe pain during the day
5 I have very severe pain during the day

How often do you have hand or wrist pain during the daytime?
1 never
2 once or twice a day
3 three to five times a day
4 more than five times a day
5 the pain is constant

How long on average does an episode of pain last during the daytime?
1 I never get pain during the day
2 less than 10 minutes
3 10 to 60 minutes
4 greater than 60 minutes
5 the pain is constant throughout the day

Do you have numbness (loss of sensation) in your hands?
1 no numbness
2 I have mild numbness
3 I have moderate numbness
4 I have severe numbness
5 I have very severe numbness

Do you have weakness in your hand or wrist?
1 no weakness
2 mild weakness
3 moderate weakness
4 severe weakness
5 very severe weakness

Do you have tingling sensation in your hand?
1 no tingling
2 mild tingling
3 moderate tingling
4 severe tingling
5 very severe tingling

How severe is the numbness (loss of sensation) or tingling at night?
1 I have no numbness or tingling at night
2 mild
3 moderate
4 severe
5 very severe

How often did numbness or tingling wake you up during a typical night during the past 2 weeks?
1 never
2 once
3 two or three times
4 four or five times
5 more than five times

Do you have difficulty with the grasping and use of small objects such as keys or pens?
1 no difficulty
2 mild difficulty
3 moderate difficulty
4 severe difficulty
5 very severe difficulty

FUNCTIONAL STATUS SCALE

On a typical day during the past 2 weeks, have hand and wrist symptoms caused you to have any difficulty doing the activities listed below? Please circle one number that best describes your ability to do the activity.

ACTIVITY	No difficulty	Mild difficulty	Moderate difficulty	Severe difficulty	Cannot do at all due to hand or wrist symptoms
Writing	1	2	3	4	5
Buttoning of clothes	1	2	3	4	5
Holding a book while reading	1	2	3	4	5
Gripping of a telephone handle	1	2	3	4	5
Opening of jars	1	2	3	4	5
Household chores	1	2	3	4	5
Carrying of grocery bags	1	2	3	4	5
Bathing and dressing	1	2	3	4	5

APPENDIX 1.2 THE QUICK DASH QUESTIONNAIRE

THE QuickDASH OUTCOME MEASURE

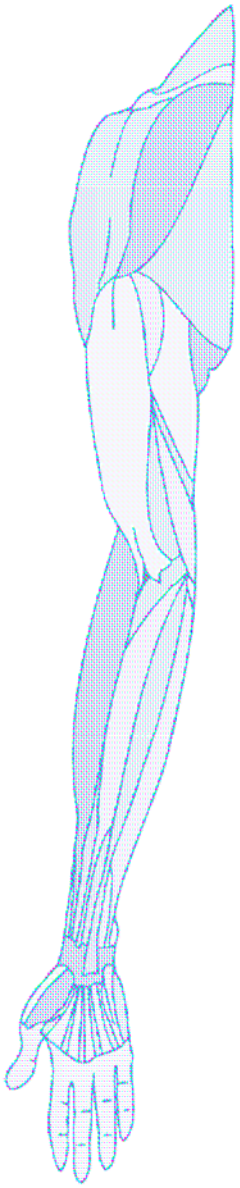
INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* of which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.



*Quick*DASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Do heavy household chores (e.g., wash walls, floors).	1	2	3	4	5
3. Carry a shopping bag or briefcase.	1	2	3	4	5
4. Wash your back.	1	2	3	4	5
5. Use a knife to cut food.	1	2	3	4	5
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*	NONE	MILD	MODERATE	SEVERE	EXTREME
9. Arm, shoulder or hand pain.	1	2	3	4	5
10. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

*Quick*DASH DISABILITY/SYMPTOM SCORE = $\left(\left[\frac{\text{sum of n responses}}{n}\right] - 1\right) \times 25$, where n is equal to the number of completed responses.

A *Quick*DASH score may not be calculated if there is greater than 1 missing item.

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is:_____

❒ I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you:_____

❒ I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.
An optional module score may <u>not</u> be calculated if there are any missing items.

