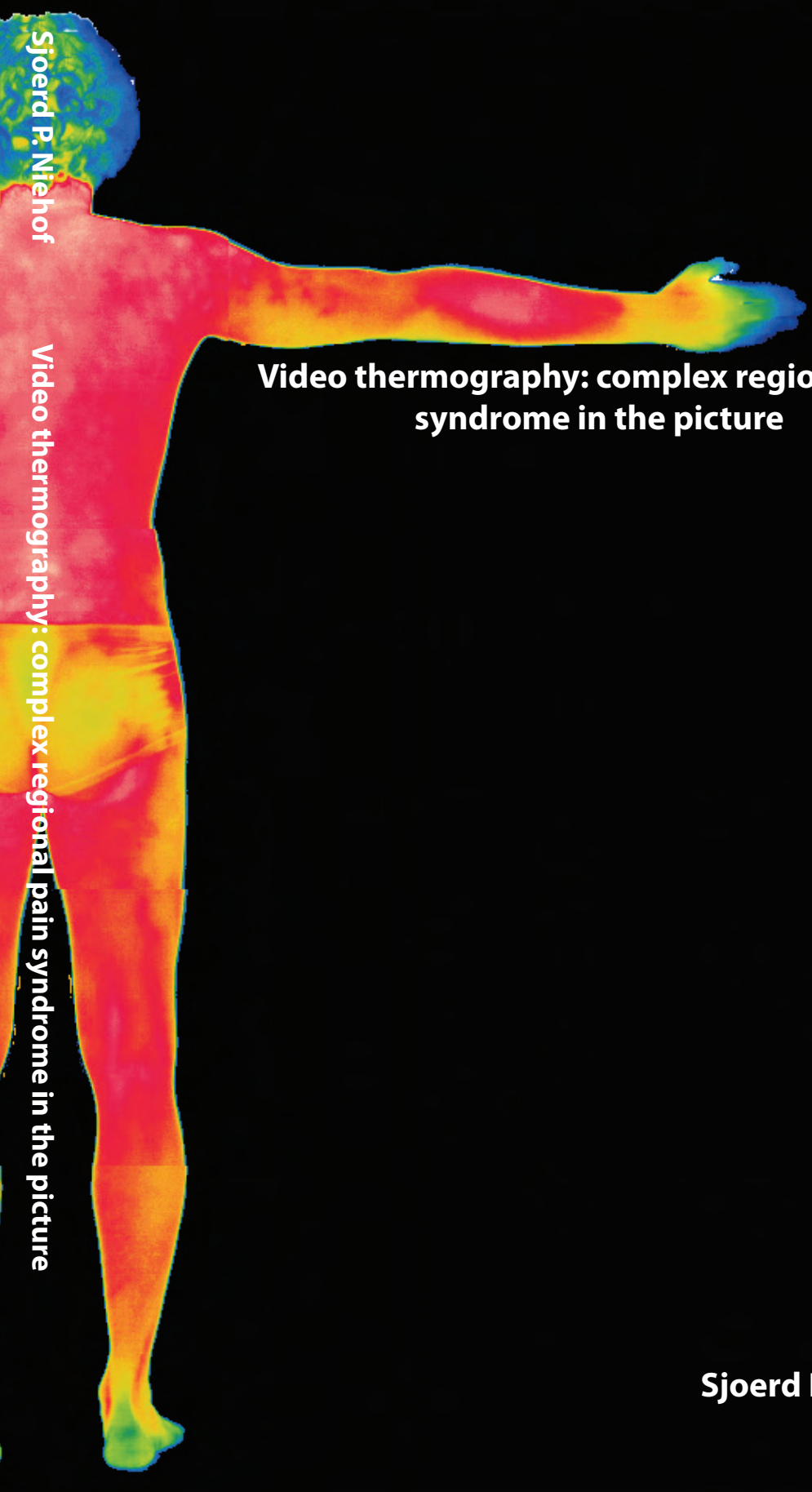

Sjoerd P. Niehof

Video thermography: complex regional pain syndrome in the picture

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# Video thermography: complex regional pain syndrome in the picture

## Video thermografie: complex regionaal pijn syndroom in beeld

**Proefschrift**

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en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

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door

**Sjoerd Petrus Niehof**

geboren te Breda

**Promotiecommissie**

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## Contents in brief

# Contents

## Abbrevations

| | |
|---|---|
| ANOVA | analysis of variance |
| AROM | active range of motion |
| AUC | area under the curve |
| CI | confidence interval |
| COVAS | computerized visual analogue scale |
| CPRS1 | complex regional pain syndrome type 1 |
| CRPS2 | complex regional pain syndrome type 2 |
| ER | emergency room |
| FLIR | forward looking infrared |
| fMRI | functional magnetic resonance imaging |
| FOV | field of view |
| IASP | International Association for the Study of Pain |
| ICC | intraclass correlation coefficient |
| IFOV | in field of view |
| IQR | interquartile range |
| ISDN | isosorbide dinitrate |
| ISS | Impairment level sum score |
| MANOVA | multivariate analysis of variance |
| MEC | medical ethical committee |
| MPQ | McGill Pain Questionnaire |
| MRI | magnetic resonance image |
| MTRE | Mennen thermo wrap equipment |
| NO | nitric oxide |
| RCT | randomized controlled trial |
| RGB | red green blue |
| ROC | receiver operative characteristics (curve) |
| SD | standard deviation |
| SPSS | statistical package for social sciences |
| TNF | tumour necrosis factor |
| VAS | visual analogue scale |

## Glossary

**Asymmetry**, correlation between temperature histograms of a pair of hands or feet, aimed at calculating the similarity/dissimilarity between two thermographic images.

**Blackbody**, a theoretical object that radiates the maximum amount of energy at a given temperature, and absorbs all the energy incident upon it.

**Cold cycle**, phase in which the body is cooled using a cold thermo suit.

**COVAS**, computerized visual analogue scale, used by observers to rate the difference between two thermographic images.

**Diagnostic phase**, determination of the diagnostic capabilities of an instrument, calculated using Receiver Operative Curve (ROC) analysis.

**Dynamic thermography**, application of various disturbing effects on temperature regulation of the human body, measured by a sequence of thermographic images, the so-called videothermography.

**Emissivity**, The ratio of the radiation emitted by a surface to the radiation emitted by a blackbody at the same temperature.

**Euclidian distance,** geometrical distance between the histogram of a pair of extremities, aimed at calculating the similarity/dissimilarity between two thermographic images.

**Initial phase**, determination of the feasibility of measurement in healthy subjects and patients.

**Likelihood ratio**, ratio between the probability of a positive/negative test value for patients and the probability of a positive/negative test value for non-patients.

**Monitoring phase**, determination of a quantitative relation of impairment in CRPS1 with measurement outcome.

**Negative predictive value**, fraction of non-patients among those with a negative test result:

**Potential phase**, determination of the relationship between impairment of CRPS1 and measurement outcome.

**Positive predictive value**, fraction of actual patients among those with a positive test result.

**Ratio**, calculation of the division of the sum of the class values in the temperature histogram multiplied by the frequency of the class of a pair of hands.

**Sensitivity**, fraction of true positives among patients.

**Specificity**, fraction of true negatives among non-patients:

**Static thermography**, a thermographic recording of an extremity without application of any disturbing factors on temperature regulation  of the extremity.

**Thermography**, recording of temperatures of an object in a two-dimensional image resulting in a matrix of temperatures of that object.

**Warm cycle**, phase in which the body is heated using a warm thermo suit

Chapter 1

# Introduction

## 1.1 Introduction

The complex regional pain syndrome (CRPS) is a painful disorder that can occur in an extremity after tissue injury or even spontaneously. There are two types of CPRS: type 1 which has no obvious detectable nerve lesion and type 2 with an obvious detectable nerve lesion. CRPS is characterized by continuing pain, sudomotor, vasomotor, sensory, motor and trophic changes. A recent epidemiologic study reported (based on the IASP criteria) an overall incidence rate of 26.2 per 100,000 persons a year (95% CI: 23.0–29.7)[1]. The clinical diagnosis of CRPS is based on various signs and symptoms. Several different criteria sets are used, the most popular of which are the International Association for the study of Pain (IASP) criteria and the Bruehl criteria sets[2]. Attempts have been made to obtain a less subjective diagnosis by using diagnostic tools such as 3-phase bone scan, X-ray, MRI, fMRI and temperature measurement devices[3]. However, none of these methods serve as a gold standard. Therefore, there is a need for a more objective assessment technique to diagnose and monitor CRPS. Such a technique might also be applicable to evaluate potential pathophysiological mechanisms involved in CRPS.

## 1.2 Inflammation and autonomic disturbance in CRPS1

In CRPS a change in blood flow, as a result of both vasodilatation and vasoconstriction, occurs frequently. The blood flow of an extremity is controlled by both central[4-6] and peripheral mechanisms[7,8] and it is believed that both of these mechanisms are (time-dependently) involved in CRPS1. Several hypotheses on the pathophysiology involved in CRPS1 have been proposed. These hypotheses can be divided into those defining afferent mechanisms (e.g. inflammation) and those defining efferent mechanisms (e.g. central sensitisation)[9]. Some afferent mechanisms involved in CRPS1 are i) immune cell mediated inflammation, ii) neuroinflammation, and, iii) local vascular endothelial derangements: i) an immune cell mediated inflammation process was reported by Huygen et al.[9-12], whereby the nerve endings trigger the release of neuropeptides at the proximal part of the nerves, most likely via the C and Aδ sensory fibres[8,9] (Figure 1.1, TNFα, IL6 and Afferent fibres); ii) neuroinflammation, higher levels of peptide extravasation after trancutaneous electrostimulation and substance P application via microdialysis catheters in CRPS patients in comparison to healthy controls were found by Birklein et al, as well as an altered axon reflex[13-15]. All these are indicators for a neuroinflammatory process[16,17]; iii) there is evidence for a local vascular endothelial derangement. Altered levels of endotholin-1 (ET-1) and nitric oxide (NO) were found in chronic CRPS1[7] (Figure 1.1, non-neural control). This could be induced by a immune cell mediated inflammation and result in local vasoconstriction[7].

Efferent mechanisms can be divided into sensory, vasomotor, sudomotor and motor changes. Focusing on vasomotor changes we can distinquish between changes in phasic

and tonic sympathetic outflow. The sympathetic nervous system uses the neurotransmitters norepinephrine, neuropeptide Y and adenosine triphophate. As a result of a continuing neuroinflammatory process, changes occur in the dorsal horn and higher centres in which neurons transmit from one to another. These changes in transmission result in different

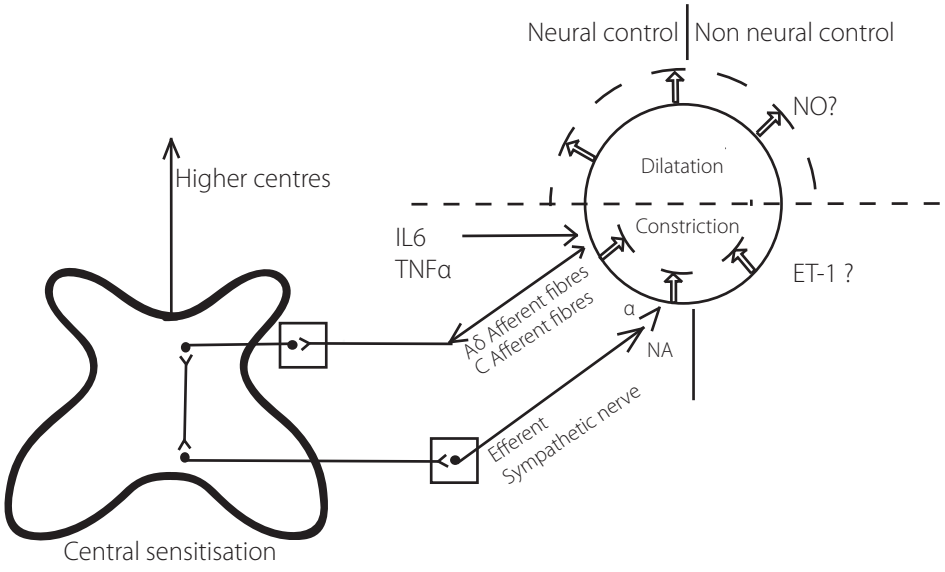



**Figure 1.1 Current hypothesis on mechanisms of vasomotor dysfunction of CRPS1.**

efferent output. A further indication that a central mechanism is involved can be derived from the fact that patients show an increased sweat production at the CRPS1 extremity. This cannot be caused by a peripheral mechanism because, unlike blood vessels, sweat glands do not initiate denervation resulting in supersensitivity[8]. However, micro-neurography does not show hyperactive sympathetic outflow and the levels of venous catecholamines are reduced in the involved extremity[18-21]. This suggests another mechanism in chronic cold CRPS, namely an adrenergic supersensitivity (Figure 1.1, α receptors). Sensitivity to a neurotransmitter can increase after an organ has been deprived of that neurotransmitter[22-25]. Under physiologic circumstances the sympathetic system downregulates the levels of the pro-inflammatory cytokines via activation of B2 receptors. In chronic inflammation there is a downregulation of the B2 receptors and an upregulation of the A1 receptors. This in turn results in higher levels of pro-inflammatory cytokines[26,27]. As a whole, these disturbances and their effect on blood flow is reflected in the surface temperature of the skin[28,29].

## 1.3 Blood flow and skin temperature

Several mathematical models have been devised to calculate skin surface temperature of

an extremity in accordance with blood flow through that extremity[30-33]. Most mathematical models have a passive and an active system component[34]. The passive component describes the thermal properties of the human body, whereas the active component describes the regulatory mechanism of blood flow through the human body in relation to, for example, body core temperature and hand temperature[35].

In most models the passive components are considered to be composed of cylindrical and spherical angular segments that together describe the thermal properties of the human body[36]. Normally, the following parts have a cylindrical representation: the head, thorax, arms, hands, fingers, legs and feets[37].

A mathematical model of the passive system that is widely used today is the Pennes bio-heat equation. This equation relates the energy transfer from blood flow to the resulting surrounding tissue temperature[38]. Pennes premise was that this capillary bed within tissue can be viewed as a blood pool because of low blood velocity in the capillary bed and large exchange area of heat.

In spite of considerable effort in the development of mathematical models of the human thermoregulatory system, to our knowledge only a few studies have simulated thermoregulation in a diseased state[39], most of which deal with breast cancer[40-44]. On an empirical level, the relationship between blood flow and skin surface temperature has also been studied. A strong correlation of r=0.98 was found between blood flow and skin surface temperature[28,29].

## 1.4 History of clinical thermographic measurement

In 1956, Dr. Ray Lawson published one of the first papers on thermography in medicine, it was entitled Implications of Surface Temperature in the Diagnosis of Breast Cancer[45]. Since then many studies have explored the use of thermography in the clinical setting. There are three types of infrared measurement techniques, namely: liquid crystal thermography (LCT), microwave thermography (MWT) and infrared thermography (IRT). Liquid crystal thermography was made obsolete by modern thermographic technology after the 1970s. Microwave thermography is still in its developmental stage, and nowadays infrared thermography is widely accepted and used. The first thermographic camera was limited in the area of spatial resolution, thermal resolution and wavelength, as well as in sampling frequency. When, for example, a whole hand had to be recorded, the spatial resolution had a maximum of 2.5•2.5 mm. The thermal resolution was amongst others limited by an 8- bit analog-to-digital converters, this resulted in a maximum of 1°C thermal resolution when operating in the temperature range that was suitable for the human skin. The early cameras recorded in the 3 µm-5 µm bandwidth and because here the human skin is still 10 to 15% reflective, this might introduce significant errors in temperature reading. Furthermore, the sampling frequency had a maximum of 0.25 Hertz[46]. Until 1980s the need for blackbodies to

calibrate the cameras further decreased the reliability of measurement and, furthermore, to achieve a high level of signal to noise ratio the thermographic camera had to be cooled by nitrogen. Needless to say there is some reluctance about the value of infrared thermography in medicine as a diagnostic and assessment instrument. Although much literature is available on thermography, many of the studies were introduced before implementation of the high-performance thermographic cameras that are available and in use today.

A search in PubMed and Web of Science on thermography as a diagnostic tool in pain resulted in a total of 446 articles that were indexed between 1965 and 2005 on this subject (see Figure 1.2).

The average number of publications per year increased between 1980 and 1992 due

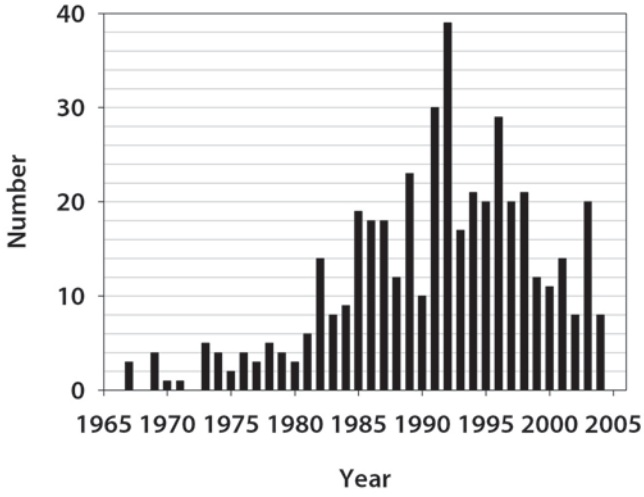



**Figure 1.2 Number of publications on thermography and pain as indexed by PubMed and Web of Science from 1965-2005.**

to the introduction of the AGA 780 thermographic camera which incorporated real-time analog recording. A second impulse was give in 1985 when the first thermographic camera was marketed that did not use liquid nitrogen as a coolant, thus resulting in a more user-friendly and no need of a blackbody due to incorporating internal calibration methods.

Modern thermographic cameras have no related quality issues that affect their ability to measure dynamic temperatures of human skin[45]. On the contrary, it is now established that thermography is an excellent tool to measure skin temperature with regards to both in accuracy and time response[47]. However, lack in standardization in the way thermographic measurements are performed[48,49], the few analyzing methods available to analyse thermographic data[50-52], and the lack in knowledge on the underlying mechanisms that

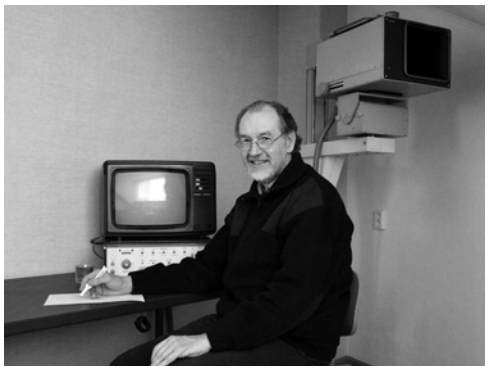


**Figure 1.3 Henk van der Veen, general practitioner , pioneer in the use of videothermography as diagnostic in painful diseases sitting in front of a large videothermograph developed by Philips biomedical systems in the early 80th.**

result in temperature differences[50], are in part responsible for the reluctance in accepting thermography in medicine[46].

## 1.5 Thermographic measurement

A thermographic (infrared) camera measures the emitted thermal radiation of a surface and translates this measurement into a matrix of temperatures of this surface[53]. The following section will briefly outline the basics of thermal radiation[54], its relation to thermographic measurement on human skin, and the type of infrared camera used in the studies presented in this thesis.

### 1.5.1 Basic concepts of thermal radiation

Heat transfer by thermal radiation, in contrast to conduction and convection, does not require matter. Thermal radiation is associated with the oscillation or transition of electrons within the matter induced by the temperature of the matter. Radiation emitted by solid matter originates from approximately 1 µm depth and is thus viewed as a surface phenomenon. Radiation can be viewed as a propagation of a collection of photons/quanta, or as electromagnetic waves with associated wavelengths. The electromagnetic spectrum comprises short wavelengths (such as gamma rays) up to long wavelengths (such as microwaves). Thermal radiation includes wavelengths from $10^{-1}$ up to $10^{2}$ µm and includes rays that are visible to the naked eye.

### 1.5.2 Radiosity

The radiosity accounts for all the radiant energy leaving a surface (skin) and thus measured by the thermogaphic camera. The absorbed ($\alpha_{ir,\lambda}$), reflected ($\rho_{ir,\lambda}$) and transmitted ($\tau_{ir,\lambda}$)

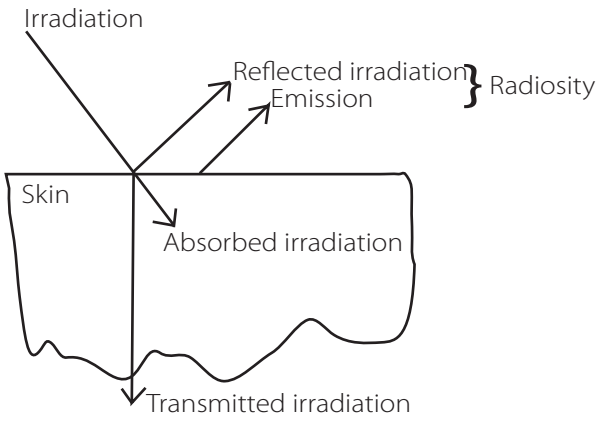



**Figure 1.4 Radiation parts that results in radiosity**

irradiation all have a coefficient associated with the specific radiative properties of matter. The relation between these coefficients is:

$$\alpha_{ir,\lambda} + \rho_{ir,\lambda} + \tau_{ir,\lambda} = 1 \qquad \text{Equation 1.1}$$

Because the skin is opaque for infrared there is no transmittance of radiation and when we average the coefficients over the wavelengths that are visible to the camera (7-13 μm), the skin acts almost like a perfect absorber (ε close to unity) with almost no reflectance[55]. Therefore, it can be concluded that the radiosity measured by the thermographic camera is to a large extent, induced by the emission part of radiosity of the human skin (see Figure 1.4). When considering emission from a real surface, such as human skin, it is useful to introduce the concept of a blackbody. A blackbody has the following ideal thermal radiation characteristics:

- A blackbody absorbs all incident radiation.
- No surface emission can exceed that of a blackbody at a given temperature and wavelength.
- A blackbody is a diffuse emitter.

Planck's law describes the spectral distribution of a blackbody's emission; because a blackbody is a diffuse emitter, the emission only depends on temperature and wavelength and has no associated direction coefficient:

$$E_{\lambda,b}(\lambda, T) = \frac{C_1}{\lambda^5 (e^{\frac{c_2}{\lambda \cdot T}} - 1)} \qquad \text{Equation 1.2}$$

Here $E_{\lambda, b}$ stands for the emission power of blackbody as a function of wavelength and temperature ($W/m^2 \cdot \mu m$), C1 is a radiation constant ($3.742 \cdot 108\ W \cdot \mu m^4/m^2$) and C2 is the second radiation constant (1.439·104 μm·K), λ (μm) is the wavelength, and T (K) is the temperature. The relation between temperature, wavelength and temperature described by Planck's law

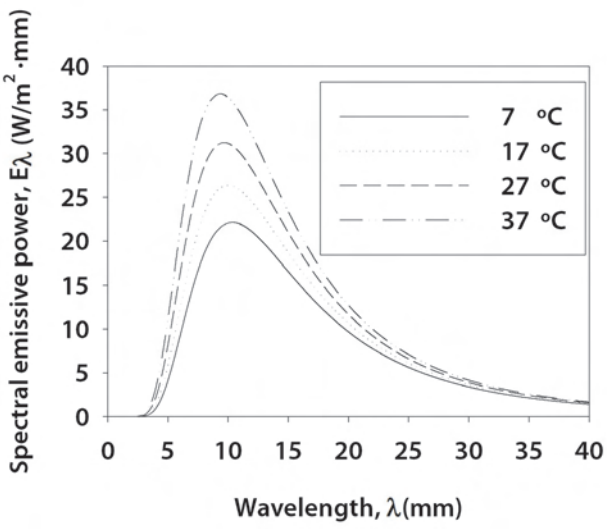



**Figure 1.5 Plancks distribution of a blackbody.**

is plotted in Figure 1.5.

By performing the integration of Planck's law at a prefixed temperature the Stephan-Boltzman law is obtained. This equation describes the total hemispherical energy that is emitted from zero to infinity wavelength emitted by an blackbody at a fixed temperature.

$$E_b = \sigma \cdot T^4 \qquad \text{Equation 1.3}$$

Here the σ is the Stefan-Boltzmann constant ($5.670 \cdot 10^{-8}$ W/m·K$^4$). It is also possible to calculate the emission between different wavelengths, the so-called band emission power; this is useful when measuring in a normal atmospheric condition (this is explained below).

The blackbody describes an ideal surface, whereas the skin is a real surface. By definition no surface can emit more energy than a blackbody therefore it is useful to define a quantity that relates the real surface emission to a blackbody surface emission. The spectral emission of a real surface differs from that of a blackbody according to the emissivity. The emissivity is the ratio of the radiation emitted by a surface (skin) to the radiation emitted by a blackbody at the same temperature. For a real surface, such as skin, this emissivity depends on the direction, wavelength, and temperature. The directional effect is small for non conductors, such as skin; typically the effect is smaller than 0.05% so the directional effect is neglected for the skin. The wavelength effect on emissivity was explored in two studies and only small influences were found[56,57]. The emissivity dependence of temperature varies considerably only across a wide range of temperatures so this part is neglected. It can be concluded that for human skin:

$$\varepsilon_n \approx \varepsilon \qquad \text{Equation 1.4}$$

The normal emissivity ($\varepsilon_n$) of human skin is set at 0.98 according to several reports[58-60], one study indicates that the emissivity should be set at 0.97[61] but this is not yet widely accepted. The total hemispherical energy in normal direction that is emitted by a real surface (skin) can be calculated by:

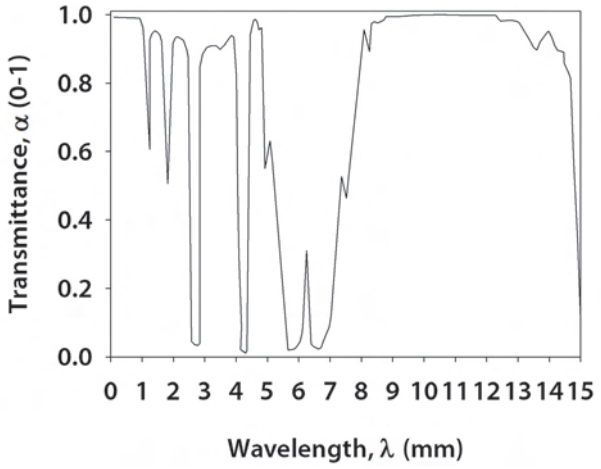



**Figure 1.6 Transmittance of air as a function of wavelength**

$$E_{skin} = \varepsilon \cdot \sigma \cdot T^4 \qquad \text{Equation 1.5}$$

Across a waveband the total hemispherical energy that is emitted is calculated by:

$$E_{skin} = \varepsilon \cdot \int_{\lambda a}^{\lambda b} E_{\lambda,b}(\lambda, T) \qquad \text{Equation 1.6}$$

This energy is transported from the skin through the air onto the detector in the thermographic camera. The relation between transmission in air according to wavelength is influenced by several factors such air temperature, air pressure, air components and particles in the air. Generally speaking there is an atmospheric window between 8-13 um were the air is almost totally opaque see Figure 1.6[62].

## 1.6 Clinimetrics

Factors that influence the reliability of thermographic measurement in patients and controls can be divided into equipment-related, subject-related and surrounding-related factors. The equipment-related factors are resolution and thermal sensitivity (described above); these influence the overall error and are generally small compared with other factors[46]. There are numerous subject-related factors such as Circadian rhythm[63-65], body mass index, stress, blood pressure and body core temperature. Some of these can be more or less controlled, whereas others have limitations regarding the smallest detectable difference (SDD) in temperature measurement. Surrounding factors include temperature and humidity,

which can be controlled. In our measurement setup attempts have been made to minimize the effect of most of these factors. One large exploring the accuracy of temperature difference in 90 healthy controls in both short-term and long-term measurement (5 years) revealed a maximum systematic temperature difference when comparing the extremities, with a maximum in feet of only 0.38ºC (0.31 SD)[66]. For clinical trials the standard error of measurement (SEM) and the smallest detectable difference (SDD) are used to describe the clinical usefulness of an instrument. The S.E.M is calculated with the following formula[67].

$$S.E.M = SD \bullet \sqrt{1-R} \qquad \text{Equation 1.7}$$

Where SD is the standard deviation and R is a reliability coefficient that can, for example, be calculated by means of an intraclass correlation coefficient[68]. The SDD is calculated with the following formula:

$$S.D.D = 1.96 \bullet \sqrt{2} \bullet S.E.M \qquad \text{Equation 1.8}$$

The 95% confidence interval CI can be calculated with the following formula.[69]

$$C.I.(95\%) = 1.96 \bullet S.E.M \qquad \text{Equation 1.9}$$

## 1.7 Aim of this project

The goal was to develop measurement set-ups using video thermography which result in outcomes that objectively reflect autonomic disturbance and inflammation in CRPS1. These outcomes should be able to improve the diagnosis of CRPS1 and further elucidate various aspects of the underlying mechanisms of CRPS1.

## 1.8 Measurement set-up

The studies presented in Chapters 2, 3, 4 and 7, make use of the following measurement set-up.In Figure 1.7 the thermographic camera (A), is positioned by a crossarm (B) above the hand that is placed inside the measuring box (C). The hand is supported by a wrist support and arch support under the palmar/dorsal side of the hand.

The study described in Chapter 5 makes use of the following measurement setup (Figure 1.8). Here a thermostatic suit (A) is connected to a thermostatic bath (B). The hands are kept well away from the thermo suit. The thermographic camera (C), is positioned above the hand that is being measured using a support (D) .

Chapter 6 makes use of the measurement set-up depicted in Figure 1.9. In this study both hands were placed on a cold plate (A), which was connected to the thermostatic bath (B). The thermographic camera (C) was positioned above the hands using a support stand (D). The laser Doppler flow (E) was also positioned above using a support stand (F).

## 1.9 Approach

In this project four developmental phases are utilized. 1) The initial phase determines

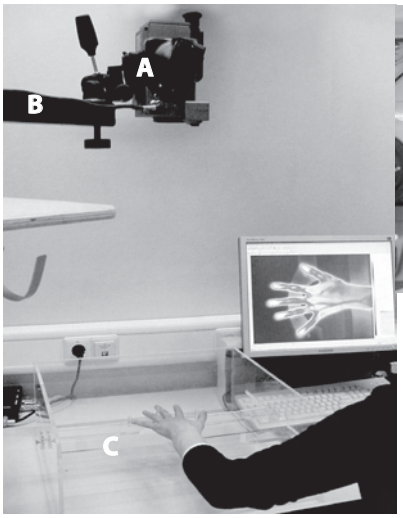



**Figure 1.7 Measurement setup used in the studies described in Chapter 2,3 and 4.**

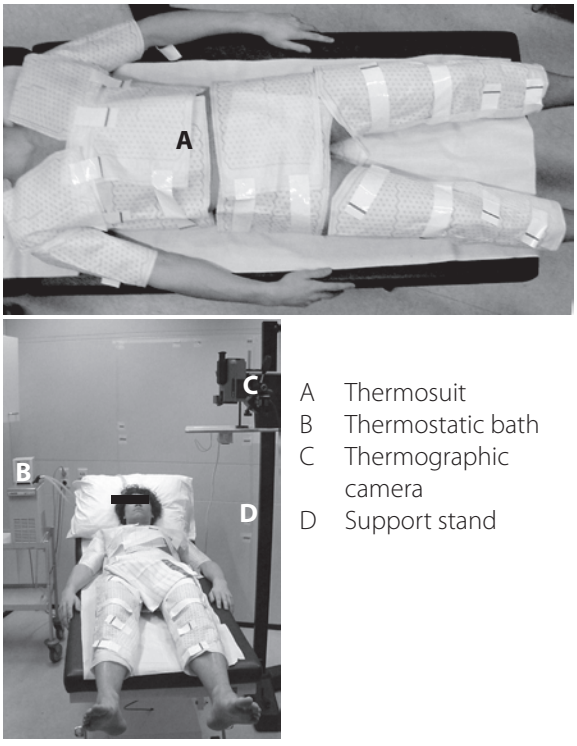
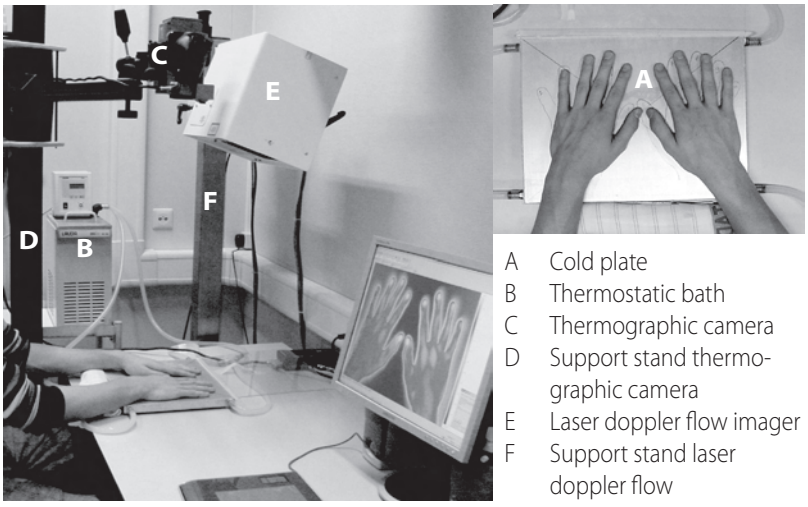



**Figure 1.8 Measurement setup used in the study described in Chapter 5.**




A Cold plate
B Thermostatic bath
C Thermographic camera
D Support stand thermo-graphic camera
E Laser doppler flow imager
F Support stand laser doppler flow

**Figure 1.9 Measurement setup used in the study presented in Chapter 6.**

the feasibility of thermography to measure and quantify temperature differences in healthy controls and patients. 2) The potential phase studies the difference between patients and controls and a possible relation between the parameters describing impairments related to CRPS. 3) The diagnostic phase determines whether thermography can be promoted as a diagnostic tool. 4) The monitoring phase determines whether thermography can be utilized as an assessment instrument of patients during intervention[69].