APPENDIX 3.1 ODDS RATIO CALCULATION FOR THE EFFECT OF GENDER

		Gender	Odds Ratio	P-value
association between baseline temp >6˚C and being normal	Right	Male	5.15 (5.7, 15.7)	0.8
		Female	4.3 (1.6, 11.5)	
	Left	Male	4.5 (1.6, 12.9	0.67
		Female	3.3 (1.2, 9.0)	
association between T_{30Sec} >1.8˚C and being HAVS	Right	Male	4.1 (1.7, 9.8)	0.7
		Female	0.8 (0.6, 1.1)	
	Left	Male	3.5 (1.4, 8.9)	0.9
		Female	4 (0.2, 67.7)	
association between $T_{5˚C}$ >300 Sec and being PRP	Right	Male	1.7 (0.3, 9.2)	0.54
		Female	3.2 (1.2, 8.5)	
	Left	Male	5.4 (0.92, 31.8)	0.58
		Female	3.1 (1.1, 8.3)	

APPENDIX 3.2 ICC VALUES FOR MULTIPLE SEGMENTS ON THE RE-WARMING CURVE

Event	Sample Size	Left Hand	Right Hand
Baseline	62	0.5	0.5
1 minute post-immersion	62		0.6
2 minutes post-immersion	62	0.6	0.6
3 minutes post-immersion	61	0.6	0.5
4 minutes post-immersion	59	0.6	0.7
5 minutes post-immersion	49	0.7	0.7
10 minutes post-immersion	6	0.7	-0.2
At removal from water	62	0.7	0.8
Temperature at 30 seconds re-warming	62	0.03	0.4
Temperature at 1 minute re-warming	62	0.5	0.7
Temperature at 2 minutes re-warming	62	0.7	0.8
Time to re-warm by 5 degrees	62	0.7	0.7

APPENDIX 3.3-A LDI REPEATABILITY ANALYSIS FOR OPERATOR [A] USING ACH

Stage	Variable	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
Baseline	Minimum 1	0.005	0.004	0.02 (0.9)	73.5%	-0.13
	Minimum 2	0.20				
	Maximum 1	0.09	0.02 *	0.11 (0.46)	31.3%	0.19
	Maximum 2	0.08				
	Mean 1	0.20	0.003 *	0.04 (0.8)	35.6%	-0.08
	Mean 2	0.20				
Max post Ionto.	Minimum 1	0.08	0.02 *	0.28 (0.6)	57.2%	0.44
	Minimum 2	0.19				
	Maximum 1	0.19	0.11 *	0.36 (0.01)	42.6%	0.51
	Maximum 2	0.20				
	Mean 1	0.001	0.02	0.34 (0.02)	43.9%	0.52
	Mean 2	0.20				
Mean post Ionto.	Minimum 1	<0.0001	0.02	0.06 (0.7)	67.3%	0.17
	Minimum 2	0.001				
	Maximum 1	0.02	0.25	0.34 (0.02)	37.8%	0.43
	Maximum 2	0.001				
	Mean 1	0.01	0.03	0.12 (0.4)	45.9%	0.27
	Mean 2	0.004				

r: Spearman Correlation Coefficient; COV: Coefficient of Variation; ICC: Interclass Correlation Coefficient; (*) paired T-Test

APPENDIX 3.3-B LDI REPEATABILITY ANALYSIS FOR OPERATOR [A] USING SNP

Stage	Variable	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
Baseline	Minimum 1	0.20	0.04	0.06 (0.7)	64.5%	0.13
	Minimum 2	< 0.0001				
	Maximum 1	0.20	0.69 *	0.07 (0.6)	46.3%	0.10
	Maximum 2	0.16				
	Mean 1	0.20	0.03	0.18 (0.3)	34.5%	0.21
	Mean 2	0.005				
Max post Ionto.	Minimum 1	0.20	0.19 *	- 0.12 (0.4)	62.4%	- 0.26
	Minimum 2	0.11				
	Maximum 1	0.04	0.01 *	0.16 (0.3)	47.6%	0.16
	Maximum 2	0.20				
	Mean 1	0.20	0.03 *	0.07 (0.7)	40.0%	0.05
	Mean 2	0.20				
Mean post Ionto.	Minimum 1	0.20	0.055	- 0.09 (0.6)	66.6%	-0.21
	Minimum 2	<0.0001				
	Maximum 1	0.11	0.004 *	0.28 (0.06)	43.1%	0.31
	Maximum 2	0.20				
	Mean 1	0.08	0.03 *	0.008 (0.96)	39.9%	0.08
	Mean 2	0.20				

r: Spearman Correlation Coefficient; COV: Coefficient of Variation; ICC: Interclass Correlation Coefficient; (*) paired sample T- Test

APPENDIX 3.4-A LDI REPEATABILITY ANALYSIS FOR OPERATOR [B] USING ACH

Stage	Variable	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
Baseline	Minimum 1	0.20	.09 *	0.2 (0.2)	50.5%	0.32
	Minimum 2	0.10				
	Maximum 1	0.20	.30 *	0.16 (0.3)	36.6%	0.28
	Maximum 2	0.05				
	Mean 1	0.001	.15	0.2 (0.2)	42.8%	0.29
	Mean 2	0.19				
Max post Ionto.	Minimum 1	0.20	.04	0.02 (0.9)	70.3%	0.10
	Minimum 2	0.001				
	Maximum 1	0.20	.24 *	0.04 (0.8)	67.5%	0.07
	Maximum 2	0.20				
	Mean 1	0.02	.07	0.02 (0.9)	42.1%	0.06
	Mean 2	0.20				
Mean post Ionto.	Minimum 1	0.20	.08	0.07 (0.7)	51.9%	0.11
	Minimum 2	0.02				
	Maximum 1	0.20	.04 *	0.10 (0.5)	54.6%	0.09
	Maximum 2	0.20				
	Mean 1	0.17	.03 *	0.80 (0.6)	37.5%	0.05
	Mean 2	0.20				

r: Spearman Correlation Coefficient; COV: Coefficient of Variation; ICC: Interclass Correlation Coefficient; (*) Paired T-Test

APPENDIX 3.4-B LDI REPEATABILITY ANALYSIS FOR OPERATOR [B] USING SNP

Stage	Variable	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
Baseline	Minimum 1	0.008	0.045	0.40 (0.02)	39.9%	0.59
	Minimum 2	0.20				
	Maximum 1	0.20	0.01 *	0.30 (0.07)	31.5%	0.46
	Maximum 2	0.20				
	Mean 1	0.20	0.02	0.32 (0.058)	32.7%	0.41
	Mean 2	0.014				
Max post Ionto.	Minimum 1	0.20	0.27 *	0.3 (0.07)	35.7%	0.46
	Minimum 2	0.12				
	Maximum 1	0.20	0.63 *	0.20 (0.2)	45.9%	0.33
	Maximum 2	0.07				
	Mean 1	0.20	0.23 *	0.16 (0.3)	39.9%	0.28
	Mean 2	0.20				
Mean post Ionto.	Minimum 1	0.02	0.009	0.44 (0.007)	34.4%	0.50
	Minimum 2	0.20				
	Maximum 1	0.08	0.16 *	0.15 (0.3)	40.8%	0.24
	Maximum 2	0.15				
	Mean 1	0.07	0.03	0.16 (0.3)	40.4%	0.10
	Mean 2	0.006				

r: Spearman Correlation Coefficient; COV: Coefficient of Variation; ICC: Interclass Correlation Coefficient; (*) paired T-Test

APPENDIX 3.5-A LDI REPEATABILITY ANALYSIS FOR OPERATOR [C] USING ACH

Stage	Variable	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
Baseline	Minimum 1	0.20	0.00 *	0.12 (0.44)	60%	-0.127
	Minimum 2	0.20				
	Maximum 1	0.20	0.004	0.15 (0.34)	29%	0.051
	Maximum 2	0.002				
	Mean 1	0.007	0.00	0.37 (0.02)	26%	0.71
	Mean 2	0.00				
Max post Ionto.	Minimum 1	0.20	0.00	0.25 (0.11)	57%	-0.002
	Minimum 2	0.00				
	Maximum 1	0.00	0.59	0.04 (0.79)	84%	0.106
	Maximum 2	0.20				
	Mean 1	0.20	0.02 *	0.45 (0.004)	50%	0.558
	Mean 2	0.20				
Mean post Ionto.	Minimum 1	0.02	0.00	0.26 (0.11)	56%	-0.024
	Minimum 2	0.20				
	Maximum 1	0.00	0.09	0.39 (0.01)	47%	0.539
	Maximum 2	0.02				
	Mean 1	0.20	0.00 *	0.67 (<0.0001)	29%	0.632
	Mean 2	0.07				