Furthermore, in this thesis the definition used for a static thermographic recording is: a image without the application of any disturbing factors on the temperature of an extremity. The static research protocol provided methods to minimize any disturbing/interfering factors. In dynamic thermographic recordings by definition a controlled disturbance was applied either to core temperature of the body or to the extremities only.

## 1.10 The thermographic camera

The thermographic camera SC2000 uses a 320x240 pixels uncooled microbolometer focal plane array as the infrared detector. The camera has the following optical image specifications; the lens has a field of view (FOV) of 24°x18° with a minimum focus distance of 0.3 m and a spatial resolution in field of view (IFOV) of 1.3 mrad. From this information, in the image the vertical size (vertical size of image), horizontal size (horizontal size of image), spot size (resolution of image) and dept of field (i.e. which portion in front of and behind the object in focused on is still in focus) was calculated (see Table 1.1).

**Table 1.1 Size, resolution and depth of field measurement of the SC2000 thermographic camera equipped with a 24°x18° lens.**

| Distance (cm) | Vertical size (cm) | Horizonal size (cm) | Spot size (mm) | Depth of field (cm) |
|---|---|---|---|---|
| 30 | 9.6 | 12.8 | 0.40 | 0.30 |
| 40 | 12.8 | 17 | 0.53 | 0.55 |
| 50 | 15.9 | 21.3 | 0.66 | 0.87 |
| 60 | 19.1 | 25.5 | 0.80 | 1.27 |
| 70 | 22.3 | 29.8 | 0.93 | 1.75 |
| 80 | 25.5 | 34 | 1.06 | 2.30 |
| 90 | 28.7 | 38.3 | 1.20 | 2.92 |
| 100 | 31.9 | 42.5 | 1.33 | 3.62 |

The thermal sensitivity of the detector is 0.1°C at 30°C, the accuracy is ±2°C ±2%. By standardizing the time the camera is switch on and by using internal calibration a accuracy of 0.1°C for sequential images can be reached. The camera is equipped with an atmospheric transmission correction based on input of distance, atmospheric temperature, and relative humidity. The emissivity correction can be set in the camera according to the emissivity of the object being measured.

## 1.11 Outline of this thesis

The chapters addressing the four developmental phases are rendered in Table 1.2 to Table 1.5. This chapter up to chapter 4 describe the developmental phase of static thermography into a diagnostic tool in CRPS1 which consequently includes all aspects of the initial, potential and diagnostic phase (Table 1.2, Table 1.3 and Table 1.5).

**Table 1.2 Chapters in this thesis that explore the parameters of the initial phase.**

| | 1. Initial phase (Chapters) | | | | |
|---|---|---|---|---|---|
| | Measurement setup | Measurement description | Validity reliability | Test-retest reliability | Time varying effects |
| Static thermography | 1,2,3,4,7 | 1,2,3,4,7 | 2,3 | 2,3 | - |
| Dynamic thermography | 1,5,6 | 1,5,6 | - | 6 | - |

Chapters 5 and 6 present the development and assessment of dynamic thermography as a diagnostic tool and elucidate some aspects of the patho-physiology concerning the vasomotor disturbances of CRPS1 fulfilling the aspects of the potential and diagnostic phases (Table 1.3 and Table 1.5)

**Table 1.3 Chapters in this thesis that explore the parameters of the potential phase.**

| | 2. Potential Phase (Chapters) | |
|---|---|---|
| | Difference between patient and control group | Correlation between measurement and CRPS impairments |
| Static thermography | 2,3 | 3 |
| Dynamic thermography | 5 | 5 |

Chapter 7 describes the use of thermography as an assessment instrument of CRPS1 within a pilot study during intervention, i.e. the monitoring phase (Table 1.4).

**Table 1.4 The chapter in this thesis aimed that explored the parameters of the monitoring phase.**

| | 3. Monitoring phase (Chapter) | |
|---|---|---|
| | Discriminant validity | Sensitivity to change |
| Static thermography | 7 | 7 |
| Dynamic thermography | - | - |

Chapter 4 presents a study on the application of the developed measurement setup and calculation methods described in Chapter 3 in a acute CRPS1 patient group (Table 1.5).

**Table 1.5 Chapters in this thesis exploring the parameters of the diagnostic phase.**

| | 4.Diagnostic phase (Chapters) | | | | | |
|---|---|---|---|---|---|---|
| | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Likelihood ratio of a positive test | Likelihood ratio of a negative test |
| Static thermography | 2,3,4 | 2,3,4 | 4 | 4 | 4 | 4 |
| Dynamic thermography | 5 | 5 | - | - | - | - |

Chapter 8 addresses the studies in relation to the developmental phases and the parameters that are part of these phases; this chapter also provides some recommendations to develop thermography.

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Chapter 2

# Reliability of observer assessment of thermographic images in Complex Regional Pain Syndrome type 1

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## Abstract

This study aimed at evaluating the sensitivity, specificity, reliability and repeatability of observer assessment of thermographic images taken from Complex Regional Pain Syndrome (CRPS) type 1.

A computer program was developed to let observers rate the difference between randomly presented thermographic images of pairs of hands of individuals. The sensitivity and specificity, and potential learning effects were measured. Effects of the colours and rank number of the images were analysed.

The sensitivity was 71% and the specificity 85%. The repeatability was 0.53 and the reliability was 0.50. No significant relation was found between the rank number and the rating. There was a significant correlation between the colour pallet and the rating (r=0.76).

Although the colour pallet used partly explained the variance in the rating scores, this study shows that observer assessment of thermographic images may distinguish between CRPS1 patients and healthy controls however the reliability and repeatability of this assessment was rather low.


## 2.1 Introduction

Complex regional pain syndrome type 1 (CRPS1) is a complication occurring after surgery or trauma, although spontaneous development has also been described. CRPS1 is characterised by signs and symptoms of inflammation and central sensitisation. The diagnosis can be made using several different criteria sets, the most popular of which are the International Association of Pain (IASP) and the Bruehl et al[1] criteria sets. The IASP criteria have a high sensitivity but a lower specificity, whereas the Bruehl criteria have a high specificity but a lower sensitivity. The IASP criteria are useful for clinical aims and the Bruehl criteria appear to be more useful in research. New IASP criteria are under discussion[2] and attempts have been made to obtain a less subjective diagnosis by using diagnostic tools such as 3-phase bone scan, X-ray, MRI, fMRI and temperature measurement devices[3]. Until now, however, none of these methods has been accepted as a gold standard. Due to the limited validity of clinical diagnoses, it may be difficult to differentiate CRPS1 from other diseases, e.g. from functional disorders with disuse. We have the impression that a false-positive diagnosis for CRPS1 is still made too often, especially in patients with complaints for which no clear explanation can be obtained about the onset of the symptoms.

There are several reports on the use of videothermography as a diagnostic tool in CRPS1 [4-7]. Temperature is one of the criteria used in diagnosing CRPS, whereby temperature at the surface of an extremity reflects the result of a complex combination of central and local regulation systems. Sherman et al [5] assessed the clinical usefulness of skin temperature patterns in diagnosing CRPS, by observing long-term relationships between changes in pain due to CRPS and patterns of near-surface blood flow. Bruehl et al[8] examined the validity

of thermogram derived indices of autonomic functioning in the diagnosis of CRPS; they found that temperature asymmetry accurately discriminated between CRPS and non-CRPS patients. Wasner et al[9] evaluated the diagnostic value of side differences in skin temperature as an index of induced disturbance to the sympathetic nervous system; they showed that skin temperature differences in the distal limbs proved useful to distinguish CRPS1 from other extremity pain syndromes with a sensitivity of 76% and specificity of 93%. Gulevich et al[6] showed a high sensitivity (93%) and specificity (89%) for stress infrared thermography in the diagnosis of CRPS; based on an estimation of 50% prior probability, the positive predictive value was 90% and the negative predictive value was 94%. In an earlier study we described a calculation method to examine the difference between videothermographic pictures of CRPS1 patients and healthy controls[10]. The mathematical method does not use the arbitrary conversion of temperature into colour, but merely the temperature data alone. Mathematical methods described in the literature used the contralateral extremity as a comparison, a method which cannot be utilised when both sides are affected. Mathematical methods used to assess thermographic images generally use point estimates to describe the temperature of the various regions and do not deal with all the available data contained in the images. A common use of thermography involves the search for thermal spots which do not fit well into the surrounding temperature (e.g. hot spot, cold spot); these spots are then given a rating by observers, according to their size and shift in temperature. Using observers to rate these thermographic images may result in subjective assessment of the colours in the images. These colours in the image can range from black to grey, red to blue, green to yellow, etc. and can also vary in their intensity, resulting in subjective rating[11]. For example, the colour red might be associated with danger[12] which could affect differences between the observers with respect to their ratings. To our knowledge the validity of observers' assessments of thermographic images in discriminating between patient and controls has not been studied before. However the advantages of using observer to rate thermographic pictures include, for example, the ability to only rate the affected extremity and to incorporate the wide range of temperature patterns that can exist in thermographic data.

The aim of the present study was to assess the ability of independent observers to differentiate between patients with CRPS1 and healthy controls based on videothermographic images. In addition, to explore a possible learning effect and to ascertain the influence of the colour pallet used. We also hypothesised that there would be a relation between the ISS of CRPS1 patients and the observers' rating of their thermographic pictures.

## 2.2 Materials and methods

This controlled study was approved by the Medical Ethical committee of the Erasmus MC (MEC no 198.780/2001/24), and all participants gave informed consent. Thirteen patients

with CRPS1 in one upper extremity were sequentially included. The diagnosis for CRPS1 was based on the Bruehl criteria[1,13]. Thermographic images with visual signs of abnormality (e.g. visual oedema and visual limited range of motion) were excluded.

Measured were a Visual Analog pain Score (VAS), the McGill Pain Questionnaire, the difference in active range of motion (AROM), and the difference in volume average temperature between the uninvolved and involved hand. The ISS was calculated according to Oerlemans et al[14]. The control group consisted of 13 healthy volunteers without any history of vascular abnormality.

## 2.3 Measurement procedure

Videothermographic images were recorded following a standard protocol. Patients were acclimatised in a room with a mean temperature of 23°C (range: 22.5 to 23.5) and a relative humidity of 50% (range: 45 to 55) during 15 minutes.

Measurements of the involved and uninvolved extremity were made with the hands placed in a plexiglas frame. Plexiglas has a high emission factor (0.92) and is a bad conductor of heat. The frame has positioning points between digit 1 and digit 2, and between digit 3 and digit 4, which allows to record comparable parts of the extremity in different patients. The plexiglas frame is placed in a box of the same material to minimise the influence of airflow.

Skin temperature of both hands was registered with a computer-assisted infrared thermograph (ThermaCAM SC2000, Flir Systems, Berchem, Belgium). The thermal sensitivity is 0.05°C at 30°C, the spectral range 7.5 to 13 µm, and the built-in digital video has 320x240 pixels (total 76.800 pixels). Data were obtained through a high speed (50 Hz) analysis and recording system (ThermaCAM Researcher 2001 HS, Berchem, Belgium) coupled with a desktop-PC. Thermograms were stored on hard disk (14-bit resolution) awaiting further analysis. With an interval of -40°C to 120°C this results in a resolution of 9.8x10-3 °C per bit, which fits well in the range of the thermal sensitivity. The thermograph camera produces a matrix of temperature values. Each temperature value represents a pixel in the picture measured. The distance between the camera and the hand being measured was adjusted to 68 cm; thereby the resolving capacity on the hand is 0.8x0.8 mm2. To obtain only those pixels that represent the hand, the data are filtered by a threshold. On average one hand is represented by 23.540 pixels.

## 2.4 Measurements

A total of 35 independent observers (anaesthesia residents, Erasmus MC) were asked to assess the thermographic images. To become accustomed to the interpretation of thermographic images, the observers first received an explanation about the technique (Table 2.1)

**Table 2.1 Explanation given to the observers before they rated the thermographic images.**

| | Contents of explanation |
|---|---|
| 1 | Explanation of the technique of thermography: how it works, what it records. |
| 2 | Look for patterns that you think are not normal, e.g., not a gradual decline but a sudden increase/decrease in temperature, so-called "hot spots" or "cold spots". |
| 3 | Look for a difference in temperature between the two hands. |
| 4 | Explanation about how the rater scale works (COVAS). |
| 5 | Random presentation of the thermographic images. |

Examples of images with obvious differences in typical characteristics between a normal and a CRPS extremity were shown, and instruction was given about assessment with a Computerised Visual Analog Scale (COVAS). A COVAS is a slider with a scale ranging from zero to ten. In this study zero represented no CRPS and ten the full-blown CRPS. A computer program was developed to present at random the individual hands from a pair simultaneously. So the left and right hand of either a patient or of a healthy control was shown at the same time. The observers where asked to rate the difference between the images on the COVAS scale. In order to measure the intra-rater reliability, the raters had to rate each picture twice on the covas; they were not informed that all images would be shown twice. The influence of a possible learning effect was ascertained using the rank number in which the individual images were presented. To measure the impact of the colour red on the rating of the images, the difference in the percentage of the amount of red between the involved and uninvolved extremity was calculated.

## 2.5 Statistical analyses

The analyses were performed with SPSS 12.01. The sensitivity and specificity of the ratings were calculated with receiver operative characteristics (ROC) curve analysis. Statistical comparison of the ROC curves was performed using the software program ROCkit 0.9, which incorporates a method developed by Metz et al[15] to compare correlated ROC curves[16]. Intra- and inter-observer reliability were estimated by calculation of the intraclass correlation (ICC) based on the two-way random model of either absolute agreement or consistency. In this analysis both the observers as well as the images were considered as a random sample. A possible relationship between colour red and the obtained score were analysed with a

MANOVA for repeated measurements analysis using the scores as a within- subjects effect, the images as between-subject factor, and the percentage of the colour red as a covariate. The following definition was used to describe the colour red, in the RGB colour channels the value of the red channel varied between 30 and 255 and the green and blue channels were both set to zero. The percentage of the total amount of red present in the picture was calculated. A potential effect of rank number of the images on the rating was analysed with a MANOVA for repeated measurements, using the above-mentioned model. A level of $p<0.05$ was considered to be statistically significant.

## 2.6 Results

Thirteen patients were included in the study, 11 women and 2 men (mean age: 44 years, SD 13.1, range: 33 to 58); presents demographic data of these patients. Thirteen healthy volunteers, 10 women and 3 men (mean age 28 years, range: 22 to 44) comprised the control group (Table 2.2). The independent raters were residents in anaesthesia who were not experienced in the assessment of thermographic images. Figure 2.1 presents a typical recording of a healthy subject and a CRPS1 patient.

The ISS of the patient presented in Figure 2.1 (nr. 11) is 54% (see Table 2.2). The average difference score of the raters of these thermographic images of the patient were the first time 4.8 (SD 2.3) and the second time 4.9 (SD 2.1). The average difference score of the raters of these thermographic images of the patient were the first time 1.5 (SD 1.1) and the second time 1.4 (SD 1.1). No significant correlation was found between the ISS and the average ratings of the images. The first ratings had a sensitivity of 71% and a specificity of 85%, resulting in an overall correct classification of 81%; the second score yielded a sensitivity of 74% and a specificity of 84%, with an overall correct classification of 79%. The sensitivity and specificity for different cut- points are presented in Table 2.3. Comparison of the ROC curves of the first and second score (Figure 2.2) showed no significant differences in the area under the curve (AUC of 0.86 and 0.87 respectively). The inter-observer reliability of the ratings of the images of the CRPS patients was 0.53 ($p<0.001$), that of the healthy controls was 0.12 ($p<0.001$), and that of the CRPS patients and healthy controls combined was 0.49 ($p<0.001$).

**Table 2.2 Demographic data and percentage of total score for patients with complex regional pain syndrome type 1 (CRPS1).**

| subject no. | Age (years/ sex) | Disease duration (Months)[a] | VAS (0-10)[b] | MPQ (0-10)[c] | AROM (0-10)[d] | Vol.Diff (0-10)[e] | Temp. Diff. (0-10)[f] | Total ISS (%)[g] | Score (average/ sd)[h] | Score rep. (average/ sd)[i] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 35/f | 3 | 7 | 4 | 9 | 2 | 1 | 46 | 5.7(2.3) | 6.5(1.6) |
| 2 | 24/f | 6 | 3 | 6 | 2 | 3 | 10 | 48 | 8.1(1.8) | 8.0(1.8) |
| 3 | 40/f | 12 | 8 | 7 | 9 | 3 | 4 | 62 | 1.7(1.7) | 2.2(2.0) |
| 4 | 42/f | 4 | 5 | 9 | 6 | 10 | 3 | 66 | 5.4(2.5) | 5.1(2.5) |
| 5 | 48/f | 5 | 6 | 9 | 9 | 5 | 1 | 60 | 4.8(2.6) | 5.1(2.7) |
| 6 | 35/f | 3 | 7 | 8 | 10 | 1 | 2 | 56 | 0.7(1.4) | 1.8(2.5) |
| 7 | 72/f | 2 | 4 | 7 | 8 | 8 | 10 | 74 | 7.3(1.9) | 7.3(2.2) |
| 8 | 50/m | 13 | 3 | 6 | 9 | 3 | 9 | 60 | 5.2(2.7) | 4.7(2.9) |
| 9 | 32/f | 6 | 6 | 5 | 6 | 1 | 1 | 38 | 2.9(2.6) | 2.4(2.0) |
| 10 | 56/f | 3 | 2 | 7 | 9 | 3 | 4 | 50 | 4.5(1.5) | 5.4(1.7) |
| 11 | 26/f | 12 | 8 | 7 | 1 | 4 | 7 | 54 | 2.2(2.6) | 2.6(2.0) |
| 12 | 51/f | 6 | 5 | 3 | 3 | 4 | 3 | 36 | 6.9(1.9) | 6.3(2.0) |
| 13 | 44/f | 3 | 2 | 3 | 9 | 7 | 7 | 56 | 7.1(1.8) | 7.1(2.1) |
| Mean | 42.7 | 6 | 5.1 | 6.2 | 6.9 | 4.2 | 4.8 | 54.3 | 4.8 | 4.9 |
| SD | 13.1 | 3.9 | 2.1 | 2 | 3.1 | 2.7 | 3.4 | 10.7 | 2.3 | 2.1 |
| Mean Controls | 28 | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | 1.5 | 1.4 |
| SD Controls | 12 | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | 1.1 | 1.1 |

VAS: Visual analogue pain score; MPQ: McGill Pain Questionnaire; AROM active range of motion; Vol. diff.: volume difference between the uninvolved hand and the involved hand; Temp. diff.: Temperature difference between average temperature measured with tympanometer in the uninvolved and the involved hand; ISS impairment level sum score based on Oerlemans et al[14].

[a]Duration in months from CRPS1 on the day of measurement.

[b]Pain score with 0 representing no pain and 10 representing the maximum pain, rated on the day of measurement.

[c]McGill Pain Questionnaire, the number of words chosen from the list (maximum 20) are categorised as following: 0-2 words chosen equals 1, each subsequent ascending block are given a higher score.

[d]Active Range Of Motion, a score of 1 represents no limitation in motion, a score of 10 represents a maximum limitation in movement.

[e]Difference in volume between the uninvolved hand and the involved hand, minimum difference gives a score of 1, a maximum difference a score of 10.

[f]Difference in average temperature measured with a tympanometer between the uninvolved hand and the involved hand, minimum difference gives a score of 1, a maximum difference a score of 10.

[g]Percentage of total score is calculated by dividing the total of VAS, MPQ, AROM, Volume and Temp difference by the maximum score of 50.

[h]Average score on the images scored by 35 observers (and the standard deviation), maximum of 10 indicating the most difference.

The intra-observer reliability of the ratings of the patients' images was 0.68 (p<0.001), that of the healthy controls was 0.12 (p<0.001), and that of the patients and the healthy controls combined was 0.50 (p<0.001) (Table 2.4).

The red colour was significantly associated with the rating (r=0.86; p<0.001); although the red colour on average only comprised 37% of the total colour pallet. The presentation rank number of the images was not significantly related to their ratings.

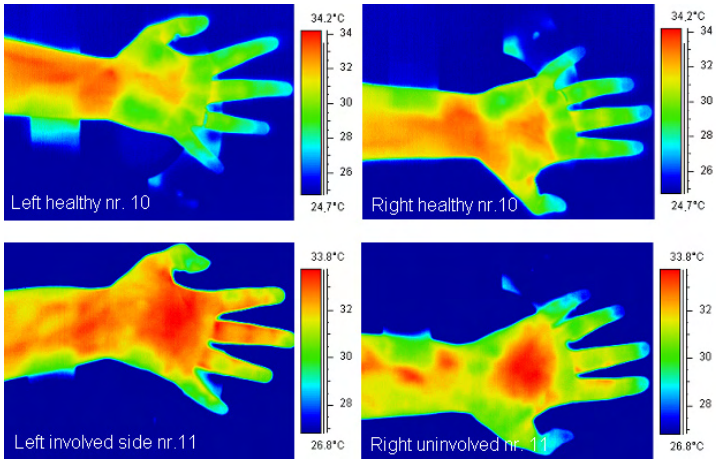


**Figure 2.1 Examples of thermographic images of a healthy individual and a CRPS1 patient.Top left: thermographic image of palmar left extremity of a healthy individual (nr. 10); top right: thermographic image of palmar right extremity of the same healthy individual (nr. 10). Bottom left: thermographic image of palmar left extremity of a CRPS1 patient (nr. 11); bottom right: thermographic image of palmar right extremity of the same CRPS1 patient (nr. 11).**

**Table 2.3 Sensitivity and specificity for different cut-off points at first and second rating.**

| Cut-off points | Sensitivity first rating | Sensitivity second rating sec | Specificity first rating | Specificity Second rating |
|---|---|---|---|---|
| >=0 | 100 | 100 | 0 | 0 |
| > 0 | 84.5 | 86.4 | 62.4 | 58 |
| > 1 | 76.7 | 82.4 | 74.4 | 73.3 |
| > 2* | 70.5 | 74.3 | 84.5 | 83.9 |
| > 3 | 64.5 | 65.7 | 86.9 | 89 |
| > 4 | 52.4 | 56 | 88.6 | 90.6 |
| > 5 | 42.4 | 44.8 | 91.2 | 92.7 |
| > 6 | 32.9 | 33.6 | 93.7 | 94.1 |
| > 7 | 20 | 19.8 | 97.1 | 96.3 |
| > 8 | 11.9 | 9.8 | 98.1 | 99 |
| > 9 | 4.5 | 4.8 | 99.4 | 99.2 |

**Table 2.4 Data on the reliability and repeatability of the scoring of the observers**

| | CRPS images | Control images | CRPS and Control images combined |
|---|---|---|---|
| Repeatability | 0.5** | 0.1** | 0.5** |
| Reliability | 0.5** | 0.1** | 0.7** |

** significant at p<0.001 level.

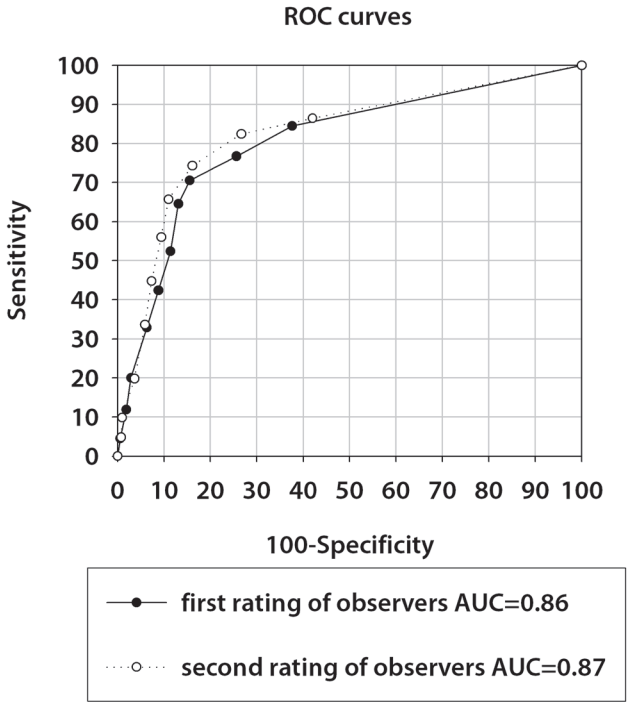


**Figure 2.2 Sensitivity and 1-specificity of the first rating and the second ratings of the observers. The first rating had an AUC of 0.86 with a cut-off point >2, a sensitivity of 72% and a specificity of 90%. The second rating had an AUC of 0.87, a cut-off point >2 and a sensitivity of 76% and specificity of 90%**

## 2.7 Discussion

In this study, the Bruehl criteria for CRPS were used as a gold standard. A lack of consensus before 1994 regarding standardised diagnostic criteria resulted in serious problems in comparing patient samples across studies addressing the diagnosis and treatment of the disorder. The publication of the standardised criteria for CRPS type 1 and type 2 by the IASP was a step forward. However, in a validation study Bruehl et al [1] showed that the sensitivity

of the Bruehl criteria was high (0.98) but specificity was poor (0.36). For clinical purposes sensitivity is extremely important, whereas for research the specificity is important. Especially for research, Bruehl et al [1] proposed modified research diagnostic criteria, which resulted in a lower sensitivity (0.70) but higher specificity (0.94).

The use of videothermography as a diagnostic tool in diseases other than CRPS1 has been studied extensively. Sherman et al[5] studied the usefulness of videothermography as a predictor of repetitive stress-induced lower limb pain disorders among American army soldiers. It was not possible from any thermographic measurement to predict those soldiers most likely to develop lower limb pain. However, the findings of the above mentioned studies are not consistent with regard to sensitivity, specificity and reliability, probably because different methods were used to analyse the thermographic data.

The present study shows that the sensitivity and specificity of the ratings of thermographic images of CRPS using independent observers, is reasonably high. There was no significant difference between the ROC curves of the initial and repeated ratings, and no significant relation between the rank number and the obtained ratings.

The intra-observer reliability of the actual difference scores in the combined healthy and CRPS images, as well as in the separate assessments of the ICC in healthy and CRPS images was moderate, particularly when considering the short time interval between the two ratings. A similar level of reliability was found between the observers.

It is generally assumed that the choice of colour used in the images (representing the range of temperature of the presented extremities) can influence the rating; particularly the colour red can be associated with abnormality. The present study confirmed this hypothesis. In a previous study we described a calculation method to differentiate between videothermographic images of patients with CRPS1 and healthy controls[10]. We found a sensitivity of 92% and a specificity of 94% with an AUC of 0.97; the repeatability was 0.87 and the reliability 0.96. In that study the colour pallet could not influence the ratings because only the underlying temperature values were used for the calculation.

The ability of the observer to validly assess hot and cold spots on thermographic images without the need for a comparison picture is of advantage when two extremities are involved. Table II shows that there is no relation between the ratings and the ISS scores of the patients. Furthermore, compared with the calculation method employed by our group in an earlier study[10], the reliability and repeatability of the scores of the raters are low. It is expected that further training, the development of a standard colour pallet and a better scale to rate the thermographic images, can address these problems[17]. Although there is no indication to use raters in the assessment of thermographic images in diagnosing CRPS1, in other types of diseases these images may produce more valid results. The results of the present study show that the observers may be able to discriminate between CRPS patients and healthy subjects, using thermographic pictures of extremities. While the slightly larger AUC of the repeated

score may reflect a possible learning effect, this remains unproven.

In conclusion, the differences between thermographic images as assessed by observers did distinguish between CRPS1 patients and healthy subjects with a reasonable high sensitivity and specificity, however, the reliability and repeatability of this assessment was rather low. It is reasonable to assume that further improvement in assessment on thermographic images using observers can be achieved, for example by standardizing and optimizing the colour pallet. However, there is some doubt if a high enough degree of accuracy can be reached using observers. Therefore, further studying of the effect of training and the choice of colour pallet is necessary. As a start, to obtain repeatable and consistent ratings, we suggest that the colour pallet should be standardised and the raters should be trained.

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# Chapter 3

## Computer assisted skin videothermography is a high sensitive quality tool in the diagnosis and monitoring of complex regional pain syndrome type I

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## Abstract

The use of thermography in the diagnosis and evaluation of complex regional pain syndrome type 1 (CRPS1) is based on the presence of temperature asymmetries between the involved area of the extremity and the corresponding area of the uninvolved extremity. The interpretation of thermographic images are however subjective and not validated for routine use. The objective of the present study was to develop a sensitive, specific and reproducible arithmetical model as the result of computer-assisted infrared thermography in patients with early stage CRPS1 in one hand. 18 patients with CRPS1 on one hand and 13 healthy volunteers were included in the study. The severity of the disease was determined by means of pain questionnaires (VAS pain, McGill Pain Questionnaire), measurements of mobility (AROM) and oedema volume. Asymmetry between the involved and uninvolved extremity was calculated by means of the asymmetry factor, the ratio and average temperature differences. The discrimination power of the three methods was determined by the receiver operating curve (ROC). The regression between the determined temperature distributions of both extremities was plotted. Subsequently the correlation of the data was calculated. In normal healthy individuals the asymmetry factor was 0.91± 0.01 (SD), whereas in CRPS1 patients this factor was 0.45 ± 0.07 (SD). The performance of the arithmetic model based on the ROC curve was excellent. The area under the curve was 0.97, the P value was <0.001, the sensitivity 92% and specificity 94%. Furthermore, the temperature asymmetry factor was correlated with the duration of the disease and VAS pain. In conclusion, in resting condition, videothermography is a reliable additive diagnostic tool of early stage CRPS1. This objective tool could be used for monitoring purposes during experimental therapeutic intervention.

## 3.1 Introduction

Complex regional pain syndrome, type 1 (CRPS1), is a chronic disease which is characterised by severe and constant burning pain, pathological changes in bone and skin, excessive sweating, tissue swelling an allodynia. The syndrome is thought to be a nerve disorder that occurs in patients after trauma or surgery at the site of an injury, most often presented in the extremities. This rare disease could simultaneously or subsequently affect nerves, skin, muscles, blood vessels and bones. The symptoms of CRPS1 vary in severity and duration. There are however different stages of the disease that are marked by progressive changes in visible signs. In the first phase, the acute stage of the disease, severe burning pain at the site of the injury is observed. Furthermore muscle spasm, joint stiffness, restricted mobility, rapid hair and nail growth, and vasospasm that affect colour and temperature of the skin can occur[1]. In the second phase, the dystrophic stage of the disease which lasts from 3-6 months, the pain intensifies, swelling spreads, joints thicken and muscles atrophy is seen. In the third phase, thechronic / atrophic stage of the disease, changes in the skin and bones become irreversible

and pain spreads in the entire limb[2]. Although it can occur at any age, the number of CRPS1 cases among adolescents and young adults is increasing. It is more common between the ages of 40 and 60 and affects mainly women (60-75%). It has been estimated that 7.2% of patients with peripheral nerve injury will suffer from CRPS1[3], whereas for wrist fractures the incidence varies from 7 to 37%[4]. How CRPS1 progresses into being such a disabling disorder is not yet known. So far it is hardly understood how a minor injury can result in such a stage with far greater pain and discomfort than was ever observed in the healing period after the initial injury[5]. It is quite certain that damaged nerves of the sympathetic nervous system, which are responsible for blood flow and temperature, play an important role in the development of CRPS1[6,7] Furthermore, the release of bio-active inflammatory mediators such as neuropeptides, cytokines and eicosanoids also attribute to the acute signs of the disease such as pain, loss of function, redness, swelling and increasing temperature[6,8,9]. Therefore CRPS1 seems to resemble neurogenic inflammation, sympathetic dysfunction or a possible interaction between both[8]. Diagnostic criteria for CRPS1 have been extensively described by Bruehl et al.[10] Diagnostic criteria sets of CRPS1 focus on many different aspects of sensory and autonomic features that generally are described vaguely[11]. Objective, diagnostic tests to perform, could include a three phase bone scans, which is sensitive within the first 20-26 weeks of the onset of CRPS1. X-rays usually will show osteoporotic changes in chronic stages of CRPS1[12]. Blood tests normally will demonstrate normal biochemistry estimations[3]. Most oedema volume measurements are not validated and therefore open to question of doubt. Thermographic imaging for measuring skin temperature reflecting vasomotor activity[13] and inflammation therefore could attribute a worthwhile tool for the diagnosis and monitoring of CRPS1 in the acute stage of the disease.

The aim of the present study was to assess the sensitivity, specificity of computer-assisted infrared thermography in patients with early stage CRPS1 in one hand. As a result an asymmetric temperature factor to characterise the presence and severity of CRPS1 is calculated. This paper describes a reliable computer-calculated method of collecting thermographic data that eliminates subjective biases, suitable for longitudinal follow-up measurements during experimental treatment of CRPS1.

## 3.2 Methods

The study was approved by the local medical ethical committee of the Erasmus MC (MEC no. 198.780/2001/24). All patients gave their informed consent. The study was performed on 18 patients, 16 women and 2 men (mean age 44.8 years, range 22-68), with the diagnosis of unilateral CRPS1 in the hand or wrist, who were referred to the Pain Treatment Centre of the Erasmus MC of Rotterdam from spring 2002 to autumn 2002 (Table 3.1). CRPS1 was diagnosed according to the criteria defined by Bruehl et al.[10] Only patients defined as phase 1 or 2, and therefore expected to exert a significant increase in temperature in the affected

hand, were subjected to the present study. Thirteen healthy volunteers, without any history of neurotrauma or vasculair disease, (10 women and 3 men) served as a control group (mean age 33.3 years, range 23 -53).

### 3.2.1 Observations and measurements

Questionnaires were used to describe pain, physical limitations and quality of life. In our study two sets of parameters to represent pain were used, the Visual analogue scale (VAS) and the McGill Pain Questionnaire (MPQ, Dutch version). The VAS is a reliable and valid instrument for the measurement of pain-intensity[14]. It is used to measure the momentary pain, the worst pain, the least pain and how much pain could be tolerated in the previous 24 hours. Scores are ranging from 0 (no pain) to 10 (most intensive pain). The MPQ is a reliable and valid tool to measure the amount of pain in a variety of complaints[15]. From the list of adjectives, the total number of words chosen was used. A maximum of 20 words can be marked in the list. The active range of motion (AROM) was used to reflect physical dysfunction. Both scores of the unaffected hand and the affected hand were measured, and the difference in range of motion from five joints were recorded (range 1-5 point per joint, 5 for maximal limitation[16]). The presence of oedema in the affected limb was measured in comparison with the unaffected hand. The percentage differences in volume was determined after successive immersion of both hands in a tube containing water of approx. 30°C. The amount of displaced water wan on-line weighed through a laboratory balance (Satorius, Breukelen, The Netherlands; accuracy 1g), based on the method described by Fereidoni et al.[17].

### 3.2.2 Skin temperature measurement with Videothermography

Skin temperature of both hands was registered with a computer-assisted infrared thermograph (ThermaCAM SC2000, Flir Systems).

The thermal sensitivity is 0.05°C at 30°C the spectral range 7.5 to 13 µm and the built-in digital video 320x240 pixels (total 76800 pixels). Data were obtained through a highspeed (50Hz) analysis and recording system coupled with a desktop-PC (ThermaCAM Researcher 2001 HS). Thermograms were stored on a hard disk (14-bit resolution) awaiting further analysis. With an interval of -40°C until 120°C this results in a resolution of 9.8x10-3 °C per bit, which fits well in the range of the thermal sensitivity. The thermograph camera produces a matrix of temperature values. These temperature values each represent a pixel in the image measured. The distance between the objective and the hand being measured was installed to 68 cm. Thereby the resolution on the hand is 0.8x0.8 $mm^2$.To obtain only those pixels that represent the extremity, the data are filtered by a threshold. On average one extremity is represented by 23540 pixels (approx. 32.5% of total pixels recorded; Table 3.2). For further analyses a frequency table is calculated. The classes consist of temperatures with an interval

of 0.1°C. Because the range of temperature is different between both hands, the maximum temperature is defined as the highest temperature in the involved hand, whereas the minimum temperature is defined as the lowest temperature in the uninvolved hand. The temperatures that do not occur in a hand, are given a class value of zero. In this way the frequency tables both represent the same range of temperature. Both hands were recorded in a predefined position with the aid of a Plexiglas curved frame with positioning points between digit 1 and digit 2 and between digit 3 and digit 4. Plexiglas was used because of the high resistance to conduct heat and the inability to conduct infrared. Furthermore the curved frame was suspended by a box of the same material to minimize influence of air flow. The emissive factor of the skin was predefined to be 0.98.

### 3.2.3 Measurement with Tympanic thermometer

Skin temperature of both hands was measured by a tympanic thermometer (M3000A, First Temp Genius®). The thermal sensitivity is 0.05°C. at 30°C. Five measuring points on both extremities were marked with a predefined matrix, based on the method described by Oerlemans et al.[18]

### 3.2.4 Calculation methods Thermography

Method 1 Asymmetry factor

This method determines the asymmetry factor (correlation) between the two calculated frequency tables derived from the images, with the following equation:

$$r(L,R) = \frac{N \cdot \sum_{i=1}^{i=\max(i)} L_i \cdot R_i - (\sum_{i=1}^{i=\max(i)} L_i) \cdot (\sum_{i=1}^{i=\max(i)} R_i)}{\sqrt{N \cdot \sum_{i=1}^{i=\max(i)} L_i^2 - (\sum_{i=1}^{i=\max(i)} L_i)^2} \cdot \sqrt{N \cdot \sum_{i=1}^{i=\max(i)} R_i^2 - (\sum_{i=1}^{i=\max(i)} R_i)^2}}$$

Equation 3.1

| | | |
|---|---|---|
| ρ | = | asymmetry factor (0<ρ<1) |
| Li | = | class values (temperature) left extremity (number of pixels) |
| Ri | = | class values (temperature) right extremity (number of pixels) |
| i | = | total number of classes |
| N | = | total number of pixels that represent an extremity |

Method 2 Ratio

This method calculates a weight factor of each class by means of the product of each class with his frequency. The product is now summed from the first till the last class. This is performed for the data of both extremities. The values of the healthy side and the CRPS1

side are now divided. A cold CRPS1 will be represented by a ratio <1 and a warm CRPS1 by a ratio >1.

Method 3 Mean difference in temperature

The mean temperature recorded by the videothermograph of each extremity is calculated. The absolute difference is determined by subtracting the mean temperature of the uninvolved extremity from the mean temperature of the involved extremity.

### 3.2.5 Calculation methods Tympanic thermometer

The mean of 5 standard points measured on each extremity is calculated. Thereafter the difference between the means is determined.

According to Oerlemans et al.[18] ISS scores from 1-10 were given for the increase of mean surface temperatures.

The following observations in the development of standardised thermographs were performed:Reproducibility. From 5 healthy controls during 5 days thermographs of both hands were obtained once a day under standardised conditions. Further more one measurement was made 6 weeks later. Room temperature was maintained between 22 and 24 °C. Prior to investigations no cold or hot drinks were taken. Persons were kept at least 15 minutes in the observation room before temperature was measured. Prior to measurements both hands were positioned on a curved Plexiglas frame, which was fixed in an open tray of the same material. The fingers were positioned divergent in order to detect temperatures in between. Asymmetry calculation made on the distribution of surface temperatures were made and the deviation within a series of 5 consecutive measurements in one week and with an interval of 6 weeks determined.

## 3.3 Statistical analysis

For comparison of non-parametric data between CRPS1 patients and healthy controls the Mann-Whitney U and Spearman tests were used. Data are given as mean ± standard deviation and median. P-values of <0.05 were considered as statistically significant. The reproducibility is calculated by Intraclass correlation (Two way mixed absolute agreement), $P<0.05$ were considered as statistical significant. The resolving capacity of the different methods were analysed with the aid of a receiver operating curve (ROC).

## 3.4 Results

Pain questionnaires, mobility and oedema, sickness impact profile

The individual patient scores of pain, both expressed by VAS and MPQ, are presented in Table 3.1.

The set of data to indicate the severity of the disease in each patient was completed by the AROM score as a measure of physical dysfunction, the hand volume difference, as indication for inflammation related oedema and the difference in the mean surface skin temperature op the hand (Table 3.1)

**Table 3.1 Demographic scores (based on Oerlemans et al. 1999b) and percent of total score.**

| No | Age/sex | Disease duration (months)[a] | VAS Pain (0-10)[b] | MPQ (0-10)[c] | AROM (0-10)[d] | Volume diff. (0-10)[e] | Temp diff. (0-10)[f] | Total ISS % [g] |
|---|---|---|---|---|---|---|---|---|
| 1 | 22F | 7 | 10 | 9 | 10 | 10 | 3 | 84 |
| 2 | 42F | 3 | 7 | 4 | 9 | 2 | 1 | 46 |
| 3 | 25F | 12 | 2 | 5 | 7 | 6 | 10 | 60 |
| 4 | 53M | 4 | 4 | 4 | 4 | 1 | 1 | 28 |
| 5 | 40F | 12 | 8 | 7 | 9 | 2 | 4 | 60 |
| 6 | 43F | 4 | 5 | 9 | 6 | 10 | 3 | 66 |
| 7 | 25F | 3 | 7 | 7 | 9 | 10 | 10 | 86 |
| 8 | 46F | 12 | 10 | 10 | 7 | 4 | 1 | 64 |
| 9 | 49F | 3 | 6 | 9 | 9 | 4 | 1 | 58 |
| 10 | 36F | 1 | 6 | 8 | 10 | 1 | 2 | 54 |
| 11 | 68F | 2 | 5 | 7 | 8 | 8 | 10 | 76 |
| 12 | 53M | 10 | 6 | 2 | 5 | 1 | 5 | 38 |
| 13 | 48F | 8 | 6 | 10 | 7 | 3 | 3 | 58 |
| 14 | 51F | 6 | 6 | 5 | 7 | 1 | 7 | 53 |
| 15 | 63F | 6 | 5 | 6 | 5 | 1 | 1 | 36 |
| 16 | 54F | 1 | 3 | 6 | 7 | 1 | 2 | 38 |
| 17 | 32F | 3 | 7 | 3 | 6 | 1 | 1 | 36 |
| 18 | 56F | 1 | 6 | 7 | 9 | 2 | 4 | 56 |
| Averages | 44.8 | 5.4 | 6.1 | 6.6 | 7.4 | 3.8 | 3.8 | 55.4 |
| SD | 12.9 | 3.9 | 2.0 | 2.4 | 1.8 | 3.5 | 3.3 | 16.5 |

[a]Disease duration, time from initial event till the day of measurement in months.

[b]VAS pain score, representing 0 = no pain and 10 = the maximum pain on the day of measurement.

[c]McGill Pain Questionnaire, the number of words chosen from a list of 20, categorized in blocks of 2 words.

[d]Active Range Of Motion, a score of 1 represents no limitation in motion, a score of 10 represents a maximum limitation in movement.

[e]Volume difference between the uninvolved hand and the involved hand; minimum difference results in a score of 1, maximum difference results in a score of 10.

[f]Temperature difference between average temperature measured with tympanometer in the uninvolved and the involved hand; a difference of 0.2 ˚C results in

a score of 1, a difference of > 2˚C results in a score of 10.

[g]Total ISS score in percents; sum of all scores (VAS, MPQ, AROM, Volume and Temperature difference), maximum score of 50.

Temperature measurements reproducibility in healthy controls

In order to determine the asymmetry factor between a single measurement of the palmar sites of both hands, videothermographs were obtained under standardised conditions as described in the Methods section. In Figure 3.1 examples of a healthy control (upper half part) and a CRPS1 patient (bottom half part) are given.

Each pixel indicated by a chosen colour depicts the corresponding temperature. Thereafter the distribution of all surface temperatures found in the restricted area of both hands was plotted as shown in the corresponding histograms. Further analysis of this set of data revealed in an asymmetry (correlation) curve (coloured regression plots right panels of Figure 3.1. Repeated measurements of 5 healthy controls, which were obtained during 5 consecutive days (reliability) revealed a intraclass correlation of 0.78 ($P< 0.02$) for the asymmetry factor. A intraclass correlation of 0.86 ($P<0,01$) was obtained with a interval of 6 weeks for the determination of the asymmetry factor (stability). In Table 3.2 the ratios healthy/CRPS1 area under the temperature histogram as presented in Figure 3.1 (middlepanels) are given.

Furthermore the asymmetry factors derived from the number of pixels per temperature as plotted in the right panels in Table 3.2 were calculated. In order to evaluate the asymmetry factor as a prognostic value, it is plotted against the results derived from the methods as presented under Questionnaires and Measurement during the development of the disease. Six patients (patient numbers 2, 4, 7, 9, 12 and 17 in Table 3.1), who received DMSO (Dimethyl sulfoxide) cream, which is a standard therapy in the Netherlands (Zuurmond et al. 1996), were monitored during 12 consecutive weeks. A representative graph of patient no.9 is displayed in Figure 3.2.

**Table 3.2 Video thermographic measurement compared to Tympanic measurement; calculation methods.**

| No | Age/ Sex | Duration disease[a] (months) | Average. diff. Video[b] (°C) | Average. diff. Tympanic[c] (°C) | Ratio[d] | Asymmetry Factor [e] | Absolute difference in total pixels left and right[f] | Number of pixels right[g] | Number of pixels left[h] |
|---|---|---|---|---|---|---|---|---|---|
| Patients | | | | | | | | | |
| 1 | 22F | 7 | 0.84 | 0.68 | 0.61 | 0.37 | 33 | 20053 | 20020 |
| 2 | 42F | 3 | 0.87 | 0.32 | 0.92 | 0.22 | 511 | 21473 | 20962 |
| 3 | 25F | 12 | 3.08 | 2.7 | 1.3 | 0.13 | 149 | 20408 | 20557 |
| 4 | 53M | 4 | 0.31 | 0.1 | 0.97 | 0.79 | 373 | 31562 | 31935 |
| 5 | 40F | 12 | 0.65 | 0.8 | 1.41 | 0.06 | 683 | 20909 | 21592 |
| 6 | 43F | 4 | 0.92 | 0.72 | 0.91 | 0.91 | 619 | 24377 | 23758 |
| 7 | 25F | 3 | 0.38 | 3.42 | 1.16 | 0.45 | 1008 | 20975 | 21983 |
| 8 | 46F | 12 | 2.39 | 0.26 | 0.55 | 0.28 | 682 | 22604 | 21922 |
| 9 | 49F | 3 | 3.09 | 0.06 | 0.97 | 0.09 | 444 | 27536 | 27092 |
| 10 | 36F | 1 | 2.26 | 0.52 | 1.14 | 0.61 | 430 | 27123 | 27553 |
| 11 | 68F | 2 | 2.55 | 2.66 | 0.31 | 0.76 | 973 | 24908 | 25881 |
| 12 | 53M | 10 | 0.46 | 1.04 | 0.82 | 0.16 | 232 | 26546 | 26778 |
| 13 | 48F | 8 | 0.26 | 0.64 | 0.96 | 0.77 | 693 | 23933 | 24626 |
| 14 | 51F | 6 | 1.09 | 1.56 | 0.93 | 0.15 | 1041 | 24088 | 23047 |
| 15 | 63F | 6 | 0.45 | 0.3 | 0.62 | 0.47 | 802 | 18973 | 18171 |
| 16 | 54F | 1 | 4.74 | 4 | 0.52 | 0.72 | 1224 | 20019 | 18795 |
| 17 | 32F | 3 | 0.26 | 0.1 | 1.01 | 0.44 | 666 | 24559 | 23893 |
| 18 | 56F | 1 | 0.85 | 0.94 | 1.01 | 0.76 | 592 | 24724 | 24132 |
| Averages | 44.8 | 5.4 | 1.4 | 1.2 | 0.9 | 0.5 | 619.7 | 23598.3 | 23483.2 |
| SD | 12.9 | 3.9 | 1.3 | 1.2 | 0.3 | 0.3 | 318.4 | 3267.2 | 3473.9 |
| Controls | | | | | | | | | |
| 1 | 47F | | 0.34 | 0.46 | 1.02 | 0.85 | 690 | 24482 | 23792 |
| 2 | 27M | | 0.27 | 0.12 | 0.96 | 0.9 | 1984 | 30042 | 28058 |
| 3 | 24F | | 0.22 | 0.76 | 1.02 | 0.91 | 731 | 28199 | 27468 |
| 4 | 53F | | 0.36 | 0.88 | 1.06 | 0.92 | 500 | 23702 | 23202 |
| 5 | 27M | | 0.46 | 0.23 | 1.02 | 0.95 | 89 | 27364 | 27275 |
| 6 | 30F | | 0.16 | 0.45 | 1.03 | 0.96 | 414 | 25341 | 25755 |
| 7 | 27M | | 0.16 | 0.56 | 0.95 | 0.87 | 480 | 29838 | 30318 |
| 8 | 47F | | 0.07 | 0.78 | 0.98 | 0.96 | 501 | 25325 | 24824 |
| 9 | 30F | | 0.47 | 0.43 | 0.98 | 0.9 | 118 | 11865 | 11983 |
| 10 | 28F | | 0.31 | 0.67 | 1.01 | 0.9 | 1262 | 10035 | 8773 |
| 11 | 30F | | 0.2 | 0.89 | 0.99 | 0.86 | 439 | 14533 | 14094 |
| 12 | 40F | | 0.32 | 0.78 | 1.15 | 0.92 | 269 | 16314 | 16045 |
| 13 | 28F | | 0.28 | 0.99 | 1.04 | 0.94 | 162 | 27987 | 27825 |
| Averages | 33.7 | | 0.3 | 0.6 | 1 | 0.91 | 587.6 | 22694.4 | 22262.5 |
| SD | 9.6 | | 0.1 | 0.3 | 0.1 | 0.04 | 521.7 | 7000.7 | 7051.2 |

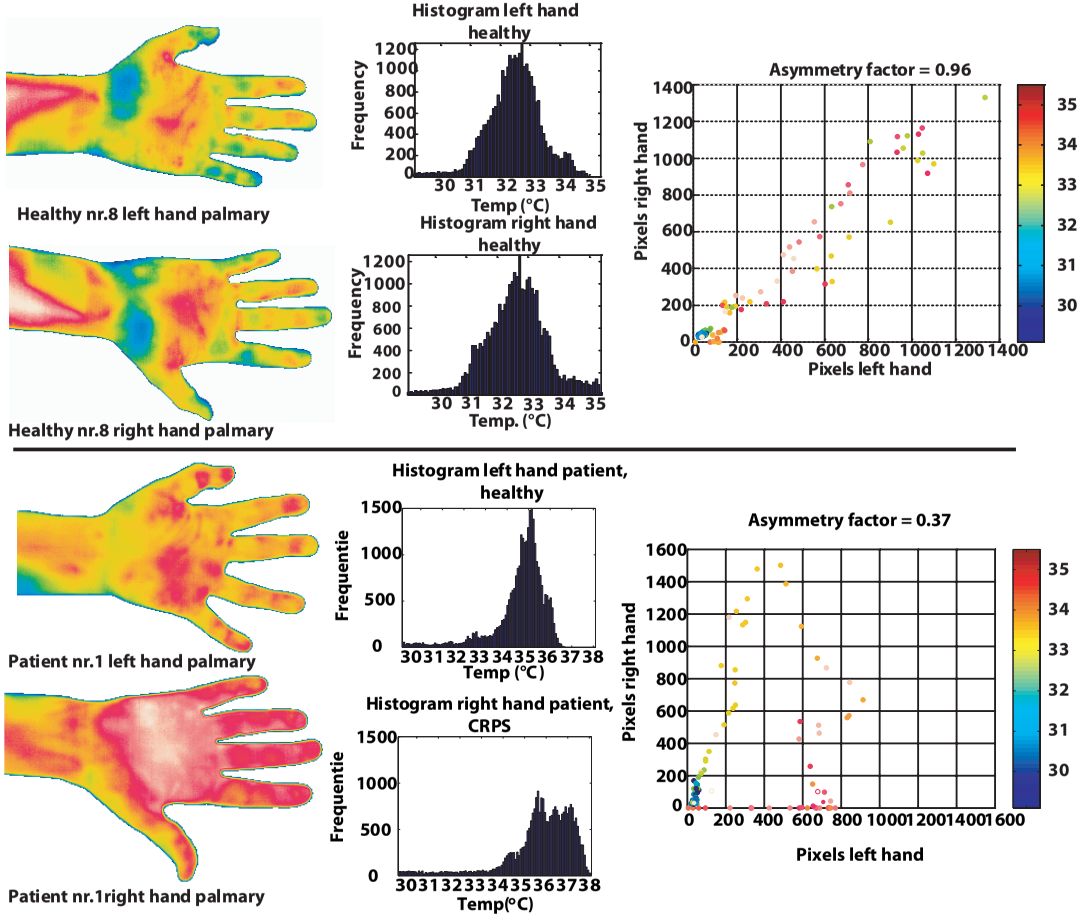


**Figure 3.1** Representative example of a single measurement of skin temperatures by a computer assisted infrared thermograph in a healthy volunteer (upper half part) and a CRPS1 patient (bottom half part). In the thermographs (left sided) each pixel indicated by a chosen colour depicts the corresponding temperature, after which the distribution of all surface temperatures found in the restricted area of both hands were plotted as shown in the corresponding histograms (middle). Further analysis of this set of data revealed in a correlation curve, in which the number of pixels of each existing temperature at the skin surface of the right hand was plotted against the left hand (coloured regression plots right panels). In fact these plots are three-dimensional, being the number of pixels per temperature in the right hand the first parameter, the number of pixels per temperature in the left hand the second parameter and the corresponding temperature the third parameter. The calculated asymmetry factor in the healthy volunteer was 0.96, whereas the asymmetry factor in the CRPS1 patient appeared to be 0.37, due to the right-shifted histogram of the CRPS1 hand.

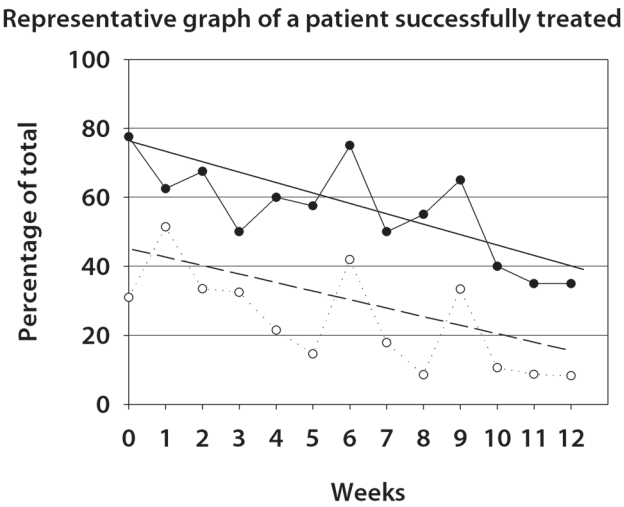


**Figure 3.2 Representative example of successful treatment of early stage CRPS1 by topical application of 50% DMSO during a follow-up period of 12 weeks (week 1: before treatment; week 13: end of treatment).Dotted line: for direct comparison in this figure the calculated temperature asymmetry factor, derived from left and right hand plotted number of pixels per corresponding temperature, was expressed as ([1-factor]x100%) .Straight black line: total scores (% of total) as a sum of VAS pain, MPQ, oedema volume and Euroqol. The correlation between these two trend analyses was 0.76 (P < 0.01).**

In order to investigate a relationship between temperature asymmetry and clinical parameters, correlations were calculated from data of the all patients as listed in Table 3.1. In Table 3.3 the significant correlations are given. The momentary VAS-pain correlated with the asymmetry factor (r = 0.40 and P = 0.04). The duration of the disease correlated negatively with the asymmetry factor (r = -0.45 and P = 0.03).

**Table 3.3 Spearman correlation coefficients between duration of the disease, VAS pain and temperature asymmetry factor in 18 patients with CRPS1**

| | Disease duration (months) | VAS pain (0-100) | Asymmetry factor (0-1) |
|---|---|---|---|
| Disease duration (months) | - | corr. 0.22<br>*P* = 0.19 | corr. -0.45<br>*P* = 0.03 |
| VAS pain (0-100) | corr. 0.22<br>*P* = 0.19 | - | Corr. 0.40<br>*P* = 0.04 |

Other clinical parameters were not correlated with the asymmetry factor. The number of pixels per paired samples selected from the right and the left hand correlated excellent in all 31 subjects (corr. 0.991, P = 0.000). Thus, the temperature asymmetry factor is not influenced by differences in the number of pixels recorded from the left extremity and right extremity. Calculated ratios are dependent from the increase of skin temperature in the CRPS1 hand,

whereas the asymmetry factors are independent from differences in temperature but reflect distribution of common temperatures. To determine which method has the highest sensitivity en specificity the ROC curves were calculated and plotted as presented in Figure 3.3.

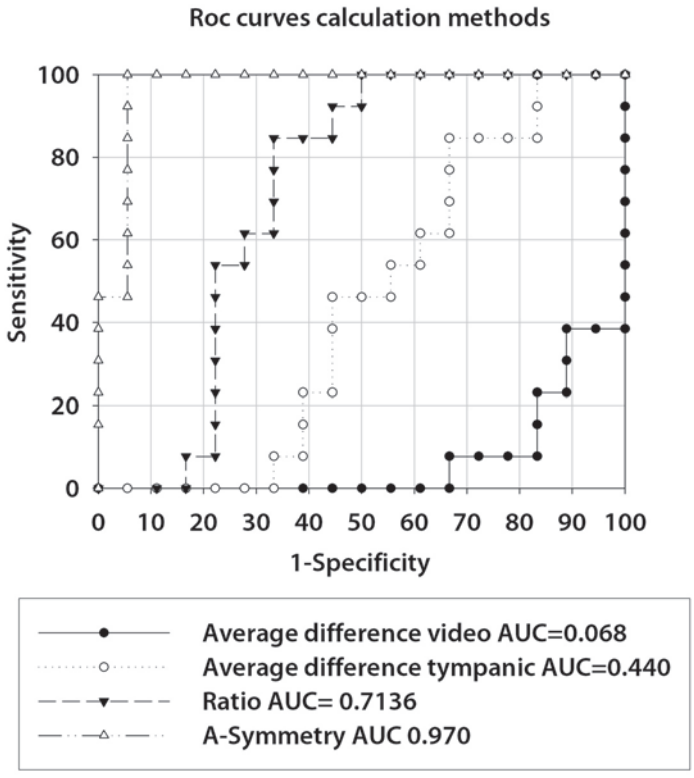


**Figure 3.3 Graphics of the calculated ROC curves comparing different methods. Area larger then 0.81 is statistical significant. The following intervals indicate guidelines of the accuracy of the tests described in this paper: (Sensitivity - specificity) : 1 - 0.9 = excellent; 0.9 - 0.8 = good; 0.8 - 0.7 = fair; 0.7 -0.6 = poor; and 0.6 - 0.5 = fail.**

Based on interpretation of the curves, the average video thermography values have no discriminating power. The average tympanic temperature has some, but not significant power. The Ratio method based on video thermography has a useful and significant power. The most discriminating power is however reached by the calculation of the asymmetry factor derived from video thermographs.

## 3.5 Discussion

In 1998 Jones already claimed a reappraisal of infrared thermal imaging of the skin. So far it was well known that abnormalities such as malignancies, inflammation and infection cause localised increases in temperature, which are shown as hot spots or as asymmetrical patterns in an infrared thermograph. The transfer of military technology for medical use has prompted this reappraisal of infrared thermography in medicine. If thermographs are captured under controlled conditions, they may be interpreted readily to diagnose certain conditions and to monitor the reaction of a patient's physiology to thermal and other stresses[19].

CRPS1 is associated with complex disturbances of the sympathetic nervous system which also controls microcirculation of the skin. Circulatory skin changes are in turn reflected by altered superficial thermal emission, which can be reliably imaged by thermography. Such thermographic findings often appear before skin or roentgenographic changes become manifest and may therefore be helpful in early diagnosis[20]

Thermography has been shown to be an effective way to monitor near-surface blood flow in the limbs and to be sensitive to changes accompanying painful conditions. The usefulness of this technique for early detection of CRPS1 has been demonstrated[21.]

Although thermography is still believed to be non-specific, one of the most exciting advantages of infrared videothermography is the readily available display which exactly detects so far unrecognised and not believed problems that affect a patient's physiology. In a number of cases at first sight the intensity and the extensiveness of the affection could be judged in comparison with the unaffected hand.

In our setup the reproducibility of repeated videothermographic measurements proved to be over 95%. The computerised regression of the number of pixels per interval of 0.1°C easily displays whether symmetry exists between both hands or not. Until now normally the mean areas ($mm^2$) of temperature above basal peak temperature, e.g. in ranges of 0.2°C, were calculated[22].

Under normal conditions the degree of thermal asymmetry between opposite sides of the body is very small. Using computerised telethermography in normal persons, the skin temperature difference between sides of the body was only 0.24 ± 0.073°C. In contrast, in patients with peripheral nerve injury, the temperature of the skin innervated by the damaged nerve deviated an average of 1.55 °C. [23]. Data obtained from 40 matched regions of the body surface of 90 asymptomatic normal individuals showed temperature differences for the leg of 0.27 ± 0.021°C and for the foot 0.38 ± 0.033°C. These values were reproducible in both short- and long-term follow-up measurements over a period of 5 years[24]. In our population of 18 patients we found a mean temperature difference between both hands, as determined by videothermography, of 1.4 ± 1.3°C (range 0.3 – 4.7°C).

In a study by Oerlemans et al.[18], in healthy volunteers, skin temperature differences between both hands were measured with an infrared tympanic thermometer to provide

insight into the relationship between dorsal and palmar temperature differences. Skin temperature of the hand differed with the site where it was measured; differences between sites changed over time. The mean absolute differences in skin temperature between dorsal and palmar aspects of the hands were similar (0.30°C and 0.25°C resp.) and comparable with differences found by Uematsu et al. The temperature differences between involved and univolved hands we found were significantly higher. This could be due to the disadvantages of contact thermography and infrared tympanic thermometry which are limited by the number of spots which can be monitored following a standardised matrix protocol and [25]. Both the surface area of a certain skin temperature and the temperature range are not considered using these methods.