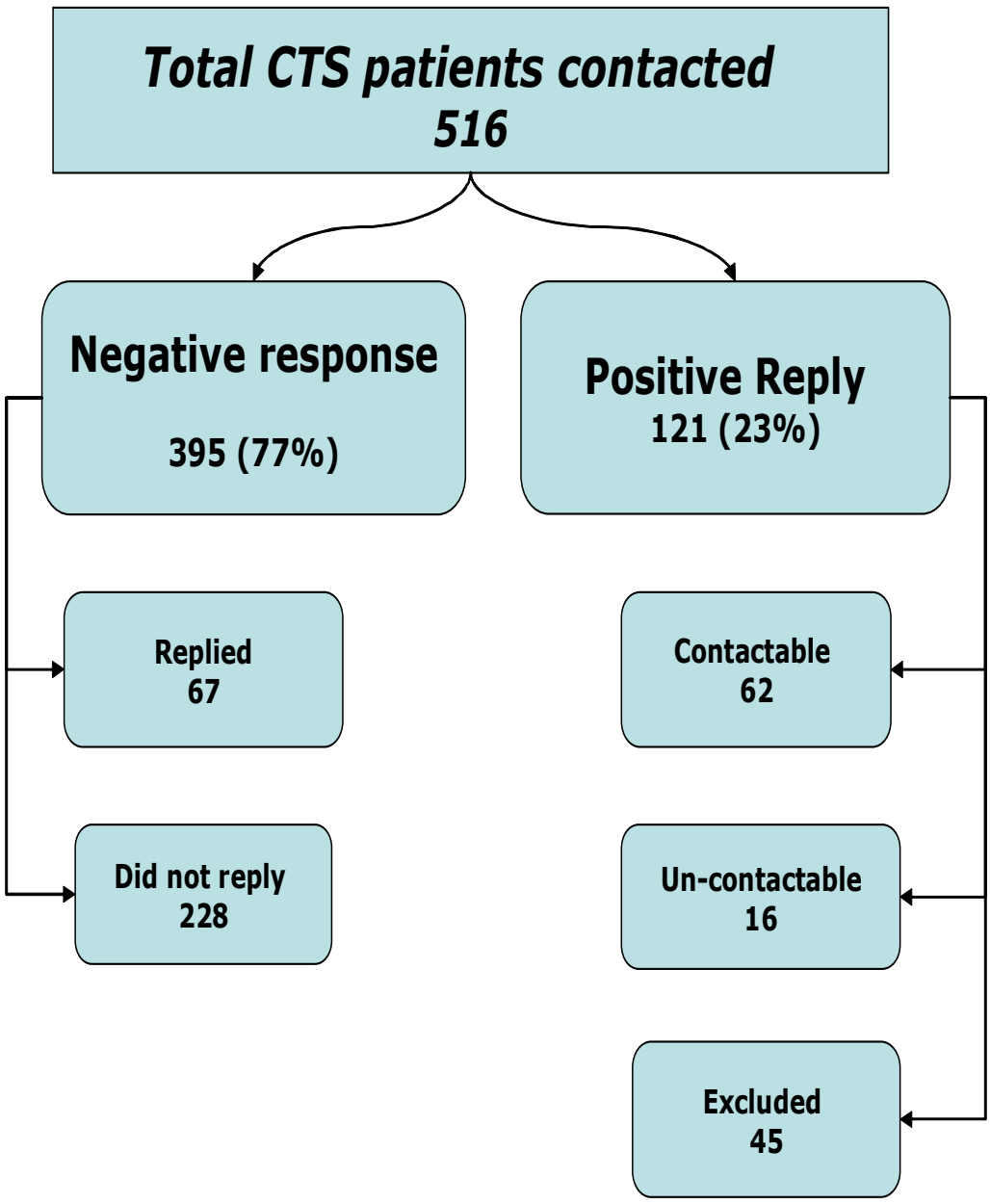
r: Spearman Correlation Coefficient; COV: Coefficient of Variation; ICC: Interclass Correlation Coefficient; (*) paired T-Test was used in the analysis.