The usefulness of thermographs for the evaluation of chronic pain has been investigated earlier. Sherman et al. already described[26] that the stability and symmetry of thermographic patterns over time among both healthy subjects and subjects whose pain remained at the same intensity across several recordings were found to be both high and consistent. They reported thermography to be an excellent tool for monitoring changes in pain related to variations in near surface blood flow. They found a good relationship between changes in pain intensity and changes in symmetry of heat patterns. Thermography had mixed usefulness in differentiating pain-free from pained subjects reporting knee pain (efficiency 98%), leg pain and back pain (efficiency 56%). In a later study these investigators reported new findings concerning the clinical usefulness of skin temperature patterns for tracking CRPS1 by assessing changes in pain. In chronic CRPS1 patients thermographs were usually cooler on the most painful side, but the amount of relative coolness was not proportional to pain intensity [27]. The authors therefore concluded that videothermography is not an appropriate tool to use alone for either single session diagnosis of CRPS1. In a large population of healthy soldiers it was impossible to predict from any thermographic measurement on the lower limbs which soldiers were most likely to develop lower limb pain of training. On the contrary, soldiers reporting lower limb pain produced abnormal thermographs. They concluded that, in general, thermographs were of little value for predicting stress-induced lower limb pain[28]. Skin temperature measurements at all finger tips under resting conditions and continuously monitored during controlled modulation of sympathetic activity have been described recently in CRPS1 patients, in patients with painful limbs of other origin and healthy individuals[29]. The results showed only minor skin temperature asymmetries between both limbs under resting conditions in most CRPS1 patients. During controlled thermoregulation, however, temperature differences between both sides increased dynamically in CRPS1 patients. The sensitivity was 32% under resting conditions and increased up to 76% during controlled alteration of sympathetic activity. Although measurements were only performed at finger tips, the authors concluded that skin temperature differences in the distal limbs are capable of reliably distinguishing CRPS1 from other extremity pain syndromes. In that study

a comparison between temperature asymmetry and intensity of pain or immobility was not made.

In another study 185 patients considered having CRPS1 were subjected to thermal stress, after which temperature patterns were evaluated and probability of CRPS1 was compared with clinical diagnostic criteria[30]. Based on clinical criteria and an estimated 50% prior probability, the positive predictive value was 90% and the negative predictive value 94%. Using the asymmetry factor derived from regression curves of temperature related pixels of left and right sided hands, we also found a positive predictive value of 92% (ROC value 0.923).

In chronic pain patients who were classified diagnostically based on computerised thermographic examination, temperature asymmetry however only accurately discriminated between CRPS1 and non-CRPS1 patients at baseline. Responses to cold challenge did not discriminate between these two groups[31]. This could be influenced by the mostly observed 'cold' CRPS1 at later stages of the disease. Considering these observations thermographic measurements should be performed at normal conditions (baseline), after thermal stresses and cold challenge. These results should discriminate between 'warm' and 'cold' CRPS1.

The question remains whether computerised videothermography is a worthwhile tool to monitor patients who are treated by experimentally applied pharmaceuticals. In our study there is a correlation between momentary pain, duration of CRPS1 and temperature asymmetry. From our data it is clear that calculations based on area under the temperature histograms do not adequatly represent progress of the disease. Parameters such as VAS, MPQ, AROM, oedema volume and temperature difference only indicate presence of the disease following the criteria as described by Bruehl et al.[10]. Therefore, further study is needed in order to correlate the asymmetry factor and other disease indicating parameters.

Acknowledgements

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**Chapter 4**

# Skin surface temperature to differentiate between Complex Regional Pain Syndrome type 1 fracture patients and fracture patients with and without symptoms

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## Abstract

Objective: To assess the validity of skin surface temperature recordings, based on various calculation methods applied to the thermographic data, to diagnose acute complex regional pain syndrome type 1 (CRPS1) fracture patients.

Methods: Thermographic recordings of the palmar/plantar side and dorsal side of both hands or feet were made on CRPS1 patients and in control fracture patients with/without and without complaints similar to CRPS1 (total in the 3 subgroups = 120) just after removal of plaster. Various calculation methods applied to the thermographic data were compared using ROC analysis to obtain indicators of diagnostic value.

Results: There were no significant differences in demographic data and characteristics between the three subgroups. The most pronounced differences between the three subgroups were vasomotor signs in the CRPS1 patients. The involved side in CRPS1 patients was more often warmer compared with the non-involved extremity. The difference in temperature between the involved site and the non-involved extremity in CRPS1 patients significantly differed from the difference in temperature between the contralateral extremities of the two control groups**.** The largest temperature difference between extremities was found in CRPS1 patients. The difference in temperature recordings comparing the palmar/plantar and dorsal recording was not significant in any of the groups. The sensitivity and specificity varied considerably between the various calculation methods used to calculate temperature difference between extremities. The highest level of sensitivity was 71% and the highest specificity was 64%, the highest positive predictive value reached a value of 35% and the highest negative predictive 84%, with a moderate 0.60>=AUC=<0.65.

Conclusion**:** The validity of skin surface temperature recordings under resting conditions to discriminate between acute CRPS1 fracture patients and control fracture patients with/without complaints is limited and only useful as a supplementary diagnostic tool.


## 4.1 Introduction

Complex regional pain syndrome (CRPS) is a complication after surgery or trauma, although spontaneous development has also been described. CRPS is characterised by signs and symptoms of inflammation and central sensitisation. The diagnosis can be made using several different criteria sets, of which the most popular are the International Association of the study of Pain (IASP) and the Bruehl criteria sets[1]. CRPS is characterised by signs and symptoms of inflammation and central sensitisation. The diagnosis can be made using several different criteria sets, of which the most popular are the International Association of the study of Pain (IASP) and the Bruehl criteria sets[1]. There are two types of CPRS; type 1 without an obvious detectable nerve lesion (CRPS1) and type 2 with an obvious detectable nerve lesion (CRPS2).

The IASP criteria have a high sensitivity but a lower specificity, whereas the Bruehl criteria

have a high specificity but a lower sensitivity. The IASP criteria are useful in the clinical setting, whereas the Bruehl criteria appear to be more useful for research purposes[2]. New IASP criteria are under discussion[3] and attempts have been made to obtain a less subjective diagnosis by using diagnostic tools such as 3-phase bone scan, X-ray, MRI, fMRI, and temperature measurement devices[4]. Due to the limited validity of clinical diagnoses, it may be difficult to differentiate CRPS1 from other related diseases. It is assumed that a false-positive diagnosis for CRPS1 is over-expressed, especially in patients with unclear complaints of symptoms such as pain[2].

Temperature is one of the parameters used in the diagnosis of CRPS1. Surface temperature of an extremity reflects the result of a complex combination of centrally regulated and locally affected thermoregulatory systems. We previously described a calculation method to examine the difference between videothermographic pictures of CRPS1 patients and healthy controls[5]. To date, only a few studies have reported on the diagnostic value of temperature differences at the early onset of CRPS1 using thermography. In 1998 Birklein et al. described the temperature development in CRPS1 after a fracture compared to healthy subjects using different sympathetic stress factors[6]; Gradl et al. reported on 158 fracture patients of whom 18 developed CRPS[7]; and Schurmann et al. investigated differences in sympathetic control of 50 CRPS1 patients compared with 50 normal fracture patients and 50 controls (no fracture); a high sensitivity and specificity was found[8]. However, none of the above-described methods has been accepted as a gold standard. Thus factors that still need to be studied further are the sensitivity, specificity, positive predictive value and negative predictive value. All this can be explored by comparing patients who develop CRPS1 after a fracture, the CRPS1 patients, to patients who develop signs and symptoms after a fracture similar to CRPS1 , the control patients with complaints . A third control group is added comprised out of patients after fracture who have no symptoms or signs of CRPS1, controls without complaints. Furthermore, to derive indices on diagnostic value, ROC curves to calculate the diagnostic value should be used. Several other factors related to thermographic recordings and analysing methods also warrant further study. On average, thermographic recordings consist of 2,300 pixels each representing a temperature on one extremity, thus calculation methods that compare the whole temperature profile of both hands should be considered. In addition, none of the earlier studies made a comparison between the palmar/plantar side and the dorsal side. The present study focuses on the validity of static skin surface temperature recording, applying different mathematical methods, to diagnose (acute) CRPS1 patients. The term "static thermography" refers to a thermographic recording of an extremity without application of any disturbing factors on temperature regulation of that extremity.

## 4.2 Methods

This study was approved by the Medical Ethics Committee of the Erasmus MC (MEC no

198.780/2001/24). All participants provided written informed consent.

Patients with various types of fractures were first seen in the emergency room (ER) at three hospitals, the Erasmus MC, the Medical Center Rijnmond-Zuid location south, and the Medical center Rijnmond-Zuid location Clara (Figure 4.1). All patients were treated with a plaster cast during 6 (IQR 4-8) weeks, depending on the type of fracture. A questionnaire on the symptoms of CRPS1 was filled out by the plaster specialist on average 2 (IQR

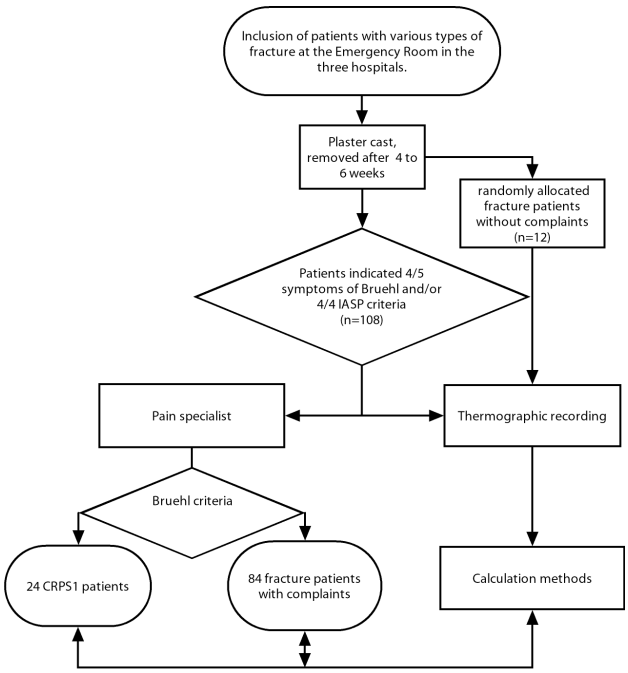


**Figure 4.1 Flowchart of the inclusion procedure of patients in the present study.**

0-5) days after removal of the plaster. Excluded were patients younger than 18 years and patients with demonstrable nerve damage in the fractured limb following CRPS type II. In addition, patients unable to fill in a Dutch-language questionnaire were also excluded. A questionnaire on the symptoms of CRPS1 was filled out by means of a short interview that addressed the anamnesis part of symptoms of CRPS1 proposed by Bruehl et al. and by the International Association for the Study of Pain (IASP)[1]. CRPS1 was considered to be present when patients had continuing pain, hyperesthesia, temperature asymmetry and/or skin color asymmetry, edema and/or sweating asymmetry, motor and/or trophic changes. When patients met 4 out of 5 of the Bruehl criteria and/or 4 out of 4 of the IASP criteria they were referred to an anaesthesiologist (FJPM) who has a wide experience with CRPS1 patients; this physican made a comprehensive physical examination after which only the

Bruehl criteria were noted for each patient. This resulted in three groups: 1) 24 fracture patients fulfilling the Bruehl criteria designated as the "CRPS1 patients", 2) 84 fracture patients with various complaints but not fulfilling the Bruehl criteria designated as "Control patients with complaints", and 3) 12 randomly selected (normal healing) fracture patients without any visible signs/complaints designated as "control patients without symptoms". To be sure that patients with pain but without CRPS1 did not developed CRPS1 after their first visit, a second visit was planned 8 weeks later**.** After the first consultation with the physician, videothermographic images were recorded following a standard protocol. The physician was blinded for the thermographic recording and the technician who performed the recordings was blinded for the diagnosis by the physician. Before the recording, patients were acclimatised in a room with a mean temperature of 23ºC (range 22.5ºC -23.5ºC) and a relative humidity of 50% (range 45%-55%) during 15 minutes. Patients were placed in a chair in an upright position.

Measurements of the involved (fracture) and non-involved (not fractured) extremity were performed on the palmar/plantar side and the dorsal side. The hands where placed in a plexiglas frame. The frame has positioning points between digit 1 and digit 2, and between digit 3 and digit 4, which allows to record comparable parts of the extremity in different patients. Based on average temperature of the palmar/plantar side, >+0.3ºC was considered as warmer and <-0.3ºC was as considered colder.

The foot temperature was recorded using a support below the ankle which enables recording of the plantar aspect of the foot; the dorsal aspect was recorded by placing the feet on the ground. To establish whether the temperature difference also spread outside of the fractured area, a thermographic recording depicting the front of the leg from the knee down to the ankle was recorded in the same upright position.

Skin temperature of both extremities was registered with a computer-assisted infrared thermograph (ThermaCAM SC2000, Flir Systems, Berchem, Belgium). This infrared thermographic camera has a resolution of 320x240 pixels. Each temperature value measured in the picture is represented by one pixel; this gives a total of 76,800 temperature values recorded in one image. The thermographic images were stored on a hard disk (ThermaCAM Researcher 2001 HS, Berchem, Belgium) awaiting further analysis.

The distance between the camera and the hand being measured was adjusted to 68 cm; thereby the resolving capacity on the hand is 0.8x0.8 $mm^2$. The distance between the camera and the feet was adjusted to 90 cm to accommodate the whole foot; thereby the resolving capacity on the feet was 1.2x1.2 $mm^2$

To obtain only those pixels that represent the hand or feet, the data are filtered by a threshold. On average one hand is represented by 23,500 pixels and a foot by 12,000 pixels.

## Calculation methods

Most of the commonly used methods calculate differences in mean skin surface temperature between the involved (fractured) and the non-involved (not fractured) extremity. However, these methods take into account the total surface extremity, or only an arbitrary region of interest such as the fingertips/toes. We developed inhouse software using Matlab to facilitate these and newly- developed calculation methods as described below.

## Absolute difference in mean hand or foot temperature

The difference between average hand/foot temperature was calculated for both the palmar/plantar side and dorsal side using the following formula:

$$\Delta\overline{T_{absolute\ extremity}} = \left|\overline{T}_{involved} - \overline{T}_{non\_involved}\right| \qquad \textbf{Equation 4.1}$$

*Absolute difference in mean fingertip temperature*

A square was placed around each finger and toe tip of the extremity. The zeros in the square, indicating background, were filtered out.

$$\Delta\overline{T_{absolute\ tips}} = \frac{\sum_{tip=1}^{5}\left|\overline{T}_{involved_{tip}} - \overline{T}_{non\_involved_{tip}}\right|}{5} \qquad \textbf{Equation 4.2}$$

*Absolute static temperature difference between wrist/ankle and fingertip/toe tip*

For the hands, 5 points at the wrist (base), 5 points at the knuckle of each finger, and 5 points at the tip of each finger were defined using software. On each hand or foot, 5 lines were automatically drawn by computer over the hand/foot, as shown in Figure 4.2a and Figure 4.2b.

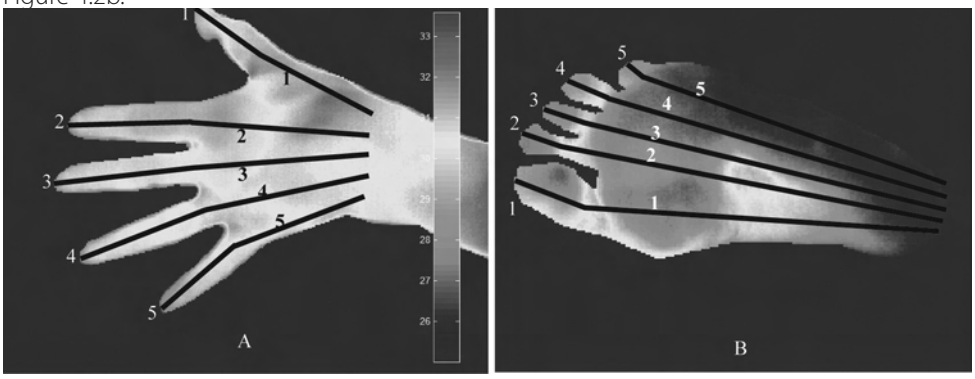


**Figure 4.2 Examples of thermographic recordings of a) hand, and (b) foot. The numbers 1 to 5 at the finger/toe tips indicate the location used to calculation the mean finger and mean toe tip temperature. The numbers 1 to 5 on the lines indicate the lines drawn by software over the hand/feet and fingers/toes.**

Hereafter a line was fitted through the temperature point that lay on the five lines. The slope, calculated by the fit, of each line was used to calculate the temperature increase/decrease across each of the fingers. The increase/decrease of each finger on the involved was subtracted from the increase/decrease of the corresponding fingers on the non-involved site. This result was summed to indicate a total difference in temperature increase/decrease between the extremities. The same procedure was applied for the calculation of foot temperatures. For this five points were defined at the ankle (base), 5 points at the base of each toe, and 5 points at the tip of each toe (Figure 4.2b). The aim of this calculation is to give an indication of the difference in vasomotor tone between the involved and non-involved side. A large decrease in temperature between wrist compared to finger tips or ankle compared to toe tip indicates a high vasomotor tone resulting in low blood flow through fingers and toes, whereas a small decrease in temperature indicates a low vasomotor tone.

## Asymmetry factor

This calculation method determines the asymmetry factor (correlation) between the temperature histogram of the involved and non-involved extremity, based on the method described by Huygen et al. [9]. The asymmetry factor describes the degree of dissimilarity (expressed in correlation coefficient ) between the temperature data obtained from the involved hand/foot compared with that from the non-involved hand/foot. A score of 1 indicates a similar temperature distribution between involved and non-involved side; a lower score indicates less similarity. This method intends to take into account al aspects of the whole temperature profile in comparing hands.

## Euclidian distance

This Euclidian distance is a measure of the distance between the temperature histograms of the involved and non-involved side [10].

$$D(Involved, Non\_involved) = \sqrt{\sum_{i=1}^{i=\max(i)} (Involved(i) - Non\_involved(i))^2} \quad \textbf{Equation 4.3}$$

| | | |
|---|---|---|
| D | = | Distance between histograms |
| Involved, Non-involved | = | Frequency value of a class |
| i | = | Bin class number |

The class width was set to 0.1ºC. This calculation effectively calculates the degree of similarity in the shape of the temperature histogram of the involved and non-involved site. The above-described calculations were used to measure the similarity of the palmar/plantar side and the dorsal side between the involved and non-involved extremity.

### Total temperature difference between fingers and toes

For the hands, 5 points at the wrist (base), 5 points at the knuckle of each finger, and 5 points at the tip of each finger were defined using software. On each hand or foot, 5 lines were automatically drawn by computer over the hand/foot, as shown in Figure 4.2a and Figure 4.2b. The temperature profile of each line on the involved hand/foot was compared with non-involved hand/foot using cross-covariance (mean-removed cross-correlation). The total difference was calculated by summing the maximum cross-correlation found on each finger, with a maximum shift of 20 pixels. This measurement intends to take into account the irregularity in temperature that is found in most CRPS1 patients. This irregularity expresses itself in so called hot spots and cold spots, this methods is able to compare local disturbance on temperature that can be a result of ,for example, a local inflammation.

## 4.3 Statistical analyses

Data analyses were performed with SPSS 14.0. One-way analysis of variance (ANOVA) was used to calculate any significant differences in age and weeks after trauma between CRPS1 patients, Control patients with complaints, and control patients without symptoms. Cross-tabs chi-square was used to test whether the signs showed a significant difference between CRPS1 patients and Control patients with complaints.

One-way analysis of variance (ANOVA) (Bonferroni test correction) was used to test whether the outcomes of the calculation methods used on the thermographic data showed a significant difference between CRPS1 patients, Control patients with complaints, and control patients without symptoms.

The ROC is used to calculated the diagnostic value. The ROC is a graph, which is a very good indicator of the discriminating power of a diagnostic method. The coordinates of the graph are defined by calculating the sensitivity and specificity at different values of the diagnostic test (in this article the various methods to calculate the temperature difference between extremities), so called 'cut-off points'. This results in a graph of the true positive rate (sensitivity) against the false positive rate (specificity) for the different possible 'cut-off points' in a given diagnostic test. The most valid diagnostic cut-off value was chosen at the highest combination of sensitivity and specificity.

The area under the ROC is a measure of the accuracy of the diagnostic test at hand, expressed in area under the curve (AUC). The accuracy is measured by an five point system: excellent (AUC of 1-0.9), good (AUC of 0.9-0.8), fair (AUC 0.8-0.7) poor (AUC of 0.7-0.6), fail (AUC of 0.6-0.5) (Metz 1978; Parker et al. 2003). More insight into the diagnostic value of thermography is gained when the positive and negative predictive values are also calculated. The positive predictive value is the proportion of patients with positive test results who are correctly diagnosed. The negative predictive value is the proportion of patients with negative test results who are correctly diagnosed. In all tests a p value $<0.05$ was considered

to be statistically significant.

## 4.4 Results

Demographic data and characteristics of the study population are given in Table 4.1. No significant difference was found in the incidence of CRPS1 patients ampong the three participating hospitals. Control patients with symptoms were significantly older compared wit the other two groups.

Table 4.1 Data on demographics of patients included in this study

| | CPRS1 patients (n=24) | Control patients with complaints (n=84) | Control patients without complaints (n=12) |
|---|---|---|---|
| Erasmus MC hospital (n=49) | 9 | 36 | 4 |
| Medical Center Rijnmond-Zuid location South (n=53) | 11 | 35 | 7 |
| Medical Center Rijnmond-Zuid location Clara (n=18) | 4 | 13 | 1 |
| Mean Age(Y) (SD) | 56 (15.4) | 54 (16) | 42 (17.7)* |
| Male/Female | 7/17 | 20/64 | 7/5 |
| Average weeks after trauma (SD) | 16 (11.4) | 16 (11) | 16 (15) |
| Location fracture upper limb (n=61) | 8 Left/4 Right (n=12) | 32 Left/13 Right (n=45) | 0 Left/ 4 Right (n=4) |
| Location fracture lower limb (n=59) | 9 Left /3 Right (n=12) | 20 Left/19 Right (n=39) | 3 Left/ 5 Right (n=8) |
| Involved side warmer[1] | 18 | 42 | 7 |
| Involved same temperature | 0 | 1 | 1 |
| Involved side colder | 6 | 41 | 4 |

*Significant difference between age of CRPS1 fracture group compared to control fracture group.

[1]Based on average temperature palmar/plantar side, >+0.3ºC was considered warmer, <-0.3 ºC was considered colder.

There was no significant difference between the three groups in the number of weeks after trauma, or in the location of the fracture. In CRPS1 patients the involved side was more often warmer than colder (18 versus 6).

Data on symptoms according to the Bruehl criteria are given in Table 4.2. By definition, control patients without complaint had no symptoms/ nor signs. Although CRPS1 patients had a slightly higher pain score (5.9) than the control patients with complaints (4.8), the difference was not significant (p=0.104). Because CRPS1 patients were included according to the Bruehl criteria a 100% scores in each category on each symptom was mandatory. The control patients with complaints also showed relatively high percentages on all symptoms, except for vasomotor signs. A marked increase was found comparing sensory and vasomotor signs of the CRPS1 patients to the controls with complaints, whereas changes in sudomotor/ edema and motor/trophic signs were more alike.Table 4.3 presents data on differences in skin surface temperature between the involved and non-involved side as calculated by the various mathematical methods for each of the three groups.

There is an overall significant difference comparing all three groups for all measurement except absolute static temperature difference between wrist/ankle and fingertips/toe tips. The difference between CRPS1 patients and control patients with complaints is significant for euclidian distance and total of difference between fingers/toes. There was a significant difference found between CRPS1 patients and control patients without complaints in the absolute difference in mean hand/foot temperature, in asymmetry factor, in Euclidian distance. The difference in temperature between involved and non-involved side (as indicated by the various calculation methods) shows a tendency to decrease; the largest difference in temperature was found in CRPS1 patients compared to the two other groups.

The differences in temperature between the palmar/plantar side and dorsal side are small and not significant; therefore only the palmar side of hands and feet are presented in Tables 4.3 and 4.4. Indicators which reflect the diagnostic value (such as sensitivity and specificity) are presented in Table 4.4.

**Table 4.2 Data on symptoms and signs of CRPS1 patients and controls with symptoms.**

| | Pain VAS median (range) | Sensory category (%) | | | Vasomotor category (%) | | | Sudomotor/edema category (%) | | | Motor/trophic category (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (0-10) | Yes | No | Missing | Yes | No | Missing | Yes | No | Missing | Yes | No | Missing |
| | | Symptoms (reported by patient) | | | | | | | | | | | |
| CRPS1 patients (n=24) | 5.9 (4.-7.0) | Per definition : 100% | | | | | | | | | | | |
| Control patients with complaints (n=84) | 4.8 (2.8-7.0) | 73 | 27 | 0 | 55 | 44 | 1 | 76 | 24 | 0 | 72 | 26 | 2 |
| | | Signs (determined by pain specialist) | | | | | | | | | | | |
| CRPS1 patients (n=24) | n.a. | 38* | 62* | 0 | 92* | 8* | 0 | 83* | 17* | 0 | 79* | 21* | 0 |
| Controls patients with complaints (n=84) | n.a. | 12 | 87 | 1 | 35 | 64 | 1 | 41 | 58 | 1 | 37 | 62 | 1 |

***Displayed symptom group significantly different between CRPS1 patients and control patients with symptoms.**

**n.a. = not available**

***significant at the p<0.05 level**

**Table 4.3 Data of various calculations on temperature difference between the CRPS fracture patients, control patients with symptoms and control patients without symptoms.**

| | | Absolute difference mean hand or foot temperature (°C) | Absolute difference mean finger/toe tip temperature (°C) | Absolute static temperature difference between wrist/ankle and fingertips/toe tips (°C) | Asymmetry factor | Euclidian distance | Total of difference between fingers/ toes |
|---|---|---|---|---|---|---|---|
| CRPS1 patients (n=24)[1] | | 1.0 (0.85) | 1.4 (1.46) | 4.3 (4.71) | 0.39 (0.38) | 2176 (1301) | 13287 (4334) |
| Control patients with complaints (n=84)[1] | | 0.7 (0.56) | 0.9 (1.00) | 4.0 (4.4) | 0.60 (0.32) | 1506 (692) | 12918 (4095) |
| Control patients without complaints( n=12)[1] | | 0.27 (0.16) | 0.5 (0.30) | 2.8 (2.0) | 0.83 (0.41) | 1549 (912) | 12535 (4573) |
| | | | | Overall differences | | | |
| Whole group | SS | 4.6 | 11.5 | 40.8 | 0.98 | 8169794 | 1.7E008 |
| | df | 2 | 2 | 2 | 2 | 2 | 2 |
| | MS | 2.3 | 5.7 | 20.4 | 0.49 | 4084897 | 5.5E08 |
| | F | 6 | 5.4 | 1.08 | 4.9 | 5.19 | 8.9 |
| | p | 0.003* | 0.006* | 0.343 | 0.008* | 0.007* | 0.000* |
| | | | | Differences between the three different groups[2] | | | |
| Difference between CRPS1 patients and control patients with complaints | | 0.3 (p=0.089) | 0.5 (p=0.18) | -0.4 (p=1.000) | -0.21 (p=0.102) | -670* (p=0.006) | 369* (p=0.038) |
| Difference between CRPS1 patients and control patients without complaints | | 0.7* (p=0.003) | 1.0* (p=0.027) | 1.6 (p=0.960) | -0.46* (p=0.007) | -626* (p=0.009) | 751 (p=1.000) |
| Difference between control patients with complaints and control patients without complaints | | 0.3 (p=0.089) | 0.4 (p=0.55) | 2 (p=0.46) | -0.23 (p=0.102) | 43 (p=1.000) | 382 (p=0.169) |

**[1]Data are mean (SD).**

**[2]Bonferonni correction**

***Significant t the p<0.05 level**

**Table 4.4 Data on receiver operative curve (ROC) analysis on temperature difference comparing CRPS1 patients to control patients with symptoms.**

| CRPS1 patients compared to control patients with complaints | Absolute difference mean hand or foot temperature | Absolute difference mean finger/toe tip temperature | Absolute static temperature difference between wrist/ ankle and fingertips/toe tips | Asymmetry factor | Euclidian distance | Total of variation between fingers and toes |
|---|---|---|---|---|---|---|
| Cut-off point | >0.99(ºC) | >0.7(ºC) | >2.0(ºC) | <0.61 | >1293 | >10925 |
| Sensitivity[1](%) | 48 (27-69) | 67 (45-84) | 63 (40-81) | 63 (41-81) | 71 (49-87) | 64 (41-81) |
| Specificity[1](%) | 64 (52-76) | 57 (45-69) | 41 (30-53) | 61 (49-72) | 36 (44-58) | 43 (31-55) |
| Positive predictive value (%)[2] | 31 | 34 | 25 | 35 | 31 | 28 |
| Negative predictive value (%)[2] | 78 | 84 | 78 | 83 | 82 | 78 |
| AUC[3] | 0.60 | 0.60* | 0.60 | 0.63* | 0.65* | 0.60 |

[1]Percentage (95% C.I.)

[2]Based on the incidence of the studied population, this was 25%.

[3]Area under the curve (AUC), each had a 95% and a C.I. of 0.50 to 0.70

* significant difference at the $p<0.05$ level.

The positive predictive value, negative predictive value and AUC are similar for all calculation methods, whereas the sensitivity and specificity differ. The absolute difference in mean hand/foot temperature was a weak predictor of CRPS1 patients, whereas average fingertip temperature, asymmetry factor, Euclidian distance and total difference in temperature between fingers and toes proved to have stronger diagnostic value.

## 4.5 Conclusion/Discussion

Significant differences between CRPS1 patients, control patients with complaints, and control patients without complaints were found as reflected by the various mathematical methods used to calculate temperature differences. ROC analysis of the diagnostic value of thermography calculated a moderate discriminating power, as indicated by an AUC of <=0.7. Furthermore, not every mathematical method showed a significant difference between the

three subgroups. The control patients with complaints showed overlap with CRPS1 patients in both symptoms and signs. Moreover, there is a large overlap between symptoms; most prominent in CRPS1 fracture patients were the displayed vasomotor symptoms, indicating that vasomotor signs belong to the most prominent signs at early onset of CRPS1; this has also been reported by others[1,6,8,11-15]. The difference in temperature between the involved and non-involved side (as indicated by the various calculation methods) shows a tendency to decrease, the highest difference expressed by the CRPS1 patients and the lowest difference observed in control patients without complaints; this phenomenon was also found in studies by Schurmann et al. and Bruehl et al.[8,11,13].

Studies on the use of thermography to discriminate between CRPS1 patients and non-CRPS patients lack consistency regarding the calculation methods used on the thermographic data (e.g. whole-hand calculations, spots, and fingertips), the statistical analyses used, as well as the description of and inclusion criteria applied. Birklein et al. was unable to calculate specificity and negative/positive predictive values because they did not include patients with symptoms similar to CRPS1 [6]. Gradl et al. used an arbitrary fixed cut-off value of >1.5ºC for fingertip/hand temperature difference and found that thermography had a low sensitivity and specificity; moreover, they did not report on positive/negative predictive values nor did they use ROC analysis to derive indices on diagnostic value at other cut-off values[12]. Shurmann et al. used only fingertip temperature to calculate the difference between the involved/non-involved extremity and did not compare other calculation methods on thermographic data[13].There is, some overlap of the absolute mean temperature difference between the involved/non-involved extremity found in CRPS patients between the present study and values reported in the literature. ROC analysis results in a range of cut-off values with an associated sensitivity and specificity.

In this study we found a difference of >0.99°C on absolute mean temperature difference between extremities to be the optimum cut-off value as indicated by ROC analysis, whereas Bruehl et al. found a difference of >0.82°C to be optimum[11]. Furthermore, in the present study a mean asymmetry factor of 0.39 was found for patients and 0.83 for control patients without complaints. In our previous study a mean asymmetry of 0.45 was found for CRPS1 patients and 0.91 for healthy controls[9]. In the literature sensitivity is reported to range from 58-93% and specificity from 86-89%[8,12,16]; none of these latter studies reported on AUC. In our study the highest sensitivity was 71% and the highest specificity 64% with a moderate AUC of >0.63. In this study the cut-off value was chosen that resulted in the highest combination of sensitivity and specificity. Different cut-off value could also have been considered however, because of the low AUC as calculated by the ROC, a different cut-off value will only alter the sensitivity at the cost of specificity. In conclusion a different cut-off does not improve the diagnostic capabilities as a whole. The positive and negative predictive values can be calculated using the calculated sensitivity and specificity combined with the incidence

of the studied population. In this study fracture patients with a high risk of CRPS1 were included, therefore in the analysis the incidence of the studied population was used. Only Gulevich et al. reported on positive predictive value (90%) and negative predictive value (94%) [16]. In our study, the highest positive predictive value was 35% and the highest negative predictive value was 84%. The reason for the high level of positive predictive value found in the study of Gulevich et al. compared to this study could be due to the sympathetic stress methods used in that study.

Although we were only interested in the diagnostic value of temperature recordings at the very early stage after the onset of CRPS1, one of the limitations of this study is a lack of follow up. Data obtained after 6, 12 and 18 weeks could emphasize the difference between CRPS1 patients and slow recovering control patients with complaints. Non of the patients with pain but without CRPS1 developed CRPS1 according to the second follow-up visit 8 weeks later.

One could argue the temperature difference in CRPS1 patients already could have spread outside the fractured area thus increasing the difference between the CRPS1 group and the control fracture group. However, the difference between the involved and non-involved leg and was not significant in any of the three groups, nor was this difference significant between the three groups.

The validity of thermographic recording to discriminate between CRPS fracture patients and control patients with complaints, at the early onset of CRPS1 is limited, therefore thermography should be considered as an additive diagnostic tool. When an abnormal pattern of temperature is identified and confirmed using the cut-off values as indicated in the results of this study a follow-up of these patients is advisable. In that case the best performing mathematical methods, that is able to evaluate all the collected thermographic data are the asymmetry factor, the euclidian distance and total of variation between fingers and toes. There is no preference of recording on palmar/plantar or dorsal side other than for pragmatically reasons.

Some studies have shown an increase in temperature difference after methods in which the sympathetic system is provoked [15,17]. Further research should focus on this aspect and investigate there effect on the temperature difference between extremities and there effect on the various indicators for diagnostic purposes.

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## Chapter 5

# Thermography imaging during static and controlled thermoregulation in complex regional pain syndrome type 1: diagnostic value and involvement of the central sympathetic system

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## Abstract

Background: Complex Regional Pain Syndrome type 1 (CRPS1) is a clinical diagnosis based on criteria describing symptoms of the disease.

The main aim of the present study was to compare the sensitivity and specificity of calculation methods used to assess thermographic images (infrared imaging) obtained during temperature provocation. The secondary objective was to obtain information about the involvement of the sympathetic system in CRPS1.

Methods: We studied 12 patients in whom CRPS1 was diagnosed according to the criteria of Bruehl. High and low whole body cooling and warming induced and reduced sympathetic vasoconstrictor activity. The degree of vasoconstrictor activity in both hands was monitored using a videothermograph. The sensitivity and specificity of the calculation methods used to assess the thermographic images were calculated.

Results:The temperature difference between the hands in the CRPS patients increases significantly when the sympathetic system is provoked. At both the maximum and minimum vasoconstriction no significant differences were found in fingertip temperatures between both hands.

Conclusions: The majority of CRPS1 patients do not show maximal obtainable temperature differences between the involved and contralateral extremity at room temperature (static measurement). During cold and warm temperature challenges this temperature difference increases significantly. As a result a higher sensitivity and specificity could be achieved in the diagnosis of CRPS1. These findings suggest that the sympathetic efferent system is involved in CRPS1.


## 5.1 Background

Complex regional pain syndrome type 1 (CRPS1) is a complication after surgery or trauma, although spontaneous development has also been described. CRPS1 is characterised by signs and symptoms of inflammation and central sensitisation. The diagnosis can be made using several different criteria sets, the most popular of which are the International Association of Pain (IASP) and the Bruehl criteria sets[1]. The IASP criteria have a high sensitivity but a lower specificity, whereas the Bruehl criteria have a high specificity but a lower sensitivity. The IASP criteria are useful for clinical aims and the Bruehl criteria appear to be more useful in research. New IASP criteria are under discussion[2] and attempts have been made to obtain a less subjective diagnosis by using diagnostic tools such as 3-phase bone scan, X-ray, MRI, fMRI, and temperature measurement devices[3]. Until now, however, none of these methods has been accepted as a gold standard. Due to the limited validity of clinical diagnoses, it may be difficult to differentiate CRPS1 from other diseases, e.g. from functional disorders with disuse. We have the impression that a false-positive diagnosis for CRPS1 is still made too often, especially in patients with complaints for which no clear explanation can be obtained

regarding the onset of the symptoms.

Temperature differences are widely regarded as a predictor in the diagnosis of CRPS and videothermography has been applied as a diagnostic tool in CRPS1[4-7]. The videothermograph is an excellent skin temperature measurement system with a high accuracy and repeatability [8]. Skin temperature is a good predictor of sympathetic activity as shown in a study in which a good correlation was found between skin temperature and skin sympathetic nerve activity [9]. Temperature at the surface of an extremity reflects the result of a complex combination of central and local regulation systems. Sherman et al. assessed the clinical usefulness of skin temperature patterns in diagnosing CRPS, by observing long-term relationships between changes in pain due to CRPS and patterns of near-surface blood flow[7]. Bruehl et al. examined the validity of thermogram derived indices of autonomic functioning in the diagnosis of CRPS; they found that temperature asymmetry accurately discriminated between CRPS and non-CRPS patients[10]. Wasner et al. evaluated the diagnostic value of skin temperature side differences as an index of induced disturbance to the sympathetic nervous system; they have shown that skin temperature differences in the distal limbs proved to be useful in distinguishing CRPS1 from other extremity pain syndromes with high sensitivity (76%) and specificity (93%)[11]. Gulevich et al. have shown a high sensitivity (93%) and specificity (89%) for stress infrared thermography in the diagnosis of CRPS; based on an estimation of 50% prior probability, the positive predictive value was 90% and the negative predictive value was 94%[5]. However, the findings of these studies are not consistent with respect to sensitivity, specificity and reliability, probably because different analysing schemes were used to assess the thermographic data. Other factors possibly influencing the discriminating power of temperature measurement in CRPS1 is the cyterian cycle of the sympathetic system. Wasner and colleagues showed an improvement in sensitivity and specificity using temperature measurement of fingertips during cold and hot challenge[12,13]. Nowadays, the infrared tympano thermometer is very popular to measure skin temperature in CRPS1. The temperature should be measured in a matrix of representative points, as described by Oerlemans et al.[14]. The average difference between the involved and contralateral extremity is calculated using the points defined by the matrix. In an earlier study we demonstrated improved sensitivity and specificity of temperature measurement when using computerized videothermography at room temperature and also introduced the asymmetry factor[15].

The main aim of the present study was to compare the sensitivity and specificity of calculation methods used to assess thermographic images (infrared imaging) obtained during cold and warm temperature provocation. The secondary objective was to obtain information about the involvement of the central sympathetic system in CRPS1.

## 5.2 Methods

Patients and controls

This study was approved by the local Medical Ethical committee of the Erasmus Medical Centre. From April (spring) 2003 through September (autumn) 2003 we included 12 patients, (11 women and 1 man) with a mean age of 51.5 (range 37-66) years. All patients gave written informed consent. A physician with considerable experience in diagnosing and treating CRPS1 (FJPM), included the patients according to the Bruehl criteria [1]. Only patients with a unilateral CRPS1 in the upper extremity were included. During the same period we studied 8 healthy volunteers (control) without a history of neurotrauma and/or vascular disease (5 women and 3 men) with a mean age of 29.4 years (range 22-48) years. Data on the patients are presented in Table 5.1

Table 5.1 Clinical characteristics of the CRPS1 patients

| Subject no. | Age(years) /sex | Time since onset of disease (months) | Dominant side | Location of CRPS1 | Precipitating event |
|---|---|---|---|---|---|
| 1 | 43/f | 10 | Left | Left | removal of tumor digit 3 |
| 2 | 49/f | 8 | Right | Right | Colles fracture |
| 3 | 52/f | 8 | Right | Left | unknown trauma |
| 4 | 51/f | 6 | Left | Right | tendon trauma |
| 5 | 63/f | 5 | Right | Right | Colles sprain |
| 6 | 56/f | 8 | Right | Right | Colles fracture |
| 7 | 66/f | 9 | Right | Right | Colles fracture |
| 8 | 41/f | 10 | Right | Left | Colles fracture |
| 9 | 47/f | 3 | Right | Left | injection into wrist |
| 10 | 56/f | 3 | Right | Right | arthrose digit 1 |
| 11 | 57/f | 3 | Right | Left | Colles fracture |
| 12 | 37/m | 6 | Left | Left | Colles fracture |
| Average | 51.5 | 6.6 | | | |
| SD | 8.7 | 2.6 | | | |

Power calculation

Data from our previous study were used to perform a power calculation; in that study the difference between the asymmetry factor of patients and controls was 0.41 and the combined SD was 0.31[15]. Considering a ratio between patients and controls of 0.65 with a significance of 0.05, for the present study the number of patients needed to obtain 80% power was 12 and the number of controls needed was 8.

General questionnaires and measurements

The severity of the CRPS1 is estimated using the total Impairment level Sum Score (ISS). The ISS total is the sum of the Visual Analogue Scale (VAS), The McGill pain questionnaire (MPQ), active range of motion (AROM), edema and temperature difference that are converted to ISS scores (ranging from 1-10). The VAS is a reliable and valid instrument to measurement pain intensity [16], with scores range from 0 (no pain) to 10 (most intense pain). The VAS is used to measure the momentary pain during rest, and pain during the cold and warm temperature cycle.

The MPQ, Dutch language version, is a reliable and valid tool to measure the amount of pain in a variety of complaints [17];

The AROM was used to reflect physical dysfunction. Scores from both the unaffected hand and the affected hand were measured, and the differences in range of motion from five joints were recorded (range 1–5 points per joint, 5 points for maximal limitation). The presence of edema in the affected limb was measured in comparison with the unaffected hand. The percentage differences in volume were determined after successive immersion of both hands in a tube containing water at approximately 30°C. The amount of displaced water was weighed on-line using a laboratory balance (Sartorius, Breukelen, the Netherlands; accuracy 1 g), based on the method described by Fereidoni et al.[18].

To comply with the standard ISS score defined by Oerlemans et al.[19], the skin temperature of both hands was measured by a tympanic thermometer (M3000A, First Temp Genius®, Tyco Healthcare Ltd, Gosport, UK). The thermal sensitivity of the thermometer is 0.05°C at 30°C. Five measuring points on both extremities were marked using a predefined matrix.

All the outcomes above were then converted to a score ranging from 1 to 10, resulting in an ISS total with a minimum score of 5 and a maximum score of 50. A score of 5 indicates the least level of impairment and 50 the highest level of impairment. The ISS total is the sum of the VAS, the MPQ, AROM, edema and temperature difference that are converted to ISS scores (ranging from 1-10), as described by previously by Oerlemans et al.[19].

Temperature challenge to experimental condition

The most effective way to alternate sympathetic vasoconstrictor activity is by whole body warming and cooling[20]. To achieve whole body warming and cooling a thermosuit was used (Thermowrap, MTRE, Akiva Industrial Park, Israel). During the experiment the room temperature was kept constant at 23±0.5 ºC. The thermosuit did not cover the head, hands and feet of the subjects. The thermosuit, connected to a thermostatic pump (Ecoline, Lauda, Lauda-Königshofen, Germany), is pivoted by water channels and in direct contact with the skin providing a high-energy transfer. The water inflow temperature was set to a temperature of 15±1.5 ºC during the cold cycle, and 45±1 ºC during the warm cycle. The flow of water was 2 l/min, effectively replacing the water in the suit almost every minute. This method allows

to achieve a controlled sympathetic activation of the vasoconstrictor neurons supplying the hands and feet[12]. Maximum vasoconstrictor activity was presumed to be reached when the mean temperature of the fingers of the contralateral side achieved room temperature during the cold cycle. Minimum vasoconstrictor activity was presumed to be reached when the average fingertip temperatures of the contralateral side was at 96% of the tympanic temperature measured at baseline. In the control group the fingertip temperature of the dominant side was considered as an indicator of maximum and minimum vasoconstrictor activity.

Temperature measurement

Skin temperature of both hands was measured with a computer-assisted infrared thermograph (ThermaCam SC2000, FLIR, Danderyd, Sweden). This thermographic camera produces a matrix (representing image points) of temperature values. The thermal sensitivity of the thermograph is 0.05°C at 30°C. The spectral range is 7.5-13 µm and the built-in digital video is 320×240 pixels (total 76,800 pixels). Data were obtained through a high-speed (50 Hz) analysis and recording system coupled with a desktop PC (ThermaCAM Researcher 2001 HS). Because calculation on the thermograms took place after the experiment, the thermograms were stored on a hard disk (14-bit resolution) awaiting analysis. The emissivity of the skin was set in the software to 0.98 and the apparent temperature was measured and also set in the software. Before each recording the camera was calibrated using the system's internal calibration of the software connected to the camera.

Baseline measurements

Baseline differences between the two hands were measured at room temperature (23ºC), with patients and controls kept in an upright position for 15 min to obtain sympathetic equilibrium with the surrounding. A thermographic image of the dorsal side of both hands was taken parallel to the hand from a distance of 70 cm incorporating the whole hand including the wrist, based on the method described Huygen et al.[15]. Thereafter, the VAS scale was used to record the pain at that moment, the MPQ was filled in, and the AROM and hand volume were measured.

Measurements during the cold cycle

After the baseline measurements the subjects put on a bathing suit/trunk, then lay in a supine position in the thermosuit (connected to a thermobath), which was already cooled to 15°C, resulting in a massive sympathetic vasoconstriction activity. Immediately temperature measurements took place every 10 min until all fingertips on the contralateral side reached room temperature (23°C) (see Figure 5.1, Cold cycle). In the control group the dominant side was considered as reference. The temperature measurements were made at 70 cm distance parallel to the hand, using a tripod to hold the videothermographic camera. The tympanic

temperature of patients and controls was measured at the end of the cold cycle. Patients were asked to indicate the pain level every 10 minutes during the entire cold cycle by means of a VAS score.

Measurements during the warm cycle

When the cold cycle was completed, the thermo bath was emptied and refilled with water heated to 40°C. This resulted in a suit temperature of 40°C within approx. 5 min while the subjects were kept in the suit. Then the temperature was set to 45°C, which was reached within 5 min. The temperature of 45°C leads to a low sympathetic vasoconstrictor activity. From then onwards temperature measurements took place every 10 min until all fingertips on the uninvolved side reached 96% of the tympanic temperature (Figure 5.1, Warm cycle). Recording of the thermographic images took place in the same way as during the cold cycle. Patients were asked to indicate their pain level during the entire warm cycle by means of a VAS score every 10 min.

## 5.3 Calculations

The temperature information in the thermographic images taken at baseline, and during the cold cycle and warm cycle, contain both the environmental temperature and the temperature of the hand. A threshold temperature was used to filter out the environmental temperature. Calculation of the fingertip temperature and the asymmetry factor was used to describe the sympathetic vasoconstrictor state every 10 min.

Average fingertip temperature

Using software, spots of approximately 30 pixels were placed on the fingertips representing 19 mm2 of the fingertips (Thermacam researcher software 2000). The average temperature of a spot was considered to be a representative temperature of a fingertip. Then, for each hand, the average fingertip temperature was calculated by averaging over all 5 spots. In patients, the absolute difference in fingertip temperature was calculated by subtracting the average fingertip temperature of the involved hand from the average fingertip temperature of the contralateral hand. The same absolute difference fingertip temperature was calculated in controls where the fingertip temperature of the dominant hand was subtracted from the non-dominant hand.

Asymmetry factor

This method determines the asymmetry factor (correlation) between the temperature histogram of the involved and contralateral extremity based on the method described by Huygen et al.[15]. The asymmetry factor is a factor describing the degree of dissimilarity between temperature data obtained from one hand compared to the other hand. A score of 1 indicates the same temperature distribution; a lower score indicates less similarity. This

calculation was applied to the thermographic recording of both patients and controls.

Discriminating power and vasomotor activity

To assess whether the temperature provocation increased the discrimination between patients and controls the following selection was used: -For the fingertip temperature; the absolute average fingertip temperature difference at baseline was compared to the maximum absolute difference between the average fingertip temperature that was reached during the total temperature cycle (Figure 5.1, A). -For the asymmetry factor; the asymmetry factor at baseline was compared to the minimum asymmetry factor that was reached during the temperature cycle. -To compare vasomotor activity span between the involved and contralateral hand, the differences between the minimal fingertip temperature and the maximal fingertip temperature during the whole temperature cycle were calculated in both the involved and contralateral hand (Figure 5.1, B) The maximum VAS pain rating that was present during the total temperature cycle was also selected in each subject.

Calculating the sensitivity, specificity, positive predictive value and negative predictive value

The receiver operating characteristic (ROC) curve is a very good indicator of the discriminating power of a diagnostic method. The coordinates of the plot are defined by calculating the sensitivity and specificity at different values of the diagnostic test, called cut-off points. The sensitivity is plotted on the vertical axes and specificity is plotted as 1 minus the specificity on the horizontal axes. This results in a plot of the true-positive rate against the false-positive rate for the different possible cut-off points in a diagnostic test. The area under the ROC curve (AUC) is a measure of the accuracy of the diagnostic test used. The accuracy is measured on a five-point scale: excellent (area of 1-0.9), good (area of 0.9-0.8), fair (area 0.8-0.7) poor (area of 0.7-0.6), and fail (area of 0.6-0.5) [21, 22]. In assessing a diagnostic test the positive and negative predictive value is needed. The positive predictive value is the proportion of patients with positive test results who are correctly diagnosed; the negative predictive value is the proportion of patients with negative test results who are correctly diagnosed. The positive likelihood ratio is the ratio between true-positive and true-negative; the negative likelihood ratio, is the ratio between false-positive and true- negative. A summary of the above is given in Table 5.1

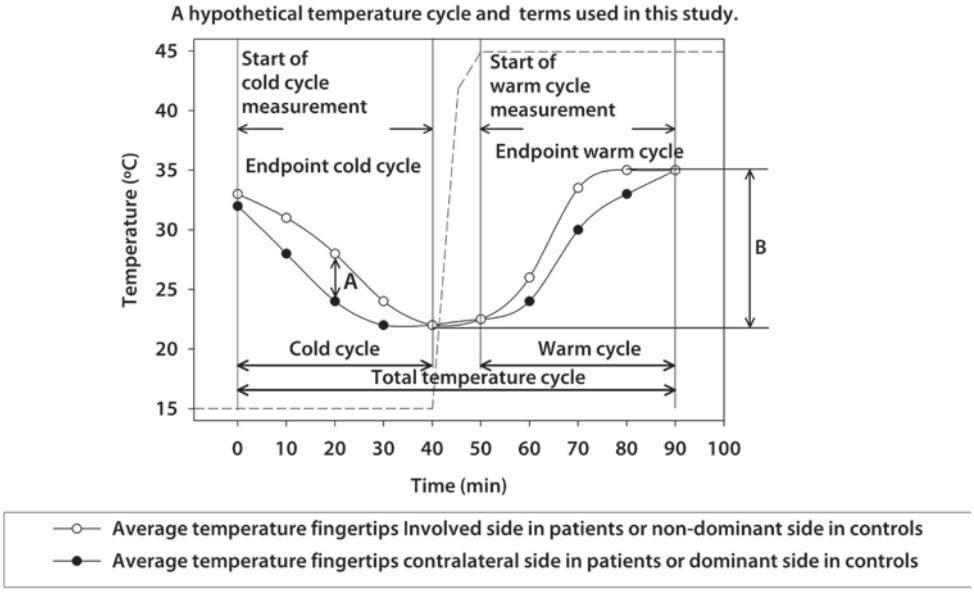


**Figure 5.1 A hypothetical temperature cycle and terms used in this study. A; maximum difference between fingertip temperature, B; temperature span during total temperature cycle.**

**Tabel 5.1 Calculation of sensitivity, specificity, positive predictive value and negative predictive value.**

CRPS1 according to the Bruehl criteria.

| | | Positive | Negative | Total | Calculations |
|---|---|---|---|---|---|
| CRPS according to thermographic results | Positive | A | B | A+B | $P.P.V. = \frac{A}{A+B}$ |
| | Negative | C | D | C+D | $N.P.V. = \frac{D}{D+C}$ |
| | Total | A+C | B+D | N | |
| Calculations | | $Sensitivity = \frac{A}{A+C}$ | $Specificity = \frac{D}{D+B}$ | | |

## 5.4 Statistical analysis

For comparison of the non-parametric data between CRPS1 patients and healthy controls, the Mann-Whitney U and Spearman tests were used. Data are given as median and interquartile range (IRQ). A p-value of <0.05 was considered statistically significant. These analyses were performed with the SPSS® 10.1 software package.

To compare the discriminating power of baseline temperature measurements with measurements of temperature during the temperature cycle, a ROC analysis was performed. The ROC curve was calculated at baseline, and using the values obtained during the temperature cycle as described earlier. Statistical comparison of the ROC curves was performed using the software program ROCkit 0.9, which incorporates a method developed by Metz et al. to compare correlated ROC curves[23]. In the present study specificity is used to indicated the discrimination between CRPS patients and healthy controls.

## 5.5 Results

To compare the average fingertip temperature and the asymmetry factor with respect to their diagnostic value, the following results were used in performing the ROC analysis.

Median average fingertip temperature

At baseline, the difference in absolute fingertip temperature difference in CRPS1 patients and controls between involved and contralateral extremities, or in controls between the dominant and non-dominant extremity, was calculated (Figure 5.1, zero min). At baseline, the median fingertip temperature difference for controls was 0.43°C (0.04-0.66°C) and for patients was 0.37°C (0.10-0.77°C) (Figure 5.2, A).

During the total temperature cycle, the maximum difference in absolute fingertip temperature difference in patients and controls between involved and contralateral extremities, or in controls between the dominant and non-dominant extremity, was calculated (Figure 5.1, maximum temperature). During the total temperature cycle the average fingertip temperature in controls was median 0.95°C (0.50-1.51°C) and in patients median 2.50°C (1.61-3.43°C) (Figure 5.2, B).

Asymmetry factor

The asymmetry factors at baseline, and the minimum asymmetry factor obtained during the vasoconstrictor changes, were calculated. At baseline, for the controls the calculated asymmetry median was 0.89 (0.85-0.94) and for CRPS patients was 0.58 (0.36-0.83) (Figure 5.2, C).

During the temperature cycle, for controls the calculated minimum asymmetry median was 0.82 (0.79-0.87) and for patients was 0.56 (0.22-0.70) (Figure 5.2, D).

ROC analysis

The results above were used in the ROC analysis. The small difference in fingertip temperature difference at baseline between patients and controls resulted in a low sensitivity and specificity, with a low AUC. The sensitivity and specificity improved when using the data obtained from the temperature cycle. In comparing the ROC curve of the baseline measurement with the ROC curve obtained from the temperature cycle a significant improvement in favor of the temperature cycle was calculated.

The clear difference in asymmetry factors at baseline and during vasoconstrictor activity results in a higher sensitivity and specificity with a higher power (Figure 5.2, A, B, C and D). Comparison the ROC curve at baseline with the ROC curve obtained during the temperature cycle showed no significant improvement in sensitivity and specificity (Table 5.2).

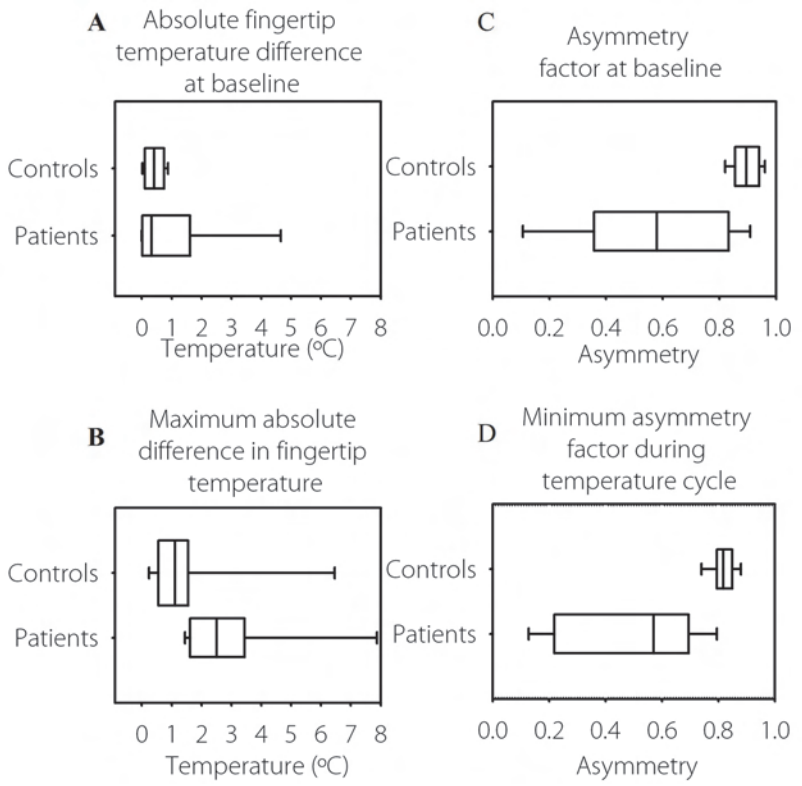


**Figure 5.2 Differences between controls and patients at baseline and during the temperature cycle.**

**Table 5.2 Sensitivity and specificity at baseline and during cold/warm cycle of temperature differenceand the asymmetry factor.**

| | \|Average fingertip temperature difference at rest.\| | \|Max. average fingertip temperature difference during temperature cycle.\| | Asymmetry factor at rest. | Minimum Asymmetry factor during the temperature cycle. |
|---|---|---|---|---|
| Sensitivity | 76% | 92% | 100% | 100% |
| Specificity | 38% | 75% | 75% | 83% |
| Positive predictive value | 62 | 85 | 100 | 100 |
| Negative predictive value | 43 | 86 | 73 | 79 |
| Cut-off points | 0.1℃ | 1.4℃ | 0.81 | 0.73 |
| AUC<br>95% interval and Std.Error | 0.48<br>0.221-<br>0.737(0.101) | 0.87*<br>0.666-<br>1.063(0.101) | 0.90*<br>0.767-<br>1,035(0.068) | 0.96**<br>0.879-<br>1.038(0.40) |
| Likelihood ratio positive test | 1.2 | 3.7 | 4 | 5.9 |
| Likelihood negative test | 0.6 | 0.1 | 0 | 0 |
| Difference in AUC | 0.39* | | 0.06 | |

*Significant at the p<0.05 level.

**Significant at the p<0.001 level.

Vasomotor activity in CRPS1 and controls

Figure 5.3, presents representative examples of average temperature measurements in three patients and in one control subject. Figure 5.4 presents the thermographic images of one representative patient during the temperature cycle.

Average fingertip temperature

Whole body cooling induced a maximal vasoconstrictor activity resulting in a lower flow rate, which in turn resulted in a lower fingertip temperature during cooling activity. After this, whole body warming was performed to completely inhibit the cutaneous activity; this resulted in a higher blood flow rate, which led to an increase in the fingertip temperature. The difference in hand temperature in controls showed a minimal difference over the whole temperature cycle (for an example of a control subject see Figure 5.3, D), whereas

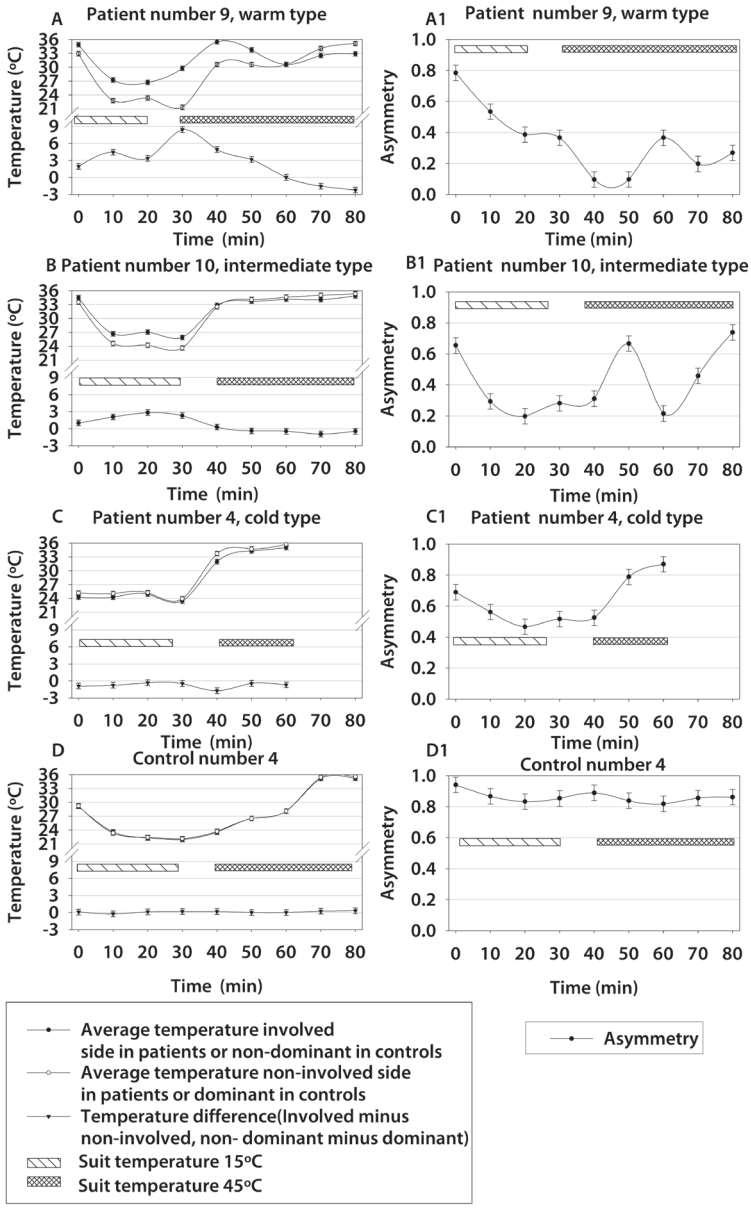


**Figure 5.3 Representative graphs of temperature and asymmetry of three patients and one control. Left column A, B, C, D presents graphs of average temperatures of fingertips and temperature difference between the finger tips during the warm and cold temperature cycle in the three regulation types. Right column A1, B1, C1, D1 asymmetry factor during the warm and cold temperature cycle in the three regulation types. and control subjects, the average fingertip temperature of the contralateral hand in patients and the dominant hand in controls were compared at the end of the warm cycle.**

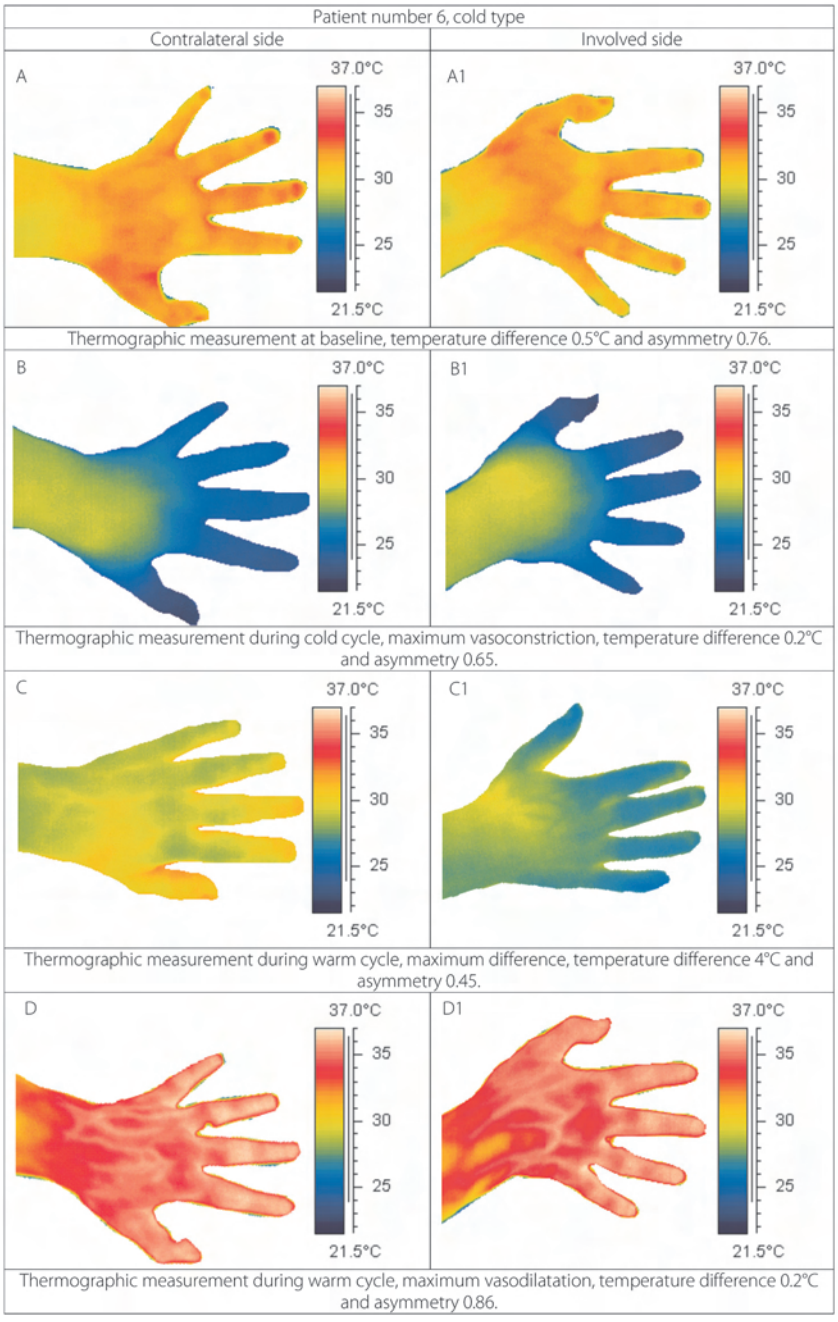


**Figure 5.4 Representative thermographic images of a patient during the temperature cycle.Left column, images of the contralateral side. Right column, images of the involved side. A, A1 baseline recordings. B, B1 maximum vasoconstriction. C, C1 maximum temperature difference. D, D1 maximum vasodilatation.**

the difference in average fingertip temperature in CRPS1 patients is not as constant as in controls (Figure 5.2 and Figure 5.3 A, B and C).