APPENDIX 3.5-B LDI REPEATABILITY ANALYSIS FOR OPERATOR [C] USING SNP

Stage	Variable	Normality (K-S Test)	Wilcoxon Signed Ranks Test	*r* (P-Value)	COV	ICC
Baseline	Minimum 1	0.02	0.00	-0.07 (0.66)	61%	-0.61
	Minimum 2	0.20				
	Maximum 1	0.001	0.003	0.49 (0.001)	25%	0.60
	Maximum 2	0.005				
	Mean 1	0.09	0.00	0.50 (0.001)	23%	0.28
	Mean 2	0.03				
Max post Ionto.	Minimum 1	0.01	0.002	0.14 (0.38)	65%	-0.01
	Minimum 2	0.09				
	Maximum 1	0.02	0.26	0.54 (<0.0001)	39%	0.71
	Maximum 2	0.20				
	Mean 1	0.20	0.00	0.78 (<0.0001)	26%	0.59
	Mean 2	0.047				
Mean post Ionto.	Minimum 1	0.18	0.00 *	0.23 (0.15)	62%	0.04
	Minimum 2	0.20				
	Maximum 1	0.00	0.18	0.61 (<0.0001)	32%	0.74
	Maximum 2	0.005				
	Mean 1	0.20	0.00	0.76 (<0.0001)	27%	0.66
	Mean 2	0.002				

r: Spearman Correlation Coefficient; COV: Coefficient of Variation; ICC: Interclass Correlation Coefficient; (*) paired T-Test was used in the analysis.

APPENDIX 4.1 RECRUITMENT FOR THE STUDY



APPENDIX 4.2 (A, B, C)

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	P-value (Mann-Whitney U)
Baseline	Right Side	<0.0001	7.3	3.9, 9.1	0.4
	Left Side	0.2	6.5	3.6, 8.9	
T5C	Right Side	0.001	376	188, 639	0.98
	Left Side	0.2	367	212, 615	

A) No statistical difference in the CPT response between the two hands in the control group.

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	P-value (Mann-Whitney U)
Mean LDIMax	Right Side	.044	0.86	0.68, 1.15	0.09
	Left Side	.007	0.79	0.61, 0.94	
Mean LDIMean	Right Side	.073	0.8	0.64, 0.99	*0.07
	Left Side	.200	0.69	0.55, 0.85	
Post-cooling Mean LDIMax	Right Side	** <0.0001	0.73	0.63, 0.84	0.8
	Left Side	** 0.07	0.72	0.62, 0.85	
Post-cooling Mean LDIMean	Right Side	** 0.002	0.64	0.57, 0.78	0.7
	Left Side	** 0.11	.69	0.59, 0.78	

B) No statistical significant difference in the LDI response to ACH between the two hands in the control group (* independent sample T-Test used; ** Shapiro-Wilk test of normality used).

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	P-value (Mann-Whitney U)
Mean LDIMax	Right Side	0.001	0.82	0.67, 0.98	0.65
	Left Side	0.04	0.85	0.68, 1.06	
Mean LDIMean	Right Side	0.009	0.77	0.62, 0.9	0.7
	Left Side	0.04	0.79	0.63, 0.94	
Post-cooling Mean LDIMax	Right Side	0.002	0.73	0.6, 0.85	0.6
	Left Side	0.3	0.78	0.69, 0.84	
Post-cooling Mean LDIMean	Right Side	0.008	0.69	0.58, 0.82	0.56
	Left Side	0.4	0.72	0.65, 0.81	

C) No statistical significant difference in the LDI response to SNP between the two hands in the control group.

APPENDIX 4.3 (A, B, C)

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	P-value (Mann-Whitney U)
Baseline	Control Group	0.0001	6.7	3.9, 9	0.17
	Carpal Tunnel Group	0.200	7.7	5.2, 9.3	
T5C	Control Group	0.001	369	200, 623	0.32
	Carpal Tunnel Group	0.200	330	206, 512	

A) No statistical difference in the CPT response between the control group and the control side of the CTS group.