To ensure the minimum vasoconstrictor activity was reached in both patient and control subjects, the average fingertip temperature of the contralateral hand in patients and the dominant hand in controls were compared at the end of the cold cycle (Table 5.3). To ensure that maximum vasodilatation was reached in both patient

**Table 5.3 Minimum and maximum fingertip temperature obtained in patients and controls at the beginning and end of the temperature cycle.**

| | Minimum median average fingertip temperature | | Maximum median average fingertip temperature | |
|---|---|---|---|---|
| | Contralateral (patients) or dominant (controls) | Involved (patients) Or Non- dominant (controls) | Contralateral (patients) or dominant (controls) | Involved (patients) or non -dominant (controls) |
| Patients | 23.5 (22.5-24.0) | 23.9(22.8-25.6) | 35.0(34.3-35.7) | 35.1(34.6-35.7) |
| Controls | 23.2(22.2-24.4) | 23.1(22.8-23.5) | 35.1(34.4-35.2) | 35.1(34.1-35.4) |

Cold, intermediate and warm regulation type classification scheme

Patients are classified into three types of regulation. The warm regulation type in whom the involved side more often had a higher in temperature than the contralateral side (Figure 5.3, A). The intermediate type, in whom the temperature difference between the fingertips of the involved side was as often high as was low during the total temperature cycle (Figure 5.3, B). The cold regulation type in whom the fingertip temperature of the involved side was more often lower than higher during the whole temperature cycle (Figure 5.3, C). This resulted in 5 regulation types classified as warm, 5 types classified as intermediate and 2 regulation types classified as cold.

Differences in temperature span and asymmetry factor during cold and warm cycle

Data from the 5 warm regulation types and the 2 cold regulation types gave an indication concerning differences between these regulation types. In the regulation types that were classified as warm, the difference between the lowest and highest temperature of the involved side was higher in comparison to the contralateral side. In regulation types that were classified as cold, the difference between the lowest and highest temperature of the involved hand was lower in comparison to the contralateral side. Because only 5 warm and 2 cold regulation types could be identified, no statistical tests were performed on these data.

From the 5 warm regulation types, 4 patients showed the largest temperature differences during the warm cycle and 1 during the cold cycle. Of the 2 cold regulation types 2 showed the largest temperature difference during the cold cycle.

Classification of patients

The severity of CRPS1 in patients was assessed using parameters describing pain, immobility, temperature, MPQ and volume; the results are presented in Table 5.4.

**Table 5.4 Disease activity scores of CRPS1 patients median ( IRQ ).**

| Age(Years) | Disease duration (months) | VAS (0-10) | MPQ (0-10) | AROM (0-10) | Vol. Diff (0-10) | Temp.diff (0-10) | Total ISS[1] (%) |
|---|---|---|---|---|---|---|---|
| 51.5 (44.0-56.8) | 6.0 (3.0-7.5) | 5.0 (3.0-6.0) | 5.5 (2.0-8.0) | 5.5 (3.0-7.0) | 2.5 (2.0-4.0) | 3.0 (1.0-4.0) | 46 (30.0-50.0) |

[1]Based on Oerlemans et al. [19] and percentage of total score for patients with complex regional pain syndrome type 1 (CRPS1). VAS visual analogue pain scale, MPQ McQill Pain Questionnaire, AROM active range of motion, Vol. Diff. volume difference between the contralateral hand and the involved hand, Temp.Diff. temperature difference between average temperature measured with tympanometer the contralateral and involved hand, ISS impairment level sum score.

In the present series of 12 patients the correlation between the ISS total and asymmetry at rest was R=-0.678 p=0.015, the correlation between disease duration and asymmetry at baseline was R=-0.634 p=0.027, and the correlation between the maximum VAS rating and minimum asymmetry factor was R=-0.622, p=0.019.

## 5.6 Discussion

In this study a thermographic camera was used to assess the results of changes in temperature in CRPS. High and low sympathetic vasoconstrictor activity was induced by whole body cooling and warming in 12 patients and in 8 healthy controls. The degree of vasoconstrictor activity in the hands was monitored by skin temperature measurement using videothermography. The acquired images were subsequently used to calculate the average temperature difference and the asymmetry factors at baseline (static measurement), and during exposure to 15°C and 45°C surrounding temperature (dynamic measurement), respectively. The relation between thermography and the factors describing the disease activity was calculated. The ROC was used to assess the discriminating power of thermography in combination with different calculation methods.

During vasoconstrictor alternations we found an increase of 2.13°C in the median temperature difference between the involved and contralateral side; furthermore, the median asymmetry decreased from 0.57 to 0.56. As a result, the discriminating power of the average temperature difference increased significantly, whereas there was no significant increase in the discriminating power of the asymmetry calculation. The largest studied population, performed by Veldman in 1993 showed that in 829 patients only 39 patients

had CRPS in more than one limb, 34 patients in two limbs, 4 in three limbs and 1 patient in all four limbs[21]. During cold and warm stress cycles no significant differences in fingertip temperatures between the involved and contralateral hands were found at maximal cooling (approx. 24°C, Table 5.3) or at warming up (approx. 34°C, Table 5.3), and no differences were found between controls and patients.

Our previous study[15] showed that average calculations on thermographic data are not the most accurate calculation method for diagnostic purposes in CRPS1 patients; therefore we postulated a new mathematic approach. This resulted in a sensitivity of 92% and a specificity of 94%[15]. Wasner et al. reported that the maximum temperature difference during external temperature provocation resulted in mean temperature differences of 4.5±0.6°C in CRPS1 patients and of 1.3 ±0.1°C in controls[13]. Although in this study no values of baseline measurements were reported[13], in another study by Wasner et al. these values where reported as median 1.8°C and range 0–9.4°C[11]. In the present study the maximum temperature difference during external temperature provocation in CRPS1 patients resulted in a maximum median temperature difference of 2.5°C (1.61-3.43°C), whereas at baseline this difference was 0.37°C (0.10-0.77°C). For controls this temperature difference increased from 0.43°C (0.04-0.66°C) to a maximum of 0.95°C (0.50-1.51°C). Therefore, the present results reproduce and confirm the results of the previous studies by Wasner and colleagues [4,10,11,13]. Although we did not include other types of diseases in this study Wasner et al. have previously demonstrated that the obtained temperature difference in CRPS patients is very specific for this patient group[13].

Temperature measurements have been studied in relation to diagnosing and monitoring CRPS. Sympathetic vasoconstrictor patterns were found to be affected in CRPS[4,13,22-24]; these studies indicate that the central sympathetic system does affect vasoconstrictor activity and is involved in CRPS. Although in the present study we have included the minimum number of subjects as calculated by the power calculation, the small number of patients could be a limitation of this study. The use of a contralateral extremity as a control can, theoretically, produce some problems. CRPS can have a small spread. Epidemiological studies on CRPS show a huge range in incidence. The largest studied population, performed by Veldman showed that in 829 patients only 39 patients had CRPS in more than one limb, 34 patients in two limbs, 4 in three limbs and 1 patient in all four limbs[21]. In the case we would have included a patient with a CRPS in the contralateral side this would have had a negative influence on the outcome. This confirms that at least two pathways could be involved in CRPS1: 1) peripheral inflammation, which generally increases temperature, and 2) disturbances in central temperature regulation, which could result in a changed (local) temperature of the injured extremity.

Previous studies mainly used baseline ('static') measurement and did not provoke vasoconstrictor activity. One study, with a set-up similar to ours, investigated the dynamics of

the sympathetic system in CRPS1 patients[11-13,25,26]. These authors provoked the sympathetic system and found that during resting conditions a CRPS patient does not show the maximum temperature difference between extremities. The studies mentioned above used a spot thermometer or a spot blood flow meter, which are only able to measure a small area of the extremity thereby neglecting increased temperature at other locations. Furthermore the obtained data were only subjected to calculations on the average temperature, thereby possibly minimizing temperature peak values.

## 5.7 Conclusions

In the present study the sensitivity had a value of 100% and the specificity a value of 75%. The results during temperature provocation revealed a sensitivity of 100% and a specificity of 83% with an increased AUC, indicating considerable improvement as a diagnostic tool. Furthermore, because of the difference between sensitivity and specificity obtained from average fingertip temperature in favor of the sensitivity and specificity obtained using the asymmetry factor, the conclusion must be drawn that temperature measurement of the fingertip alone is not sufficient.

In the present study we found no evidence that the warm type CRPS1 patients would show lower asymmetry factors during the cold cycle, or that the cold type CRPS1 patients would show higher asymmetry factors. Because the patient population of the present study consisted of 5 warm type, 5 intermediate type and 2 cold type CRPS1 patients, no conclusion about the above-mentioned effect could be drawn. However, some remarkable differences in patterns of temperature regulation were observed between the warm and cold type patients (Figure 5.3). Therefore, the cold and warm stress test is useful to differentiate between "warm" and "cold" type CRPS1.

The difference in temperature span in cold and warm type CRPS patients is another strong indicator that this disease is partially caused by central deregulation. This conclusion promotes the use of thermography as an objective monitoring tool in an intervention study, in order to reveal the contribution of both the central and peripheral regulation systems.

In summary, there was a significant increase in the difference in fingertip temperature between patients and controls during vasoconstrictor alternations in CRPS1 patients. However, this increase in discriminating power was not present when using the asymmetry factor. This indicates that baseline temperature measurement of the fingertips alone is not sufficient for diagnostic purpose. Instead, the temperature should be measured at various locations on the hand.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SPN participated in the design of the study, performed the experiment, performed the statistical analysis and drafted the manuscript. FJPMH participated in the design, coordination and inclusion of patients and helped to draft the manuscript. RWPW helped with inclusion of patients and assisted with measurement of patient during the experiment. MW helped with the experiment and performed the calculation on the thermographic images. FJZ participated in the design and coordination of the study and helped to draft the manuscript.

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# Chapter 6

## Study of a novel method to measure peripheral blood flow regulation changes

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To be submitted

## Abstract

***Introduction***: In CRPS1 changes in blood flow occur frequently, but the pathophysiology of this change is not fully understood. The diagnosis of CRPS1 is based on sets of symptoms and signs that arise out of consensus. In CRPS1 changes in blood flow between contralateral hands alter over time, even during the same day. There is need for a measurement set-up that is able to assess the blood flow independently of the surrounding factors, such as time of day, environmental temperature, and stress. This measurement set-up could then be used to monitor blood flow changes in CRPS1, elucidate aspects of its pathophysiology, and possibly improve the diagnosis of CRPS1.

***Objective***: To develop a measurement set-up able to assess blood flow changes in CRPS1 patients by disturbing the temperature regulation of an extremity by means of eliciting cold-induced vasodilatation (CIVD).

***Methods***: A measurement set-up is introduced that is able to cool down the palmar side of the hands using a cold plate. In this way the dorsal side of the hands were kept free for videothermography and laser Doppler flow measurement. A transfer function was fitted on the induced temperature CIVD curve. The parameters resulting from this fit were used to compare the CIVD reactions between contralateral hands in healthy controls.

***Results***: In healthy controls there was no significant difference between the temperature curve of the non-dominant and dominant hand. The CIVD reaction in nerve-injured patients, shortly after trauma (<9 months), was totally abolished in the injured nerve area (involved side) whereas the CIVD reaction on the non-involved side was normal. These data on CIVD reactions in a CRPS1 hand suggest that the local blood flow regulation is disturbed; however, because a diminished CIVD reaction was also observed on the involved hand it was difficult to obtain a good quantifiable CIVD reaction.

***Conclusion/Discussion***: No significant difference was found in the parameters that describe the CIVD reaction in healthy controls between the non-dominant and dominant side. The absence of CIVD in nerve-injured patients shortly after trauma suggests that the CIVD reaction is controlled by the nervous system. A reduced CIVD reaction was observed in one CRPS1 patient. Some limitations of the current measurement set-up still need to be addressed. The set-up was not able induce a CIVD reaction in every participant, and the reliability and repeatability should be tested. Some of the CIVD reactions could not be analysed due to excessive movement of the fingers and/or an unidentifiable CIVD reaction.


## 6.1 Introduction

In CRPS1 changes in blood flow occur frequently[1, 2] and the blood flow of an extremity is known to be controlled by both central (efferent)[3-5] and peripheral mechanisms (afferent)[6, 7]. It is believed that both these mechanisms are (time-dependently) pathologically involved in CRPS1. Central mechanisms include sensory, vasomotor, sudomotor and motor

changes, whereas peripheral mechanisms include immune cell- mediated inflammation[7], neuroinflammation[8-11] and local vascular endothelial derangements[6]. Because skin temperature correlates highly with skin blood flow and skin sympathetic nerve activity[12 13], changes in central and peripheral mechanisms of blood flow regulation are, in part, represented by changes in skin temperature. Video thermography is able to capture the temperature of a whole extremity in a sequence of thermal (temperature) images, without contact, and with a high level of accuracy and repeatability[14].

In CRPS1 patients the greatest difference in temperature between contralateral extremities is not necessarily observed at room temperature. Furthermore, the temperature changes in the CRPS1 hand, and between the CRPS1 hand and contralateral hands, fluctuates during follow-up over weeks, and even daily. Therefore, a set-up enabling temperature assessment under controlled thermoregulatory conditions is desirable.

Wasner et al. and also our group, evaluated temperature differences between contralateral hands in CRPS1 patients by disturbing the thermoregulation of the human body. In order to regulate the cutaneous sympathetic activity in a controlled manner, sympathetic vasoconstrictor neurones were activated by whole-body cooling and vasoconstrictor activity was abolished by inducing whole-body warming[5, 13]. These studies showed that skin temperature differences between the contralateral hands in CRPS1 patients depends mainly on the activity of the central sympathetic system[5, 13]. However, at both maximum and minimum sympathetic activity the difference in temperature between the contralateral hands disappeared completely[13].

The present study explores a novel measurement set-up in order to assess whether the disturbance of blood flow can also be measured by cooling the hands. This is investigated by provoking CIVD.

The CIVD reaction is a cyclic regulation of blood flow that is initiated when a protruding body part, in this case the palmar sides of both hands, is cooled[15, 16]. The common method to study the CIVD reaction is to submerge a protruding body part (such as hands or fingers) in cold water and measure the fingertip temperatures with thermocouples and/or the blood flow with a laser Doppler flow device. A water temperature of 5ºC was found to be the optimal temperature to provoke a CIVD reaction. A common method to qualify the CIVD reaction is to define parameters that in effect summarize the shape of the measured CIVD curve. Such parameters include minimum temperature of the fingertip, maximum temperature of the fingertip and peak (at minimum temperature of fingertips) to peak time (at maximum temperature of fingertips)[16].

Until now, the majority of studies focused on finding covariates influencing the CIVD reaction in healthy subjects and elucidating aspects of the mechanism responsible for the CIVD reaction. According to Daanen et al. these factors can be grouped into experimental factors and individual factors[16]. Experimental factors include ambient temperature, body

temperature, cooling medium, surface area cooled, and altitude. Individual factors include, age, gender, physical fitness, mental stress, acclimatization to cold, adaptation to cold, cold resistance training, diet, alcohol ingestion, tobacco smoking, and vascular pathology.

Several hypotheses on the mechanisms responsible for the CIVD reaction have been described. Two hypotheses prevail; i) The axon reflex theory states that the cold stimuli excites the receptive unmyelinated nerve endings, probably via A-delta nerves; these impulses are transmitted centrally and via the axon branches. The sensory nerve endings then release vasoactive substances resulting in vasodilatation[17]. ii) The decreased release of norepinephrine; the sensitivity of the norepinephrine receptors increase in cold conditions[18] and this will induce a reduced blood flow as a result of vasoconstriction. The further decrease in tissue temperature may result in reduction of adrenergic neurotransmission, such as norepinephrine due to the cold (numbing of the nerve ending). As a consequence of this reduced adrenergic output an increase in blood flow will occur as a result of a decreased vasoconstriction.

To be able to test whether the CIVD reaction is indeed a nerve-related phenomena, nerve-injured patients were included in the study.

To quantify the CIVD reaction, a non-linear estimate of the parameter that defines two first-order transfer functions in series is fitted to the CIVD response; a triangular shape input is assumed. The measurement setup and the analysing methods were developed with the aim to be able to compare the CIVD reaction between contralateral hands in healthy controls, and for future measurement of CRPS patients.

## 6.2 Materials and method

### 6.2.1 Subjects

This study was approved by the local Medical Ethical committee of the Erasmus Medical Centre (MEC-2005-037). From 2005 through 2006 a neurologist included 5 nerve injury patients (1 man; 4 women) with a mean age of 40 (SD 15) years. In addition 16 healthy controls (3 men; 13 women) with a mean age of 30 (SD 7) years were included. At this stage one CRPS1 patient according to the Bruehl criteria[1], was included to test the methodology in patients. All participants gave written informed consent.

### 6.2.2 General questionnaire and measurement

The severity of the impairment of the CRPS1 patient is estimated using the total Impairment level Sum Score (ISS). The ISS total is the sum of the Visual Analogue Scale (VAS), the McGill pain questionnaire (MPQ), active range of motion (AROM), edema and temperature difference that are converted to ISS scores (ranging from 1 to10)[19]. These outcomes are converted to

a score ranging from 1 to 10, resulting in an ISS total with a minimum score of 5 and a maximum score of 50. A score of 5 indicates the least level of impairment and 50 the highest level of impairment (severity of disease).

### 6.2.3 Applying disturbances, cold plate

For this study an aluminium plate (30wx29bx3h cm) perforated by two water channels, one water channel for each hand, was fabricated in-house. The water channel for the left hand and the water channel for the right hand were both provided with an inlet and outlet port. The outlet of the thermostatic bath (Ecoline, Lauda 104, Lauda-Königshofen, Germany) was separated into two outlets using a Y-connector and connected to the inlet of the right and left water channels. The inlet of the thermostatic bath was separated into two inlets using a Y-connector and these were connected to the outlets of the right and left water channels. The water temperature was maintained at 5°C and pumped through with a flow rate of approximately 2 litres per minute. The connection of two inlets and outlets and the flow rate ensured that the left and right side of the plate provided a homogenous temperature field for both the left and right hands. The palmar side of the hands was placed on the cooling plate. The cold plate set-up allowed to dissipated thermal energy of palmar side of the hands resulting in a lowering of the temperature of the hands. Both hands were pre-cooled in a water bath at 10°C for 1 minute to shorten the total time of measurement to approximately 30 to 45 minutes.

### 6.2.4 Measurement of disturbance, measurement devices

During the experiment, thermographic and laser Doppler flow measurement were obtained. The thermographic camera (ThermaCam SC2000, FLIR, Danderyd, Sweden) recorded the temperature of the dorsal side of the hand once every 2 seconds (sampling frequency of 1/2 Hz.). The thermographic image included temperature recordings of the fingertips down to the wrist. The thermal sensitivity of the thermograph is 0.05°C at 30°C; the spectral range is 7.5–13$^{\mu}$ m; and the built-in micro bolometer has 320×240 pixels (total 76,800 pixels). Data were obtained through an analysing and recording system coupled with a desktop PC (ThermaCAM Researcher 2001 HS).

The laser Doppler flow imager (MoorLDI2-II, Moor Instruments, Axminster, UK) has a visible red laser with a wavelength of 633 nm and a maximum power of 2 mW. The laser beam was directed on each of the fingertips and Doppler measurements were taken every 7 seconds (sample frequency of 1/7 Hz). The bandwidth of the laser Doppler was set to 20 -15 KHz, the DC gain to 2, the Flux gain to 2, and the constant was set at 2. Data were obtained through an analyzing and recording system coupled with a desktop PC using software provided by the manufacturer (MoorLDI measurement, v4.0).

### 6.2.5 Data processing

The thermographic images were converted to Matlab® matrix format using the Thermacam researcher (ThermaCAM Researcher 2001 HS, FLIR, Danderyd, Sweden). The converted images were analysed using software written in Matlab® (Matlab R14, 2004). This software provided the following methods enable to obtain the temperature readings for further study:

- Background filtering.
- Automatic software identification of fingertips.
- Automatic movement tracking of fingertips using normalized cross correlation.
- Definition of a circle area around the fingertips (taking the width of the finger below the top as the circle radius).
- Calculation of the average temperature of each of the fingertips.

The software used to collect laser Doppler flow data generated a table with Flux and DC values with the sampling interval.

### 6.2.6 Procedure of measurements

The following sequence of steps were followed during the experiment (Figure 6.1):

- Pre-cooling of both hands in the water bath until the fingers reached a temperature of approximately 12°C.
- Placing the hands on the cold plate for a maximum of 45 minutes.

During this time the video thermographic data and laser Doppler flow data were collected.

### 6.2.7 Analysing the CIVD reaction.

A theoretical example of a CIVD response is presented in Figure 6.1; this shows the pre-

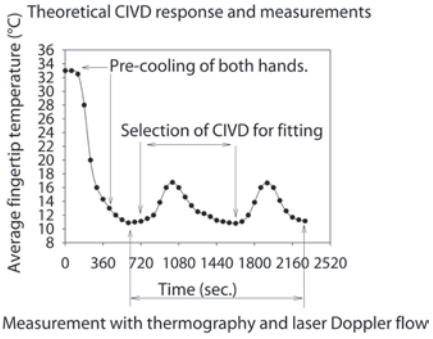


**Figure 6.2 Parameter estimated by the fitting of the transfer function**

cooling and the resulting CIVD responses after placing the hands on the cold plate.

For digiti 2, 3 and 4 on each hand, a start and end time of the CIVD response was selected. The starting (Temp-start) and ending temperature of the CIVD curve were selected (Temp-end).

To be able to quantify the CIVD response, two first-order transfer functions in series were fitted on the collected temperature data. The fit was initiated by roughly selecting a starting

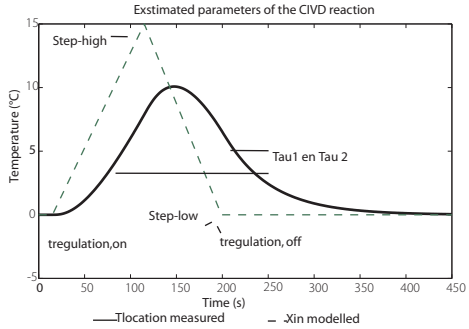


**Figure 6.2 Parameter estimated by the fitting of the transfer function**

and ending time of the CIVD cycle:

$$\frac{T_{fingertip}}{X_{in}} = \frac{1}{t_1 s + 1} \cdot \frac{1}{t_2 s + 1}$$ **Equation 6.1**

Xin was assumed to follow a triangular wave (see Figure 6.2), the slope of the triangular shape is defined by the estimated Step-high and Step–low. The roughly selected starting time ($t_{regulation,on}$) and ending time ($t_{regulation,off}$) was more precisely estimated by the fitting. For an example of a CIVD reaction and the parameters estimated by the fit of the transfer function and the input ($X_{in}$) see Figure 6.2.

For the fit of the transfer function, the temperature at which the CIVD curve started was subtracted from the whole temperature curve.

## 6.3 Statistic analysis

Each of the parameters estimated were averaged for digiti 2 to digiti 4 for each hand. For nerve injury patients the transfer function was only fitted to the non-involved side. A paired sample t-test was used to compare the contralateral hands of healthy controls. For controls the dominant hand was compared with the non-dominant hand. For CRPS1 patients the non-involved hand was compared with the CRPS1 hand.

## 6.4 Results

In this study 5 nerve-injured patients with a relatively short trauma duration were included; in 2 of these patients the ulnar nerve was damaged and in 3 the median nerve was damaged (Table 6.1). Of the 16 participating controls, 10 were analysed; in 2 controls no CIVD reaction could be induced, in 1 the hand moved considerably during the trial, and in 3 controls the CIVD curve was not identifiable.

**Table 6.1 Demographic data on the study participants; values are mean (SD).**

| Group | N | age | Male<br>Female | Trauma duration (months)[a] | Involved side<br>Dominant side | Involved location[b] | BMI[c] | CIVD[d] | Analysed[e] |
|---|---|---|---|---|---|---|---|---|---|
| Nerve Injury | 5 | 40(15) | 4<br>1 | 7(1) | 3 Right<br>1 Left | 3 Median<br>2 Unlnar | 25(3) | 5Y/0N | 5Y/0N |
| Controls | 16 | 30(7) | 3<br>13 | - | 11 Right<br>5 Left | - | 23(2) | 14Y/2N | 10Y/6N |
| CRPS1 | 1 | 52 | 1<br>0 | 20 | 1 Right | Whole hand | 26 | Y | Y |

[a]Since onset of symptoms.

[b]Median is the area inervated by the median nerve, and ulnar is the area inervated by the ulnar nerve.

[c]BMI, body mass index.

[d]Cold-induced vasodilatation could be induced.

[e] Parameters estimated by the fit.

The body mass index (BMI) of the groups was similar. The severity of the disease of the analysed CRPS1 patient was measured with the impairment level sum score (ISS) and is presented in Table 6.2.

**Table 6.2 Severity of CRPS1 in one patient expressed as total ISS.**

| CRPS | VAS Pain | MPQ | AROM | Volume diff. | Temp diff. | Total ISS |
|---|---|---|---|---|---|---|
| | (0-10)[b] | (0-10)[b] | (0-10)[c] | (0-10)[d] | (0-10)[e] | % [f] |
| N=1 | 7 | 7 | 4 | 3 | 5 | 52 |

[a]VAS pain score, representing 0 = no pain and 10 = the maximum pain on the day of measurement.

[b]McGill Pain Questionnaire, the number of words chosen from a list of 20, categorized in blocks of 2 words.

[c]Active Range Of Motion, a score of 1 represents no limitation in motion, a score of 10 represents a maximum limitation in movement.

[d]Volume difference between the uninvolved hand and the involved hand; minimum difference results in a score of

1, maximum difference results in a score of 10.

[e]Temperature difference between average temperature measured with tympanometer in the uninvolved and the involved hand; a difference of 0.2 ˚C results in

a score of 1, a difference of > 2 ˚C results in a score of 10.

[f]Total ISS score in percents; sum of all scores (VAS, MPQ, AROM, Volume and Temperature difference), maximum score of 50.

[g]Cold induced vasodilatation.

The CIVD response was analysed by fitting a transfer function (as described in the Method section) on the CIVD of digiti 2 to digiti 4. In 4 out of the 5 nerve-injured patients no CIVD reaction occurred in the digit(i) with nerve injury. For an example of a CIVD response in a nerve injury patient and the result of the fit see Figure 6.3 No fit was performed on the

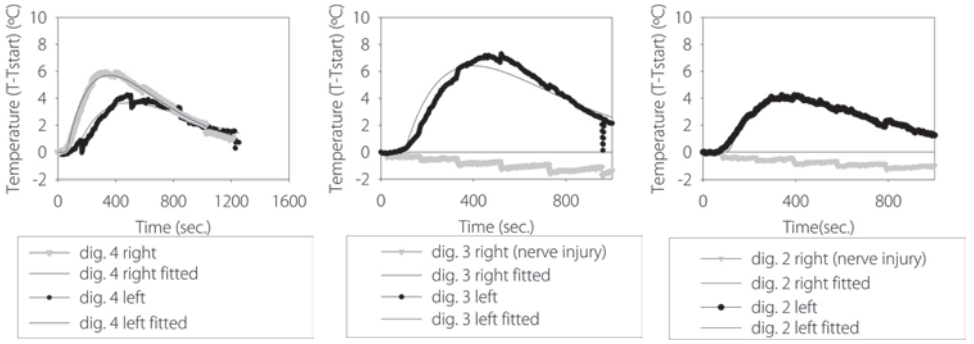


**Figure 6.3 Cold induced vasodilatation reaction of a median nerve injury patient.**

extremity that was affected by the nerve injury, because of the absence of the CIVD reaction in the nerve injured fingers. There is a clear absence of CIVD reaction on the nerve injured side.

In controls the average CIVD response of digiti 2 to digiti 3 of the dominant side was compared with the non-dominant side. For a typical example of a CIVD reaction of digiti of the dominant and the non-dominant side and the fit result see Figure 6.4.

Figure 6.5 shows the CIVD reaction of the CRPS1 patient; there is a clear reduction of CIVD

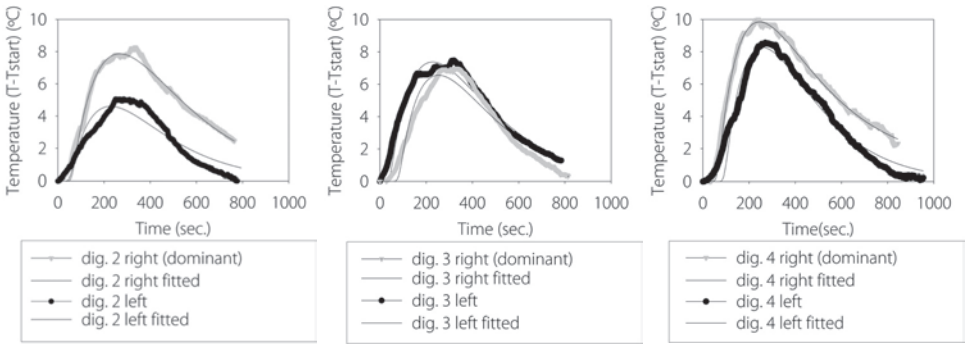


**Figure 6.4 Cold induced vasodilatation reaction in a healthy control.**

reaction in the involved hand. The average parameters defining the fit of the transfer function and the input on the CIVD of controls, the non-involved side of the nerve-injured patients, and the CRPS1 patient are presented in Table 6.3.For healthy controls, when comparing the non-dominant with the dominant side, none of the parameters differed significantly; only

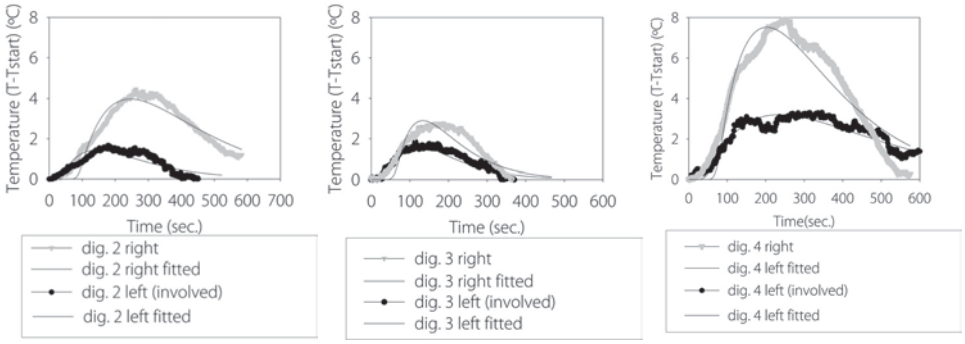


**Figure 6.5 Cold induced vasodilatation reaction in a CRPS1 patient.**

the time regulation on and the step low did not correlate significantly. The R-square of the fit in healthy controls was reasonable. The average onset temperature of the CIVD, temp-start was comparable between the contralateral hands with a relatively small standard deviation. The average temperature, after the CIVD occurred, temp-end was also comparable between sides.

In nerve injury patients no fits were made on the involved (nerve injured) side. Because

of the small number of nerve injury patients (n=5), no between groups statistics were calculated. The R-square of the fit in the non-involved side was reasonable. The average onset time of the CIVD was 12ºC in the non-involved side, this is comparable to the healthy controls

In the CRPS1 patient is was difficult to obtain a CIVD curve and therefore the R-square of the fits on the involved and non-involved side are low.

The movement of the fingers prevented fitting on the flux data. To indicate the shape of the blood flow an example of the flux as measured with laser Doppler during a CIVD is presented in Figure 6.6.

## 6.5 Discussion

In this study a novel method was introduced to measure the CIVD reaction in 16 healthy controls and in 5 nerve-injured patients. In the control group no significant differences were found in the CIVD reaction between the non-dominant side and the dominant side; the parameters were well correlated with no significant differences. Only the time regulation on, and the step low did not correlate (the mean of this latter parameter was almost zero). The similarity in the CIVD reaction between the extremities has been found before; however, in the present study the fitting enabled comparison of the whole CIVD response and not just the usual parameters as described in the Introduction section. During a CIVD reaction these parameters, i.e. the minimum temperature of fingertips, the maximum temperature of fingertip, and peak (at minimum temperature of fingertips) to peak time (at maximum temperature of fingertips)[16] are only able to quantify a small part of the CIVD reaction.

The absence of a CIVD reaction, as observed in 4 of our 5 nerve-injured patients, indicates that the nervous system is involved in the CIVD reaction. In one patient a CIVD reaction could be provoked in each finger of both hands. It is likely that the extent of nerve damage (e.g. distance between nerve endings) in conjunction with the time lapsed after trauma, plays a decisive role in this mechanism. Nevertheless, the two hypotheses mentioned in the Introduction are still open for debate; either the axon reflex or the reduced release of norephineprine could result in the same outcome.

In our CRPS patient there was a difference in the CIVD reaction between contralateral extremities. A difference in CIVD reaction has also been reported in patients with Raynaud's disease and spinal muscular atrophy[20, 21]. However, in the present study the parameters of the CIVD on the non-involved side were also dissimilar to the parameters found in healthy controls and the non-involved side of our nerve-injured patients. In CRPS1 patients neuro-inflammation has been documented previously as well as a local disturbance of endothelial function[9, 11, 22]; therefore, CIVD might allow us to measure the regulation of blood in the involved extremity of CRPS1 patients.

Some limitations to the method used in the present study need to be addressed. Firstly, we

were unable to provoke a CIVD response in all our subjects; this was also reported earlier by Chen et al.[23, 24]. In our study this was not caused by the inability to cool down the extremities, and several other reports have indicated that a low core body temperature results in the inability to provoke a CIVD reaction[25]. Therefore, in the future studies, the core temperature should be measured during the study. Our set-up was not able to cool down the thumb (digiti 1) due to the anatomical position of the thumb. The pink (digiti 5) cooled perfectly but did not show a measurable response in every subject, possible due to the reduced thermal capacity of this digiti.

The fitting of the transfer function on the CIVD reaction to estimate the parameters, was performed adequately in our healthy controls and in the non-involved side of the nerve-injured patients, as indicated by the high R-square. To our knowledge, the first attempt to fit a model to the CIVD reaction assuming a triangular-shaped input to the model, was by Shitzer et al.[26] They also achieved good results using a trapezoidal blood flow input to calculate the temperature. In our set-up the laser Doppler flow measurement confirmed the triangular-shaped input of blood flow (Figure 6.6) However, in the CRPS1 patient the R-square of the fit was lower than in the healthy controls and the nerve-injured patients; this should be addressed in future studies. The measurement with laser Doppler flow was not successful; this was caused by the movement of the subject's fingers during the experiment. Therefore, we recommend to secure the hands on the plate (without disturbing the blood flow) in future studies.

In conclusion, this new method provides a tool to assess the peripheral regulation of the blood flow. It seems that the effect of inflammation on the nerve endings and endothelium dysfunction can be studied using this new method. Once the mechanism of the CIVD reaction is better understood, it might be possible to model the observed change in the CIVD reaction in CRPS1 patients.

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# Chapter 7

## Vasodilative Effect of Isosorbide Dinitrate Ointment in Complex Regional Pain Syndrome type 1

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## Abstract

Background: In complex regional pain syndrome type 1 (CRPS1) vascular changes occur from the initial, inflammatory event onto the trophic signs during chronicity of the disease, resulting in blood flow disturbances and marked temperature changes. Pharmacotherapeutic treatment is generally inadequate.

Aim: To determine whether local application of the nitric oxide donor isosorbide dinitrate (ISDN) could cause vasodilation and thereby improve tissue blood distribution in the affected extremity.

Methods: In a pilot study five female patients with CRPS1 in one hand were treated with ISDN ointment 4 times daily during 10 weeks. As a primary objective videothermography was used to monitor changes in blood distribution in both the involved and contralateral extremities.

Results: Patients treated with ISDN showed an increase of 4-6°C in mean skin temperature of the cold CRPS1 hands, reaching values similar to that of the contralateral extremities within 2-4 weeks time, suggesting normalization of blood distribution. This was confirmed by an improvement in skin colour. In three patients the VAS pain declined, whereas in the other two patients the VAS pain was unchanged over time.

Conclusions: In this pilot study topical application of ISDN appears to be beneficial to improve symptoms for patients with cold type CRPS1, but further study is needed.


## 7.1 Introduction

Complex regional pain syndrome (CRPS) is a painful disorder which usually occurs after an often minor precipitating event or trauma such as a fracture, sprain or after surgery. The main characteristics are continuous pain, marked changes in tissue blood flow and skin surface temperature, edema and sweating, movement disorders and trophic changes of the skin, and the severity of the symptoms is disproportionate to the initial event.[1,2] The diagnosis of CRPS is entirely based upon consensus-derived clinical criteria.[3-5] In the Netherlands, the incidence of CRPS1 is approximately 2.6% for different fractures, which results in approximately 5100 new patients yearly, of whom a substantial part will not recover.[6,7] The female to male ratio is approximately 3:1, with a median age of 52.7 years at onset.[8] The hand is affected twice as often as the foot.

The therapeutic potential is limited and insufficient to induce recovery.[6] Analgesics and local anesthetics are used to suppress continuous pain. The long-term prognosis for recovery is poor. Due to pain and severe trophic disturbances, chronic CRPS1 can even lead to amputation of the dystrophic extremity.

The pathophysiology of CRPS1 is not unravelled yet, but growing evidence indicates the involvement of exaggerated inflammatory processes. Both central and peripheral mechanisms have been proposed to play a prominent role.[6] Central sensitization leading to

exacerbations of pain is thought to be the result of neuroimmune activation of cells in the peripheral nervous system.[9] During the neurogenic inflammation neuropeptides,[10] cytokines, and other mediators are released.[11] This leads to a so-called 'warm dystrophy' with signs of inflammation such as redness, increased skin temperature, loss of function and pain.[5,6,12]

During the chronic, disabling stage of the disease signs of extravasation and edema change into atrophy; regional blood flow declines and increased skin temperature changes into diminished temperature.[13,14] These findings point to impaired microcirculation that affects nutritive blood flow in superficial and deep tissues.[15,16] The microcirculation is regulated by neural and endothelial factors and the contribution of the latter could be crucial. Recently we have shown that in patients with an intermediate type of CRPS the endothelin-1 (ET-1) levels in skin blister fluid were increased in affected extremities, whereas the nitric oxide (NO) levels, measured as NO2 + NO3 (NOx), were decreased.[17-19] As a consequence the ET-1 related vasoconstriction will be overexpressed in comparison with the diminished vasodilative activity of NO.

This pilot study investigates the effects of topical application of the NO donor isosorbide dinitrate (ISDN) on the tissue blood distribution. This vasodilator might be effective in the re-normalization of the disturbed balance between ET-1 and NOx and the diminished microcirculation, thereby reducing tissue acidosis and the resulting pain.

## 7.2 Materials and methods

## 7.3 Subjects

Five female patients with mean age 49.6 ± 7.1 years were selected to be treated in an open label study with ISDN. The mean duration of the disease was 39.8 ± 23.9 months, and all patients were diagnosed as stable cold CRPS 1.

The Medical Ethics Committee of the Erasmus MC approved the study protocol (MEC 2004-159). The research has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and written informed consent was obtained from all participants. The study was internationally registered with the trial registration number ISRCTN60226869.

The patients received 4 times daily (at 8 a.m. and 12 a.m. and at 4 p.m. and 8 p.m.) 1 gram ointment containing 1% (10 mg) ISDN during 10 weeks. The medication was supplied by the local pharmacy department.

## 7.4 Thermographic measurements

Registration of skin surface temperature by means of computer-assisted video thermography is an objective parameter to study the long-term effects of pharmaco-therapeutics.[20,21] Changes in skin temperature of the extremities are caused either by local inflammation of the tissue or by changes in blood flow in vessels located just underneath the skin. Besides

inflammation, vasodilation and enhanced blood distribution also cause a visible increase in skin temperature. In contrast, a decrease in local skin temperature, as normally observed in chronic CRPS1, is directly related to diminished tissue blood distribution.[22]

Under normal conditions the degree of thermal asymmetry between opposite sides of the body is very small. Using computerized thermography in healthy persons, the skin temperature difference between both sides of the body is less than 1% or < 0.25ºC.[21,23,24] Therefore, in the present study a difference in matched regions of > 1ºC was considered to be a significant disease-related effect.

The skin temperature of both hands was registered with a computer-assisted infrared thermographic camera (ThermaCAM SC2000, Flir Systems, Berchem, Belgium) following a standard protocol.[19,20] Thermographic images of the CRPS1 hand and the contralateral hand were compared and the mean temperature (in °C) and the differences in temperature (maximal minus minimal temperature) of the hand and the fingertips were determined as described before.[20,21]

## 7.5 Measurements of pain and muscle force

The patients used a weekly diary to record daily pain (Visual Analogue Scale (VAS), recorded in 0-100 millimetres), co-medication and the occurrence of any adverse events. This pain score was recorded 3 times daily, at 8 a.m., 12 a.m. and 8 p.m.

Pain intensity was assessed with the McGill Pain Questionnaire-Dutch Language Version (MPQ-DLV), measured by counting the total number of words selected.[25,26]

The force of the elbow extensor and flexor muscles was measured using a MicroFet 2 dynamometer (Hoggan Health Industries Inc, West Jordan, UT, USA). The elbows were positioned on a table with 45 degrees of flexion and the dynamometer was first placed on the dorsal and then on the ventral side of the distal forearm, just proximal of the processes styloideus ulnae. The patient was asked to resist the movement of the examiner with maximal force, according to the 'break' method.[27,28] The value of three measurements was noted.

The maximal isometric grip force of the hands was measured with a Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, Il, USA), with the adjustable handle in the second position. The dynamometer was held freely, the forearms rested on a table with both elbows flexed at 90° without touching the trunk. The wrist was held at between 0° and 30° dorsiflexion and between 0° and 15° ulnar deviation. The subjects were asked to exert maximal force to the dynamometer. The value of three trials was noted and the results are expressed as means ± standard deviation.[29-32]

## 7.6 Results

A marked and continual increase in skin surface temperature of the CRPS1 affected hand of more than 4 ºC was observed in all patients within two weeks, reflecting improved tissue

blood distribution. Although ISDN was applied locally, systemic effects were observed within one week, reflected by a simultaneous increase of temperature in the contralateral side. Representative thermographic images taken before and after two weeks treatment are presented in Figure 7.1 and the calculated mean temperatures and derived data are given in Table 7.1.

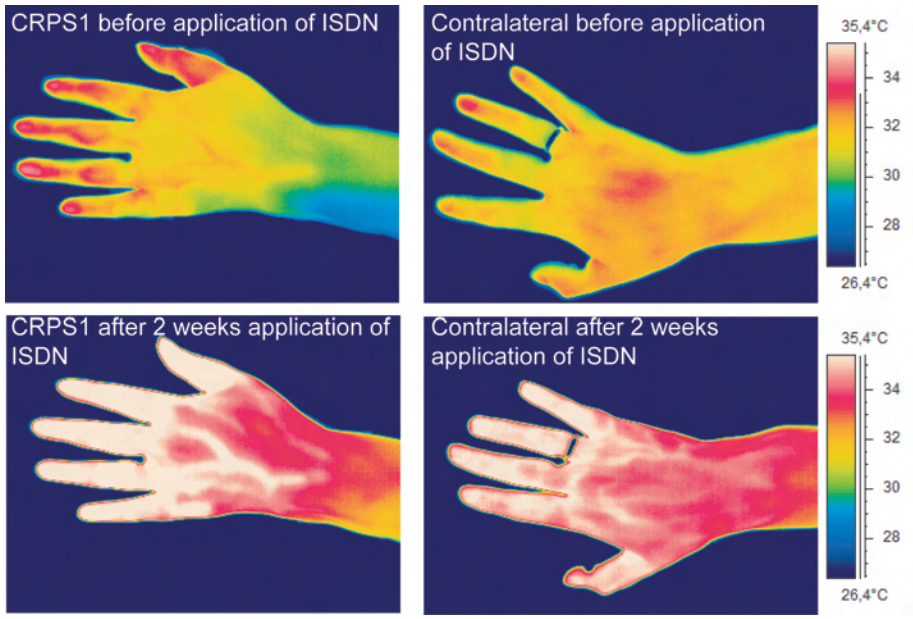


**Figure 7.1 Representative videothermographic images of the dorsal side of the left CRPS1 hand and the contralateral right hand. The upper panel represents images before ISDN, and the lower panel images after two weeks of ISDN treatment. Effects observed during the following eight weeks were similar to the images obtained two weeks post-treatment.**

**Table 7.1 Thermographic data: mean temperature in °Celsius ± SD in 5 patients before treatment, after 2 weeks ISDN and after 10 weeks of treatment**

| Week | CRPS fingertips[1] | Contralateral fingertips | CRPS hand[2] | Contralateral hand |
|---|---|---|---|---|
| 0 | 28 ± 4.5 | 30 ± 3.8 | 29 ± 3.7 | 32 ± 1.9 |
| 2 | 34 ± 1.3 | 34 ± 1.1 | 33 ± 1.5 | 34 ± 1.1 |
| 10 | 33 ± 2.1 | 31 ± 4.0 | 33 ± 1.6 | 31 ± 3.0 |

[1]The mean fingertip temperature was calculated from 5 fingers

[2]The mean hand temperature was calculated from the whole hand as shown in Figure 7.1.

Three patients reported headache during the first two weeks. Figure 7.2 shows that the VAS of three patients improved, whereas two patients did not report any change in VAS

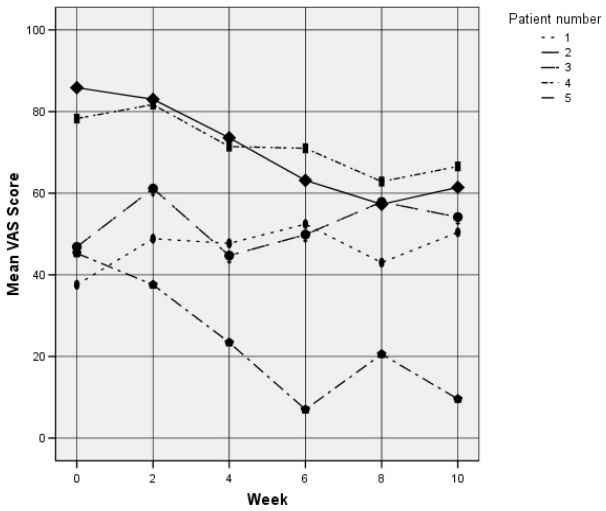


**Figure 7.2 Visual Analogue Scale (VAS) ranging from 0 to 100 millimetres. The five patients registered their pain scores daily at 8 a.m., 12 a.m. and 8 p.m. in the week preceding each clinical visit. The figure shows the median pain score before and during 10 weeks of ISDN treatment. In three patients the VAS score diminished, but in two patients the score remained practically unchanged.**

pain. At the end of the 10-week treatment period the mean difference in VAS pain score had decreased from 41 ± 10 to 34 ± 15 mm, and the MPQ was slightly improved from 15 ± 3.4 to 14 ± 6.3 selected words.

One patient's hand was dystonic without any voluntary movement, this did not change after treatment. The muscle force of the elbow flexors in the remaining four patients improved from 63 ± 48 to 103 ± 58 Newton (N), and the extensor muscles from 59 ± 31 to 77 ± 13 N. Although the isometric hand grip force improved in three patients, the mean score in all four patients decreased from 87 ± 76 N before treatment to 79 ± 75 N after 10 weeks (difference not significant).

## 7.7 Discussion

This is the first study in which the NO donor ISDN has been used to induce vasodilation in CRPS1 patients. Although the role of NO in CRPS has not yet been fully elucidated, an in vitro study has shown an increased production of NO from interferon-γ stimulated peripheral blood monocytes obtained from CRPS patients.[33] As indicated above, our previous studies showed an inverse relationship between increased ET-1 and diminished NOx in CRPS compared with contralateral blister samples.[17,19] This inverse relationship has also been observed in vascular homeostasis where endothelium dysfunction plays a prominent role.[34] In male patients with erectile dysfunction, significantly increased venous plasma ET-1 levels and decreased venous NO levels were found.[35]

In view of the assumed diminished tissue blood flow, the focus should not be on inhibition of the NO synthase but, on the contrary, NO donors should be supplemented.[36]

Transdermal ISDN ointment has been reported to increase the hand vein diameter.[37] The same NO donor has also been successfully used in the treatment of anal fissures,[38] chronic painful diabetic neuropathy,[39,40] and obstructed hand veins.[37]

In the current pilot study we found that local application of ointment improved tissue blood distribution in CRPS1. The study does, however, have some limitations. Since only five patients were included, the changes in temperature can be considered to be no more than an indication for the effect of the medication. There was no control group, nor were patients and investigators blinded. To show the effects of a NO donor on the endothelial dysfunction more information is needed on the changes in NO/ET-1 values.

However, an interesting finding was that the VAS scores improved most in those patients complaining about 'a cold pain deep within'. The combined use of descriptive questionnaires like the Neuropathic Pain Scale,[41] the McGill Pain Questionnaire and the VAS might reveal more about the nature of these changes. It would be interesting to also investigate whether the changes in muscle force correlate with changes in patient's arm-hand activity level. A larger double-blind randomized controlled trial is needed to address all these questions.

In conclusion, NO seems to function as a controlling mechanism against ET-1–induced vasoconstriction in the chronic, cold stage of CRPS1. Prolonged vasodilation induced by NO donors could result in an improved blood distribution as the first step towards remission of this severely invalidating disease.

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Chapter 8

# General discussion

## 8.1 Introduction

The aim of this thesis is to evaluate the use of videothermography as a diagnostic tool in the Complex Regional Pain Syndrome (CRPS), and to gain more insight in the pathophysiology of CRPS. To fulfil this aim, we developed static and dynamic measurement setups for videothermography. First, we discuss the results of the thermographic measurements and their contribution to the elucidation of the pathophysiology of CRPS1. Next, we discuss the diagnostic and monitoring capabilities of thermography. Thereafter, we discuss the methodological considerations of these studies and the choice of the location of thermographic measurements in the human body. Finally, we discuss the relation between vasomotor function and pain, and the applications of videothermography in medicine.

## 8.2 Main Results

**Pathophysiology**

Static videothermographic measurements we revealed a significant difference in temperature between pairs of extremities in CRPS1 patients compared to patients without CRPS1 and to healthy controls. These results were also documented in earlier studies, but these studies described patients at a relative late stage in the development of the disease[1-4]. In our work, we found a significant difference in temperature between pairs of extremities in an early stage in the development of CRPS1 (Chapter 4)[5].

Using static thermography, we were, not able to distinguish between the local (Figure 8.1; neural and non neural control) and more central mechanisms (Figure 8.1; central sensitisation) which influence the blood flow of an extremity. Dynamic thermography on the other hand, allows to make a distinction between these local and central effects[6]. Dynamic thermography enables assessment of the central sympathetic contribution to temperature differences between the extremities. Provocation of the sympathetic system is induced by whole body heating and cooling; this results in minimum, maximum and intermediate vasoconstriction[7]. In consequence, the temperature difference between extremities further increases. Our experiments are described in Chapter 5 (Figure 8.1; central sympathetic provocation). Although this result has been reported in other studies,[5,7] we were able to capture the whole extremity in one thermographic image. This measurement clarified that the blood flow of the whole extremity was affected. It would not be possible to draw such a conclusion using a single spot type of temperature measurement, such as a tympanic temperature measurement device or a laser Doppler flow device. Furthermore, the difference in temperature between extremities as measured by thermography totally disappeared in a state of maximum vasoconstriction and minimum vasoconstriction (Chapter 5). As a result we can conclude that the local vascular system is at least in part, still capable of constricting and dilating. We can also conclude that the sympathetic afferent system is involved in CRPS1 and plays a role in the pathophysiology. The conclusion that the local vasomotor system

is (in part) still functioning is further supported by the vasodilator effect that is achieved by application of a nitric oxide donor, isosorbide dinitrate (ISDN), in patients as measured by thermography (Figure 8.1; NO donor) in Chapter 7. Furthermore, in a study in which anti-TNFα was given, a decrease in temperature as measured by thermography was found (Figure 8.1; Anti-TNFα)[8]. Other influences on the pathophysiology of CRPS1 that affect the

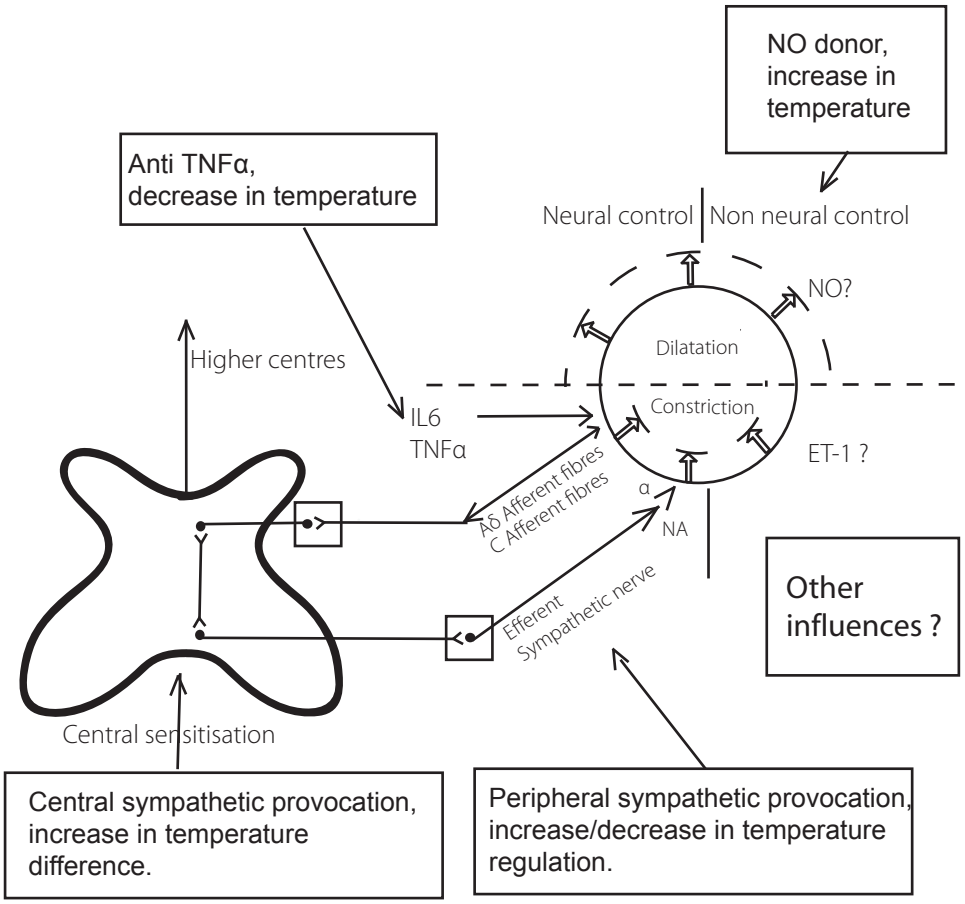


**Figure 8.1 Part of the pathophysiology of CROS1 explored in this thesis.**

blood flow regulation should be studied in the future.

In chapter 6 local disturbance of temperature, by provoking a CIVD[9] reaction, in both nerve injured and CRPS1 patient compared to healthy controls revealed that local regulation of blood flow is also disturbed in the CRPS1 extremity. (Figure 8.1, peripheral sympathetic provocation).

**Diagnostic value**

We have concluded that, central and peripheral mechanisms controlling blood flow are definitely involved in CRSP1. Therefore thermography could play an important role as a diagnostic tool in CRPS1. The diagnostic value of temperature difference between extremities has been studied before but mostly using a tympanic temperature measurement device[3,7,10-13]. The few studies investigating thermography as a diagnostic device in CRPS, used a average calculation of temperature differences on thermographic images and did not make use of ROC analysis. Nevertheless, they concluded that the temperature difference between extremities could be a valuable tool in the diagnosis of CRPS[10,14,15]. By applying methods that are able to take into account the temperature profile of a whole hand, we anticipated an increase in performance of thermography as a diagnostic tool[16]. We started by using human observers to rate the difference in temperature between the thermographic images (Chapter 2). The increase in sensitivity and specificity using the ratings of the human observers compared to calculation of average temperatures, confirmed the need for a method that uses all the recorded thermographic data. However, the lack of reliability and repeatability and the influence of the chosen colour pallet on the ratings of the observers that was found in this study the need for a more mathematical approach (Chapter 2). In Chapter 3, by applying a mathematical approach to analyse thermographic images an increase in sensitivity was found and the lack of reliability and repeatability was reduced, and the influence of the color pallet was abolished[16]. This mathematical method and the diagnostic value of static thermography was further studied in Chapter 4. Although the temperature difference between contralateral extremities of CRPS1 fracture patients and fracture patients was significant, ROC analysis revealed only moderate diagnostic value. Although the mathematical methods developed to analyze the thermographic data are imperfect, the static thermographic measurement alone, in our opinion, is not specific enough to diagnose CRPS1 patients. An increase in temperature difference was found by the use of controlled thermoregulation in a study comparing CRPS1 patients to healthy controls and patients with other types of pain. However, in that study a tympanometer was used to measure spots on the hand[7]. In the studies in Chapter 5 and 6 (dynamic thermography) an increase in temperature difference, measured with thermography, between a pair of hands of a CRPS1 patient compared to healthy controls was found making use of controlled thermoregulation. This indicates that CRPS1 patients do not show the largest possible difference in resting condition. Therefore, it is likely that an increase in diagnostic capabilities is obtained when the sympathetic system is provoked[10,13] and an even further increase is likely to be found when this is measured with thermography. In conclusion, it is mandatory to apply dynamic thermography in the diagnosis of CRPS1 patients.

**Monitoring of CRPS1 during pharmacotherapy**

Chapter 3 presents an example of a graph of a patient who received DMSO (dimethyl

sulfoxide) cream and who was followed with thermography. The thermographic recording each week was related to the impairment level sums score (ISS). A correlation was found between the impairment of CRPS1 and the videothermographic outcome (Chapter 3); this relationship was confirmed in Chapter 5. The capability of thermography to monitor the effect of local vasomotor active components (such as ISDN) on vasomotor activity was assessed in a pilot study described in Chapter 7. In this study the influence of a potent vasodilator could be readily assessed by thermography. Furthermore in a study by Huygen et al. in which anti-TNFα was given, the increase in vasomotor tone could be assessed by thermography. However, a distinction should be made in types of pharmacotherapy used and using thermography to monitor patients. If pharmacotherapy is directly aimed at vasodilatation, such as ISDN, it is unlikely that there is a direct relation between impairments of the CRPS1 disease and static thermographic measurement. In this type of study it is recommended to make use of dynamic thermographic measurements. Nevertheless, static thermographic measurement are able to show whether pharmacotherapy aimed at vasodilatation is successful in terms of increased/ decreased blood flow (quantitative measurement). On the other hand, if pharmacotherapy is not directly aimed at vasodilatation (anti-TNFα) and an increase or decrease in temperature is measured it is more likely to be related to impairments of the CRPS1 (qualitative measurement). When comparing the temperature of extremities the possible systemic effect of pharmacotherapy should also be taken into account.

Another point that has to be stressed is that the temperature of the extremities of patients does tend to fluctuate over time. Therefore, if a qualitative relation between impairments of CRPS is desired, it is again recommended to further develop a method to measure the sympathetic function in CRPS1 patients, using dynamic thermography.

**The developmental phases**

In this thesis, both static and dynamic thermographic measurement setups have been evaluated. For static thermography most of the initial phase has been evaluated (Table 8.1; static thermography). If there are time varying effects in controls they are in part reflected by the way validity was calculated in Chapter 3.

**Table 8.1 Parts covered of the initial developmental phase in this thesis.**

| | | Initial Phase | | |
|---|---|---|---|---|
| | | Validity Reliability | Test-retest reliability | Time varying Effects |
| Static | Chapter 2 | 0.5 | 0.53 | - |
| Thermography | Chapter 3[2] | 0.78 | 0.86 | - |
| Dynamic | Chapter 5 | - | - | - |
| Thermography | Chapter 6 | - | - | - |

[2]Tested on healthy controls.

The time varying effects in static thermography in patients is now being studied in two placebo-controlled randomized-controlled trials. This is the only valid method to assess standard error of measurement (SEM) and smallest detectable difference (SDD) in patients, because of the fluctuation in their impairments over time. For the laborious dynamic thermographic measurement the decision was first to determine if the method was applicable and then to determine the factors described in Table 8.1. In the potential phase the difference between the patient group and a control group, and a relation between impairment of CRPS1 and thermography measurement was determined (see Table 8.2). As was described earlier, in each of the studies described in this thesis a significant difference between extremities in temperature was found in CRPS1 patients. The primary goal of the potential phase is to show the difference between patients and controls. The results in Chapter 3 clearly show that a mathematical method increases the sensitivity and specificity as well as the repeatability and reliability as compared to the method using human observers. An indication of a possible relation between thermography and the impairment of CRPS1 was found by calculating the correlation between the asymmetry factor and the ISS impairment found in CRPS1 patients (see Table 8.2). This needs to be determined further in a clinical trial in order to calculate the SDD and SEM, see also below (section 8.3). Parts covered of the potential developmental phase in this thesis Table 8.2.

**Tabel 8.2 Potential phase in this thesis.**

| Potential Phase | | | | |
|---|---|---|---|---|
| | | Difference between patient and control group | | Correlation between measurement and CRPS impairments[1] |
| | | Patients | Controls | |
| Static thermography | Chapter 2 observer score (0-10) | 4.8±2.3 | 1.5±1.1 | n.s. |
| | Chapter 3 average temperature difference (°C) | 1.4± 1.3 | 0.3±0.1 | n.s. |
| | Chapter 3 asymmetry | 0.45 ± 0.07 | 0.91± 0.01 | n.s. |
| Dynamic thermography | Chapter 5 median temperature difference (°C) | 2.50 (1.61-3.43) | 0.95 (0.50-1.51) | n.s. |
| | Chapter 5 asymmetry | 0.56 (0.22-0.70) | 0.82 (0.79-0.87) | -0.678 (p=0.015) |
| | Chapter 6 | - | - | - |
| | Chapter 6 | - | - | - |

[1]Based on the ISS total score and asymmetry factor

n.s. = not significant.

In preparation of this thesis, the monitoring phase was not yet sufficiently studied.

From the results on diagnostic capabilities (Table 8.3) it is clear that mathematical methods based on comparison of all individual temperatures, instead of averaging all individual temperatures, increase the discrimination between CRPS1 patients and patients/controls. Nevertheless static thermography recordings do not provide sufficient stand-alone diagnostic capabilities. A further increase can be expected when using dynamic thermographic recordings.