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	P-value (Mann-Whitney U)
Mean LDIMax	Control Group	<0.0001	0.8	0.65, 1.05	0.3
	Carpal Tunnel Group	0.03	0.76	0.59, 0.98	
Mean LDIMean	Control Group	0.003	0.77	0.59, 0.92	0.3
	Carpal Tunnel Group	0.2	0.68	0.54, 0.92	
Post Cooling Mean LDIMax	Control Group	<0.0001	0.72	0.62, 0.84	0.2
	Carpal Tunnel Group	0.002	0.68	0.58, 0.80	
Post Cooling Mean LDIMean	Control Group	0.001	0.67	0.58, 0.78	0.3
	Carpal Tunnel Group	0.001	0.63	0.54, 0.76	

B) No statistical difference in the LDI response to ACH between the control group and the control side of the CTS group.

		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	P-value (Mann-Whitney U)
Mean LDIMax	Control Group	<0.0001	0.84	0.67, 1.02	0.3
	Carpal Tunnel Group	0.041	0.76	0.64, 0.97	
Mean LDIMean	Control Group	<0.0001	0.78	0.62, 0.94	0.3
	Carpal Tunnel Group	0.014	0.71	0.61, 0.9	
Post Cooling Mean LDIMax	Control Group	<0.0001	0.74	0.61, 0.85	0.4
	Carpal Tunnel Group	<0.0001	0.71	0.62, 0.8	
Post Cooling Mean LDIMean	Control Group	0.001	0.7	0.58, 0.82	0.2
	Carpal Tunnel Group	<0.0001	0.64	0.57, 0.77	

C) No statistical difference in the LDI response to SNP between the control group and the control side of the CTS group.

APPENDIX 4.4A/B STUDIES ON THE MEDIAN NERVE SUPPLIED DIGITS (INDEX AND MIDDLE FINGERS)

Controls and CTS groups comparing the control side					
		Normality (Kolmogorov-Smirnov)	Median	Interquartile range	P-value (Mann-Whitney U)
Baseline	Control Group	<0.0001	7.1	5.4, 9.2	0.2
	Carpal Tunnel Group	<0.0001	7.8	4.2, 9.9	
T5C	Control Group	<0.0001	395	202, 573	0.16
	Carpal Tunnel Group	0.028	338	183, 468	

A) The control group compared to the control side in the CTS group – no statistical differences.

		Normality (Shapiro-Wilk)	Median	Interquartile range	P-value (Mann-Whitney U)
Baseline	Control	<0.0001	7.8	5.4, 9.9	0.9
	Affected	0.002	8.1	4.1, 10	
T5C	Control	0.028	338	183, 468	0.4
	Affected	0.004	405	153, 624	

B) The affected and control side within the CTS group – no statistical differences.

WHITE FINGER SCREEN QUESTIONNAIRE

1. PRESENT EMPLOYMENT

Does your present or previous work in this company involve the regular or occasional use of any of the following:-

	YES	NO
(a) Pedestal Grinding		
(b) Hand held Cutting / Grinding Tool		
(c) Hand held Nailing or Riveting Tool		
(d) Pneumatic Drilling		
(e) Pneumatic De-burring Tool		
(f) Chisels		
(g) any other Vibrating Tools		

If YES to (e), or (f) or (g) give details:

_____

_____

_____

How many hours a week?_____How many years?_____

2. PREVIOUS EMPLOYMENT

Have you been employed using any of the tools or processes detailed in 1 above before coming to this company?

YES	NO

List of tools or processes with estimated vibration exposure

	Year of Starting	Year of Finishing
(a)_____		
(b)_____		

3. OUT OF WORK VIBRATORY ACTIVITIES

Do any of your hobbies expose you to hand/arm vibration?

YES	NO

4. PREVIOUS INJURY TO FINGERS, HAND,ARM, SHOULDER OR NECK

Have you ever injured any of the above serious enough to have medical treatment?

YES	NO

If YES, what was

(a) The nature of the injury:_____

(b) When did it occur? _____

(c) What treatment did you have? _____

(d) Has it left any after effects?

YES	NO

If YES:-
(e) What after effects do you notice? _____

_____

_____

5. CONNECTIVE TISSUE DISEASE

Have you suffered from:-

	YES	NO
(a) Polyarteritis Nodosum		
(b) Systemic Lupus Erythematosus		
(c) Dermatomyositis		
(d) Scleroderma		

If YES:
(e) When did it first begin? 19_____

(f) Are you on treatment?	YES	NO

If YES
(g) Specify: _____

6. VASCULAR DISEASE

Have you ever had any of the following?

(a) Injury to blood vessels of the arm or hands	YES	NO
(b) Embolism or thrombosis of the arm or hands	YES	NO
c) Coronary thrombosis or angina	YES	NO
(d) Pains in legs on walking	YES	NO
(e) Migraine	YES	NO
(f) High blood pressure	YES	NO

If YES,
(h) When did it occur? 19_____

(i) Did it leave any after effects?	YES	NO

If YES,
(j) What after effects did you notice? _____

(k) Are you receiving treatment	YES	NO

If YES,
(1) Specify:_____

7. NEUROLOGICAL DISEASE

Have you ever suffered from:-

(a) Stroke

(b) Peripheral Neuritis

(c) Pernicious Anemia (Subacute Combined Degeneration)

(d) Injury or Nerve damage to upper limbs or neck?

If YES,
(e) When did it occur? 19_____

(f) Are you on treatment?

If YES,
(g) Specify:_____

8. RHEUMATOID ARTHRITIS/DEGENERATIVE DISEASE

Have you ever been diagnosed to have arthritis of the neck, arms or hands	YES	NO

If YES,

(a) When was diagnosis made? 19_____

(b) Are you on treatment	YES	NO

If YES,

Specify:_____

9. SMOKERS

I have smoked regularly since: 19____

At present I smoke about:

☐ Cigarettes per day ☐ Ozs Rolling tobacco per week

☐ Cigars per week ☐ Ozs Pipe tobacco per week

EX-SMOKERS

I smoked regularly from: 19____

I stopped in 19____

Before I gave up I was smoking:-

☐ Cigarettes per day ☐ Ozs Rolling tobacco per week

☐ Cigars per day ☐ Ozs Pipe tobacco per week

NON-SMOKERS

I have never smoked ☐

10. HAND SYMPTOMS

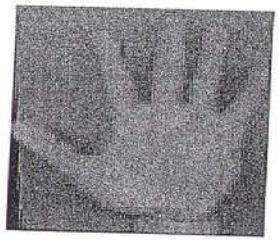
Do you experience whiteness of the fingers? | YES | NO |

WHITENESS OF THE FINGERS

(a) When did you first notice this? Year commenced: 19____

(b) Indicate extent of fingers affected:

LEFT HAND



RIGHT HAND

(c) Frequency of attacks: _____

(d) Do attacks occur throughout the year? | YES | NO |

APPENDIX 5.1 DATA COLLECTION SHEET

Study No: _____ Visit No: ____ Date of Visit ___/___/___

Category: Controls / carpal tunnel / hand injury

No. on re-warming data base:

HISS score (for hand injuries):

Informed Consent Signed Yes/ No

Copy to Patients Notes Yes/No

GP

Letter to GP ___/___/_____

Exclusion Criteria:

Already in another research study	Yes/No
History of Raynaud's Phenomenon	Yes/No
Exposure to vibration	Yes/No
Central or peripheral cyanosis on arrival at examination	Yes/No
On vasoactive medication	Yes/No
History of Diabetes I/II	Yes/No
Abstained from caffeine, alcohol in last 12 hrs	Yes/No
Abstained from smoking in last 6 hrs	Yes/No

Demographical details :		**On Examination:**	
Height(m) ------- Weight(kg) -------		Hand Dominance	R / L
BP 1	-------/-------	Cyanosis	Yes/No
BP 2	-------/-------	Allan's Test	Yes/No
BP 3	-------/-------	Assessment for Peripheral Neuropathy	Yes/No
Average	-------/-------		