**Table 8.3 The diagnostic phase in this thesis.**

| | | Sensitivity (%) | Specificity (%) | AUC | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|---|---|
| Static thermography | Chapter 2[1] score | 71 | 85 | 0.86 | - | - |
| | Chapter 3[1] average[2] | 50 | 50 | 0.068 | - | - |
| | Chapter 3[1] asymmetry | 92 | 94 | 0.97 | - | - |
| | Chapter 4 average[3] | 48 | 64 | 0.60 | 31 | 78 |
| | Chapter 4 asymmetry | 63 | 61 | 0.63 | 35 | 84 |
| | Chapter 5[1] average[3] | 76 | 38 | 0.48 | - | - |
| | Chapter 5[1] asymmetry | 100 | 75 | 0.90 | - | - |
| Dynamic thermography | Chapter 5[1] asymmetry | 92 | 75 | 0.87 | - | - |
| | Chapter 5[1] average[3] | 100 | 83 | 0.96 | | |
| | Chapter 6 | - | - | - | - | - |
| | Chapter 6 | - | - | - | - | - |

[1]Based on comparison with healthy controls.

[2]Based on the difference in average temperature of the whole hand.

[3]Based on the difference in average temperature of fingertips.

The disease state of the studied population, expressed in the impairment level sum score (ISS), in Chapter 2 was comparable to the disease state of the study population described

in Chapter 3. The sensitivity, of the scoring method described in Chapter 2 increased when compared with the mathematical method used in Chapter 3. The specificity increased and the AUC also increased. Therefore, it is mandatory to used a method to assess thermographic images that is based on comparison of all individual temperatures instead of averaging all individual temperatures. This is further supported by the decrease in the ability to distinguish between patients and controls comparing the scoring method developed in Chapter 2 to the average temperature calculation (comparison of averaging of all individual temperature readings) in Chapter 3. However, in Chapter 4, a study on diagnostic capabilities on a large population, comparing CRPS1 patients with patients with clinical symptoms similar to CRPS1, resulted in moderate diagnostic capabilities. Furthermore, the results of static thermography that were also calculated in Chapter 5 in addition to the results of dynamic thermography, indicated a loss in diagnostic power when the severity of CRPS1 decreases. To counteract this decrease, dynamic thermography was studied in Chapter 5 and Chapter 6. Here an increase was found in the ability to distinguish between patients and controls during measurement of the effect of disturbance on thermoregulation. A more patient-friendly method for the application of dynamic thermography is currently being developed.

## 8.3 Methodological considerations

Most methods used to analyse thermographic data assume some sort of symmetry between extremities, and try to define asymmetry. This assumption concerning symmetry implies the non-involved extremity in CRPS patients is not affected by the disease. Although there are reports that the non-involved extremity is also affected, in a large study on 829 chronic CRPS1 patients only 39 (4.7%) of these patients were affected in more than one extremity[17].

When an assessment instrument is developed into a diagnostic instrument, the diagnostic value can only be adequately evaluated if there is a gold standard available. The gold standard used in this thesis is the Bruehl criteria and these (as do all criteria) introduce a diagnostic bias. As a result of this a bias in parameters that describe diagnostic value is introduced[18]; therefore it is not possible to conclude that thermography is more accurate in the diagnosis of a CRPS patient. One way to address this problem is to perform a prospective study. The question addressed in this type of study is: can thermography measurement predict wheter a type of pharmacotherapy is going to be successful in a patient? In other words, can thermography define subgroups in CRPS1?

To assess the monitoring capabilities, the calculation of smallest detectible difference SDD and SEM, should be performed within a placebo-controlled radomized controlled study. By applying this method, the unknown fluctuation of impairment of acute chronic CRPS1 patients is taken into account.

## 8.4 Anatomical aspects concerning the location of thermographic measurement

In this thesis the distal part of the extremities (hands and feet) were chosen as the measurement location in patients and in controls. However, CRPS1 does tend to spread further beyond this area into the involved arm or leg. Therefore, an effect on blood flow and thus temperature beyond the hand/foot area is expected. Nevertheless, this distal recording was chosen because of the low ratio of skeletal muscles in hands and feet compared to this same ratio in the arms and legs. In hands it was estimated that the metabolic heat production was 0.25 Watt in resting conditions[19,20]. No such estimation could be found for the feet, but it is likely that the temperature in resting condition in the feet can also be totally attributed to blood flow through the feet. Therefore, it is unlikely that the thermographic recording beyond the area of hands or feet would contribute to the value of thermography as an assessment instrument. Indeed, in the study performed in Chapter 4 a large increase and decrease in blood flow was found as a result of a change of core skin temperature using a thermo suit. This indicated that the blood flow in the hands makes a large contribution to the thermoregulation of a human body. This was also demonstrated by Hirate et al. in an experiment in which the body core temperature was measured with occluded and without occluded hands; they found an increase of 0.2°C of body core temperature with the hands in the occluded state during exercise[21]. No significant differences were found in the choice of comparison of palmar/plantar or dorsal thermographic recordings on the sensitivity to change in blood flow as demonstrated in the study of Chapter 4. However, a slight increase in the sensitivity was found in most of the studies using the palmar/plantar recordings of hands or feet, as was found in Chapters 2, 3 and 4.

### 8.4.1 Blood supply to the hand

The hands are innervated by the radial and ulnar artery and they connected in the palmar arch and in the superficial palmar arch. From the palmar arch the digiti are innervated by arterioles that run parallel to the digiti and on return open up into the deep superficial veins of the hand. On both the palmar and dorsal side of the hand there is a network of capillaries connecting the arterioles to the veins.

### 8.4.2 Blood supply to the feet

The largest arteries supplying the feet are the anterior tibial artery and the posterior tibial artery. The anterior tibial artery connects through the deep arcuate artery and the dorsal metatarsale arteries to the digit arteries on the dorsal side; they connect to the dorsal venous arch. The posterior artery splits into the lateral plantar artery and the medial plantar artery

and connect via the plantar arch; these arteries lay more superficial compared to the dorsal arteries. The plantar arch innervates the toes via digiti arterioles that run parallel to the toes; they connect to the deep plantar venous arch. On both the plantar and dorsal aspect of the feet there is a network of capillaries connecting the arterioles to the veins.

In conclusion, the largest supply of blood flow is through the palmar side of the hands and through the plantar side of the feet. As a result, a change in blood flow will have the most effect on temperature on the palmar/plantar aspects of the extremities.

By mapping the thermographic data on the geometrical data obtained from a 3-dimensional imager, a 3-D thermographic image can be obtained.

## 8.5 Videothermography and pain.

It is still difficult to obtain objective and reliable data on pain and pain intensity from patients suffering from acute or chronic pain. Afferent pain nerves can be divided into myelinated (α-delta) and unmyelinated fibres (C-fibres). The α-delta responds to mechanical or temperature stimuli and produces an acute, sharp and short-lasting pain via the neurotransmitter glutamate acting on the AMPA receptors located in the dorsal horn. The C-fibres respond to a wide variety of painful stimuli (e.g. mechanical and thermal as well as metabolic factors) and produce a slow, burning and long -lasting pain. The C-fibres transmit pain sensation not only via the AMPA receptor but also produce an additive effect via the NMDA receptor. This NMDA receptor only acts on prolonged stimuli. One of hypothesis on the relation between pain and the vasomotor system is described below[22].

The activated (by pain-ful stimuli) and sensitised afferent fibres (C-fibres) activate macrophages through the release of substance-P. The macrophages start to release cytokines, such as TNF-α and IL-6. This release further enhances the afferent fibres and induces vasoactive components via the efferent fibres, either locally (axon reflex) or centrally (central sensitisation); therefore, the pain is partly reflected in neurovascular dysfunction. It is likely that in other types of disease the pain, apart from somatic pain, is also partly reflected by vasomotor dysfunction.

To increase our understanding of the relation between pain and temperature we devised a pilot to measure feet of a diabetic patient. Figure 1.2 shows a plantar thermographic recording of the feet of a 45- year-old men (BMI > 30 kg/m$^2$) with type II diabetes.

The spread of pain due to tissue destruction and the influx of inflammatory cells (which release mediators such as TNF-α and IL-6) of a disturbed blood tissue distribution (via axon reflex), could be visualized by videothermography. The exact localization, but possibly the spread and intensity of pain, could be represented by the amount of changed skin surface area, as well as the difference in skin temperature per spot. This was a static measurement, without forced exercise prior to the thermograph. No clear visible signs of vascular deformities were registered. Thermographic evaluation, however, clearly shows asymmetry between

both feet. Remarkable, however, is the elevated temperature in the toes, most pronounced in the right foot (shown on the left side in Figure 1.2). These temperatures are 3-4 °C higher than the mean temperature (coloured green/blue). Moreover, in the 'risk spots' in the right diabetic foot, as indicated with arrows 1-3, the temperature is much higher than in the left foot, where minor red spotted areas were noticed see arrows 4-6. Without knowledge of these thermographic outcomes, the patient only reported painful spots on the right foot,

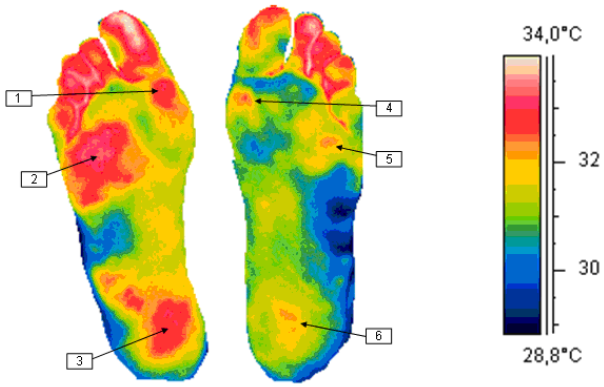


**Figure 8.2 Thermograph of the feet of a diabetic patient**

indicated with arrows 1-3.

This indicates that videothermography is indeed a worthwhile tool to distinguish between area of painful tissue. These results further suggest that early diagnosis could be achieved with this method, even faster and better than the patient's own awareness.

A large number of blinded observations in this type of chronic pain patients should be performed to investigate the relationship between pain, pain intensity, allodynia and thermographic changes due to vascular abnormalities.

## 8.6 Medicine and thermography

Asymmetrical thermograms occur in response to a variety of abnormalities, especially vasomotor dysfunction. Thermography demonstrates aspects of the function/dysfunction of the vasomotor function rather than of the anatomy. Some example of other techniques for blood flow measurement are indicator-dilution, electromagnetic flow meters, plethysmography, electric-impedance plethysmography, and ultrasonic flow meters. Both the indicater-dilution method and the electromagnetic flow meter are invasive methods. The indicator-dilution method involves injection of a fluid into the bloodstream after which it can be visualized. The electromagnetic flow meter measures the magnetic flux that

is induced by the blood flowing through a magnetic field. These methods are not able to assess rapid changes. The plethysmography method involves measuring the volume change induced by the pressure change between heart beats; this method is very accurate but can only be used to track total blood flow changes of, for example a whole finger or hand. Electrical-impedance plethysmography involve tracking the impedance change as a result of blood volume change; this method has only been used in experimental setups. An example of an ultrasonic measurement setup is a laser Doppler flow setup, this method is capable to measure non-invasively, and we are currently performing simultaneous measurements of skin blood flow and skin temperature with a laser Doppler flow imager and a videothermograph. The advantages of thermography are obvious, this technique is able to non-invasively track rapid changes in blood flow in a large area by measuring temperature with a high resolution. There are several disadvantages related to thermographic measurements. Summarising the shortcomings found on thermography as reported in the literature, the following factors could be defined: the lack of standardization in the manner in which thermographic measurements are performed, the sparse analyzing methods available to analyse thermographic data, the lack of knowledge regarding the underlying mechanisms that result in temperature differences, and the need for a dynamic measurement. In this thesis a standardized measurement and protocol was developed, several analysing methods were developed and the underlying mechanism of altered blood flow in CRPS1 was studied and described. Furthermore, a start was made to a dynamic measurement setup. By addressing these short comings, thermography was developed into a tool that provides information that is helpful in the diagnosis of CRPS1 and capable to monitor during interventions.

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Chapter 9

# Summary

In this thesis videothermography is developed and evaluated as a diagnostic and monitoring tool in Complex Regional Pain Syndrome type 1 (CRPS1). This work is conducted within four pre-set developmental phases: namely, the initial, potential, monitoring and diagnostic phases. Two main methods of measurement were developed and evaluated, namely: i) static videothermography: recording of a thermographic image of an extremity without application of any disturbing factors on temperature regulation and ii) dynamic videothermography: recordings of a sequence of thermographic images during application of various disturbing effects on temperature regulation of the human body. The recorded thermographic images were analysed by means of various mathematical methods and their additive value in the assessment of CRPS1 was studied.

Chapter 1 (Introduction) addresses the pathophysiology of CRPS1, which is not yet fully elucidated. The diagnosis can be complicated and is entirely based on criteria which are defined by symptom groups. There is a need for an objective assessment technique to diagnose and monitor CRPS1. Such a tool could also have potential additive value in the evaluation of the pathophysiological mechanisms involved in CRPS1.

Its is established that both local inflammation and autonomic disturbances are part of the pathophysiology of CRPS1. As a result, changes in skin blood flow and sweating frequently occur and, in part, are also reflected in a change in skin temperature. This change in temperature can be measured with videothermography which is able to record, without skin contact, the temperature of the body or an extremity.

In Chapter 2 (static videothermography: initial and potential phases) explores the quantification of observer assessment of static thermographic images. The acquired data allowed to determine the sensitivity, specificity, reliability. A total of 35

observers were asked to rate the difference between randomly presented thermographic images of pairs of hands of patients and of healthy controls on a scale from 0 to 10. Each image was rated twice by each observer.

The sensitivity, specificity, and potential learning effects were calculated by using observers' ratings of 13 pairs of hands of CRPS1 patients and of ratings of 13 pairs of hands of healthy controls. Effects of the colours pallet and the rank number of the image on the rating of the observers of the images were also analysed.

In conclusion, though the choice of colour pallet partly explained the variance in the rating scores, this study showed that ratings of the observers' assessment of thermographic images may distinguish between CRPS1 patients and healthy controls. However, the reliability and repeatability of this observer assessment was relatively low.

Chapter 3 (static videothermography: initial, potential and monitoring phases) presents a mathematical model that we developed to analyse the thermographic images in an attempt to increase the sensitivity, specificity, reliability and repeatability. This mathematical model was compared with conventional methods which calculate the

temperature difference between thermographic images. In our study, in 13 healthy controls where compared to 18 CRPS1 patients using this mathematical model. The performance of the mathematical model based on the ROC curve and repeated measurement analysis was excellent. When comparing our newly developed mathematical method with conventional methods, a marked increase in discriminating power, reliability and repeatability was found. This study confirms that analysing thermographic data using a mathematical approach is strongly recommended.

In Chapter 4 (static videothermography: diagnostic phase), thermographic recordings of the palmar/plantar side and dorsal side of both hands or feet were taken in 24 CRPS1 fracture patients diagnosed by the Bruehl criteria and in 96 fracture patients with/without a suspicion of CRPS1. The diagnostic value is described and mathematical results on analysis of thermographic images are compared. A significant difference in temperature between extremities was found when comparing CRPS1 fracture patients with fracture patients without a suspicion of CRPS1. The highest level of temperature difference between hands was found in the CRPS1 fracture patient group. However, the AUC of the various applied mathematical methods was relatively low. In conclusion, the validity of skin surface temperature recordings using static videothermography to discriminate between acute CRPS1 fracture patients and fracture patients with/without complaints is limited and only useful as a supplementary diagnostic tool.

Chapter 5 (dynamic videothermography: initial, potential, and diagnostic phases) presents an experimental set-up to elucidate the involvement of the sympathetic system on the temperature of an CRPS1 extremity diagnosed by the Bruehl criteria. Whole body cooling and warming was induced in 12 CRPS1 patients and in 8 healthy controls to provoke maximum and minimum vasoconstriction. The temperature difference between the hands in CRPS1 patients increased significantly when the sympathetic system was provoked. During body cooling and warming the mean difference in temperature between extremities in the CRPS1 patients increased. At both the maximum and minimum vasoconstriction no significant difference was found between fingertip temperatures of a pair of hands in both the patient and control group. These findings suggest that the sympathetic efferent system is involved in CRPS1. Furthermore, an increase in temperature difference between pairs of hands during sympathetic provocation indicates that more information on the disease state can be obtained using a temperature provocation method.

Chapter 6 (Dynamic videothermography, developmental phase): In this pilot study a measurement set-up capable to assess local blood flow disturbances in CRPS1 was developed. The palmar side of both hands of a healthy control groups, nerve injury patients and in a CPRS1 patient, were placed on a cold-plate. This cold-plate disturbed the temperature regulation of the extremity and provoked a cold induced vasodilatation (CIVD) in the participants. A function was fitted on this resulting CIVD curve to enable comparison

of CIVD reactions between contralateral extremities in the three groups.

In healthy controls, the CIVD reaction was comparable between the non-dominant and dominant extremity. In nerve injury patients shortly after trauma (<9 months) the CIVD reaction is almost totally abolished in the injured nerve area. The data on the CIVD reactions in a CRPS1 extremity suggest local blood flow regulation seems to be disturbed. This novel method to assess the peripheral blood flow regulation in CRPS1 patients should be further studied. In the future it might be possible to use this method to unravel underlying mechanisms of disturbed blood flow in the CRPS1 extremity of patients.

Chapter 7 (static videothermography: monitoring phase) describes the application of videothermography to monitor patients during pharmacotherapeutic treatment. The result of local application of a nitric oxide donor, isosorbide dinitrate (ISDN) on vasomotion was measured using videothermography in 5 female patients. An increase of 4-6°C in mean skin temperature of the cold CRPS1 hands was measured, reaching values similar to that of the contralateral extremities within 2-4 weeks after application of ISDN, suggesting normalization of blood distribution. This was confirmed by an improvement in skin colour. These results imply a promising application of videathermography to monitor skin surface temperature during pharmacotherapeutic treatment of patients.

Chapter 8 (Discussion) The primary aim of this project was to evaluate thermography in the diagnostic, monitoring and determination of the pathophysiology of CRPS1 patients.

***Diagnostic value***, Though the developed mathematical developed to analyze the thermographic data are imperfect, in our opinion, static thermographic measurement alone is not specific enough in the diagnosis of CRPS1 patients.

An increase in temperature difference was found by the use of controlled disturbance on thermoregulation. Therefore it is likely that an increase in diagnostic capabilities is attained when the sympathetic system is provoked. In conclusion dynamic is mandatory in the diagnosis of CRPS1 patients.

***Monitoring of CRPS1 during pharmacotherapy***, Thermography is able to monitor the effect of pharmacotherapy. Static thermography measurement can reveal whether pharmacotherapy aimed at vasodilatation is successful in terms of icreased blood flow (quantitative measure). One points needs to be stressed: the temperature of an extremities of patients tend to fluctuate over time. Therefore, if a qualitative relation between the impairments of CRPS is required, it is recommended to develop a method to measure the sympathetic function in CRPS1 patients thus applying dynamic thermography.

***Pathophysiology of CRPS1***, Thermographic measurement was able to show that the temperature and, therefore, the blood flow was disturbed in the whole CRPS1 extremity. The increase in temperature difference between extremities observed during various controlled disturbances on thermoregulation shows the sympathetic system in CRPS1 patients is

involved. However, at maximum and minimum disturbance of the thermoregulation no significant difference in temperature between extremities in was observed. This finding is further supported by the observed vasodilatation using a potent pharmaco agent (Nitric oxide) aimed at vasodilatation in CRPS1 patients in one of our studies. Therefore, we can conclude that the local vascular system, at least in part, is still capable to constrict and dilate. The contribution of inflammation on temperature difference was also confirmed in an earlier study using inflammatory suppression agents.

Beside the measurements techniques described is this thesis en studied within CRPS1, there a numerous disease within medicine in which thermographic measurement could be valuable.

Chapter 10

# Samenvatting

In dit proefschrift werd videothermografie geëvalueerd als onderzoeksinstrument naar het Complex Regionaal Pijn Syndroom (CRPS1). Deze evaluatie werd uitgevoerd met behulp van voorgedefinieerde ontwikkelingsfases, zijnde de initiële, potentiële, monitor en diagnostische fase. Twee meetmethoden werden ontwikkeld en geëvalueerd: i) Statische videothermografie, een thermografische opname van een extremiteit zonder het toepassen van verstoring op de temperatuurregulatie van het menselijk lichaam en ii) Dynamische videothermografie, het maken van een serie thermografische opnames tijdens het toepassen van verstorende effecten op de temperatuurregulatie van het menselijk lichaam. De opgenomen thermografische beelden werden geanalyseerd middels toepassing van diverse methoden en hun waarde in de beoordeling van CRPS werd bestudeerd.

Hoofdstuk 1 (introduction) De pathofysiologie van CRPS1 is niet geheel bekend en de diagnose van CRPS1 is gecompliceerd en geheel gebaseerd op criteria van geclusterde symptomen. Hierdoor is er behoefte aan een objectieve meettechniek die in staat is CRPS1 te diagnosticeren of te monitoren en die mogelijkheden biedt om nieuwe pathofysiologische mechanismen binnen CRPS1 te toetsen. Eerdere studies wijzen uit dat CRPS1 patiënten zowel een lokale ontsteking als autonome verstoringen hebben. Als gevolg hiervan vinden er vaak veranderingen in huiddoorbloeding en in zweetsecretie plaats. Deze veranderingen worden voor een gedeelte vertegenwoordigd door een verandering in huidtemperatuur. Deze verandering in temperatuur kan gemeten worden door middel van videothermografie, waarmee zonder contact met de huid te maken de temperatuur van een extremiteit in zijn geheel gemeten kan worden.

In hoofdstuk 2 (statische videothermografie, initiële en potentiële fase) werd de kwantificering van een score aan thermografische beelden door beoordelaars beschreven. Met behulp van deze gegevens kon de sensitiviteit, specificiteit, betrouwbaarheid en reproduceerbaarheid bepaald worden. Vijfendertig beoordelaars werden gevraagd om de verschillen tussen, in willekeurige volgorde aangeboden handenparen van patiënten en gezonde controles, te beoordelen op een schaal van 0 tot 10. Elke afbeelding werd twee keer beoordeeld door dezelfde beoordelaar. De sensitiviteit, specificiteit en potentiële leereffecten werden berekend met behulp van de scores die door de beoordelaars aan 13 paar CRPS1 handen en 13 paar handen van gezonde controles werden gegeven. Het effect van het kleurenpallet in het plaatje, alsmede het effect van de nummering van de plaatjes op de score van de beoordelaars, werd geanalyseerd. Geconcludeerd kan worden dat, hoewel het gekozen kleurenpallet een gedeelte van de variantie in de score verklaart, deze studie aangetoond heeft dat beoordelaars waarschijnlijk goed in staat zijn om onderscheid te maken tussen thermografische plaatjes van CRPS1 handen en gezonde controles. Evenwel is de betrouwbaarheidsscore en de reproduceerbaarheidsscore van de beoordelaars laag.

In hoofdstuk 3 (statische videothermografie, initiële, potentiële en monitor fase) werd een rekenkundig model ontwikkeld om de thermografische plaatjes te beoordelen

in een poging de sensitiviteit, specificiteit, betrouwbaarheid en reproduceerbaarheid te vergroten. Het rekenkundig model werd vergeleken met conventionelere methodes die de verschillen in temperatuur tussen thermografische opnames berekenen. In deze studie werden 13 gezonde vrijwilligers vergeleken met 18 CRPS1-patienten, gebruikmakend van dit rekenkundig model. De uitkomst van de rekenkundig model, gebaseerd op ROC-(curve)analyse en herhaalde metingen, was uitstekend. In de vergelijking van de conventionele methodes met deze mathematische methode werd een uitgesproken verhoging in onderscheidend vermogen, betrouwbaarheid en reproduceerbaarheid gevonden. Deze studie bevestigt dat het beoordelen van thermografische beelden middels een rekenkundig model sterk de voorkeur geniet..

In hoofdstuk 4 (Statische videothermografie, diagnostische fase ), werden videothermografische opnames van dorsale, palmaire of plantaire zijde van de handen of voeten gemaakt bij 24 CRPS1-patiënten na een fractuur en 96 patiënten met en/of zonder een verdenking op CRPS1. De diagnostische waarde, berekend middels ROC, werd beschreven en de resultaten van rekenkundige model werden vergeleken. Het temperatuurverschil tussen handparen bij het vergelijken van CRPS1-fractuurpatiënten en fractuurpatiënten met en zonder verdenking van CRPS1 was significant. Het hoogste temperatuurverschil tussen handen werd gevonden in CRPS1 patiënten met een fractuur. In de vergelijking van de verschillende rekenkundige modellen werd een matige oppervlakte onder de curve (AUC) gevonden. Samengevat, de bruikbaarheid van huidoppervlakte temperatuur metingen, met behulp van statische videothermografie, om onderscheid te maken tussen acute CRPSP1-fractuurpatiënten en fractuurpatiënten met en zonder klachten, is beperkt en kan alleen toegepast worden als aanvullende diagnostiek.

In hoofdstuk 5 (dynamische videothermografie, initiële, potentiële en diagnostische fases); wordt een experimentele opzet beschreven, welke in staat is om de invloed van het sympathische systeem op de temperatuur van een extremiteit te beoordelen in CRPS1-patiënten gediagnosticeerd middels de Bruehl criteria. Afkoeling van het gehele lichaam en vervolgens algehele verwarming (temperatuurprovocatie) werd geïnduceerd in 12 CRPS1-patiënten en in 8 gezonde controles, met als doel een toename of afname van de sympathische vasoconstrictore activiteit te bewerkstelligen. Het verschil in temperatuur tussen de handen van CRPS1 patiënten verhoogde significant tijdens provocatie van het sympathische systeem. Het temperatuur verschil tussen de handen van CRPS1 patienten verhoogde significant tijdens deze temperatuur provocatie. Er was geen significant verschil in temperatuur tussen een paar handen bij zowel de maximale als minimale vasoconstrictie toestand in zowel de patiëntengroep als de controlegroep. Een verhoging van temperatuurverschil tussen handen geeft aan dat het sympatische syteem betrokken is bij the pathofysiologie van CRPS1 patienten. Waarschijnlijk is deze methode informatief in de diagnose en het monitoren van CRPS1-patienten.

Hoofdstuk 6 (Dynamische videothermografie, ontwikkel fase): In deze pilot studie werd een meet opstelling ontwikkeld waarmee het mogelijk is om locale bloed stroom verstoringen in CPRS1 te meten. De handpalmen van beide handen van gezonde vrijwilligers, zenuwletsel patiënten en een CRPS1 patiënt, werden op een koude plaat geplaatst. Deze koude plaat verstoorde de lokale temperatuurregulatie van de extremiteit en provoceerde een koude geïnduceerde vasodilatatie (CIVD). Vervolgens werd er een functie gefit op de CIVD om vergelijking tussen de groepen mogelijk te maken. In gezonde vrijwilligers was de CIVD vergelijkbaar tussen de handen. In zenuwletsel patiënten kort na het trauma (<9 maanden) was de CIVD reactie bijna niet aanwezig. De data van de CIVD reactie in CRPS1 patiënten geven aan de lokale bloeddoorstroming regelingen waarschijnlijk verstoord zijn de CRPS1 extremiteit. Deze methode moet nog verder worden bestudeerd, in de toekomst is het misschien mogelijk om deze techniek te gebruiken om het mechanisme achter de verstoorde doorbloeding in de CRPS1 extremiteit te achterhalen.

In hoofdstuk 7 (Statische videothermografie, monitor fase), wordt de toepassing van videothermografie beschreven om patiënten in een onderzoekssetting te kunnen volgen gedurende een farmacotherapeutische interventie. Het resultaat van de lokale toediening van een stikstofoxide donor, isosorbide dinitraat (ISDN), op vaatverwijding werd gemeten middels videothermografie bij 5 vrouwen met CRPS1. Binnen 2 weken na behandeling werd een verhoging in gemiddelde handtemperatuur van 4-6°C gevonden in de koude CRPS1 hand. Deze temperatuur was vergelijkbaar met de contralaterale kant wat duidt op normalisatie van de doorbloeding, wat mede bevestigd werd door een verbeterde huidskleur. Uit de resultaten blijkt de veelbelovende toepassing van videothermografie om huidoppervlaktetemperatuur in beeld te brengen gedurende een farmacotherapeutische behandeling van patiënten die verband houdt met onderliggende vasculaire systemen.

In hoofdstuk 8 (Discussie): Het primaire doel van dit project (zie begin) was om thermographie te evalueren als intrument/toepassing in het stellen van de diagnose CRPS1, in het monitoren van CRPS1-patiënten en om gedeeltes van de pathosfysiologie te verhelderen.

Diagnostische waarde; hoewel de ontwikkelde mathematisch model om thermografische beelden te analyseren niet perfect zijn, is naar onze mening de statische thermografische meting niet specifiek genoeg om de diagnose te stellen bij CRPS1-patiënten. Een verhoging in temperatuur( verschil) tussen extremiteiten werd gevonden door gebruik te maken van een gecontroleerde verstoring van de thermoregulatie. Om die reden is het waarschijnlijk dat een verbetering in diagnostische waarden verkregen kan worden wanneer het sympathische systeem word geprovoceerd. Concluderend, dynamische thermografie moet verder worden ontwikkeld.

Monitoren van CRPS1 gedurende farmacotherapie; thermografie is in staat om de effecten van farmacotherapie te monitoren. Statische thermografische metingen geven

aan of farmacotherapie gericht op vasodilatatie succesvol is als het gaat om het meten van een verhoging van bloeddoorstroming (kwantitatieve meting). Een punt moet worden benadrukt: de temperatuur van een extremiteit van een patiënt heeft de neiging te fluctueren gedurende de tijd. Als een kwantitatieve relatie nodig is, wordt het aanbevolen om een dynamische meting te verrichten.

Pathosfysiologie; thermografische metingen waren in staat om te laten zien dat temperatuur, en daarmee de bloeddoorstroming, verstoord was in de gehele extremiteit. De verhoging in temperatuurverschil gevonden gedurende een gecontroleerde verstoring van thermoregulatie, geeft aan dat het sympatische systeem betrokken is bij CPRS1. Echter, bij maximale en minimale verstoring van thermoregulatie kon geen significant verschil in temperatuur tussen extremiteiten worden gevonden. Deze bevinding wordt verder ondersteund door de waargenomen vasodilatie, welke ontstaat bij het toepassen van Nitric oxide, gericht op vaat verwijding in CRPS1-patiënten. Hieruit volgt de conclusie dat het lokale vasculaire systeem, tenminste voor een gedeelte, nog steeds in staat is om te contracteren en te dilateren. De contributie van ontsteking op het temperatuur verschil werd bevestigd door het dempen van de ontsteking middels een ontstekingsremmer.

Naast de meettechnieken beschreven in dit proefschrift en bestudeerd binnen CRPS1, zijn er nog tal van aandoeningen binnen de geneeskunde waarin thermografie een plaats zou kunnen innemen.

## List of publications


**Galvin, E. and Niehof, S., Further evidence that temperature measurement is a useful indicator of regional anesthesia outcomes. Anesth Analg 2007;104: 740-1; author reply 741-2.**

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**Groeneweg, J.G., Huygen, F.J.P.M., Heijmans-Antonissen, C., Niehof, S. and Zijlstra, F.J. Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. BMC Musculoskelet Disord 2006;7: 91.**

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**Niehof, S., Huygen F.J.P.M., Stronks D.L., Klein J. and Zijlstra F.J. Reliability of observer assessment of thermographic images in Complex Regional Pain Syndrome type 1. ACTA ORTHOPÆDICA BELGICA 2007;73: 31-37.**

**Niehof, S., Huygen, F.J. van der Weerd, R.W., Westra, M., and Zijlstra, F.J. Thermography imaging during static and controlled thermoregulation in complex regional pain syndrome type 1: diagnostic value and involvement of the central sympathetic system. Biomed Eng Online 2006;5: 30.**

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**VERRUKKELIJK**

## Curriculum Vitae

Sjoerd Niehof was born on 22 february 1977 in Breda. After Lower General Secondary Education in Breda (mavo Ginneken) he continued to study electronics and telecommunication at an intermediate technical school (MTS) in Breda and graduated while following some first year electronic courses from the Technical College (HTS Breda ). He then continued to Eindhoven and studied applied physics direction medical technology at the technical College (HTS, Fontys Hogeschool). He graduated at the end of 2002 on a project using videothermography on patients at the Pain treatment centre in the ErasmusMC. He then was asked to finish this project and give technical support to the research taking place at the pain treatment centre. This resulted in the work described in this thesis.


Sjoerd P. Niehof
Video thermography: complex regional pain syndrome in the picture