Date of repeat Study ----/----/----

APPENDIX 5.2 THE POST-COOLING RESPONSE TO MICRO-VASCUALAR STIMULATION

		Normality (Shapiro-Wilk)	Median	Interquartile range	P-value (Mann-Whitney U)
For ACH					
Post-cooling Mean LDIMax	Control	<0.0001	0.72	0.62, 0.84	0.37
	HI	<0.0001	0.68	0.59,0.76	
Post-cooling Mean LDIMean	Control	<0.0001	0.67	0.58, 0.78	0.25
	HI	0.001	0.65	0.55, 0.67	
For SNP					
Post-cooling Mean LDIMax	Control	0.001	0.74	0.61, 0.85	0.009
	HI	0.8	0.92	0.8, 1.08	
Post-cooling Mean LDIMean	Control	0.007	0.7	0.58, 0.82	0.035
	HI	0.4	0.84	0.79, 0.98	

APPENDIX 5.3 HAND INJURY SEVERITY SCORES FOR THE SAMPLE RECRUITED IN THE STUDY

Subject	VWF Questionnaire (digital blanching)	HISS Score
HI 4	Absent	165
HI 6	Absent	110
HI 7	Present	130
HI 8	Absent	15
HI 9	Absent	N/A
HI 10	Absent	24
HI 11	Absent	6
HI 12	Absent	3
HI 13	Absent	2
HI 14	Absent	8
HI 15	Present	N/A
HI 16	Absent	4
HI 17	Absent	3
HI 18	Absent	N/A

APPENDIX 6.1 PATIENT FOLLOW-UP CHART IN THE REGISTRAR LED CLINIC

Name
DOB
Sex
Hospital No.

(Affix addressograph) Seen By:

Initial Visit Date:

Right /Left Handed Occupation

Symptoms in Right / Left / Both Duration of symptoms

Off work because of symptoms Yes/No Smoker Yes/ No

Diabetic Yes/No

Test		Right	Left
Levine Katz score	Symptom Severity Score		
	Functional score		
Tinel's Sign			
Phalon Test			
Reverse Phalon Test			
Pinch Power			
Grip Power			
2 Point Discrimination			
Semmes-Weinstien Monofilament Test			
VA Score			
Nerve conduction study			
Plan	Injection		
	Surgery		

Injection Pathway:

Test		Right	Left
At 2 months			
VA score			
Re-inject			
Post re-injection assessment (2 months)			
VA score			
Surgery/follow up			
At 6 months			
Tinel's Sign			
Phalon Test			
Reverse Phalon Test			
Pinch power			
Grip power			
VA Score			
Semmes-Weinstien Monofilament Test			
2 Point Discrimination			
Levine-Katz score	Symptom severity score		
	Functional score		
The Quick DASH outcome score			
Outcome	Discharge		
	Surgery		
At 12 months (contact by mail)			
Levine-Katz score	Symptom Severity Score		
	Functional score		
The Quick DASH outcome score			

Surgery Pathway:

At 2 weeks			
Wound healing			
Dressing type			
Tinel's Sign			
Phalon Test			
Reverse Phalon Test			
Pinch power			
Grip power			
VA Score			
2 Point Discrimination			
Semmes-Weinstien Monofilament Test			
Levine-Katz score	Symptom severity score		
	Functional score		
The Quick DASH outcome score			
At 6 months			
Tinel's Sign			
Phalon Test			
Reverse Phalon Test			
Pinch power			
Grip power			
VA Score			
2 Point Discrimination			
Semmes-Weinstien Monofilament Test			
Levine-Katz score	Symptom severity score		
	Functional score		
The Quick DASH outcome score			

At 12 months			
Tinel's Sign			
Phalon Test			
Reverse Phalon Test			
Pinch power			
Grip power			
VA Score			
2 Point Discrimination			
Semmes-Weinstien Monofilament Test			
Levine-Katz score	Symptom severity score		
	Functional score		
The Quick DASH outcome score			

APPENDIX 6.2 DEMOGRAPHICAL VARIATION BETWEEN THE INJECTION AND THE SURGERY GROUPS

Category	Data type	p-value
Age	Normally distributed	0.46*
Sex	Categorical data	0.35**
Dominance	Categorical data	0.27
Smoking	Categorical data	0.07
Affected side	Categorical data	0.65
Duration of symptoms	Skewed sample	0.29***
Off work	Categorical data	0.41

* T-Test, ** X^2-test, *** Mann-Whitney Test